THE NATURAL AND MODIFIED HISTORY OF CONGENITAL HEART DISEASE

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Futura, an imprint of Blackwell Publishing

Blackwell Publishing, Inc./Futura Division, 3 West Main Street, Elmsford, New York 10523, USA
Blackwell Publishing, Inc., 350 Main Street, Malden, Massachusetts 02148–5020, USA
Blackwell Publishing Ltd, 9600 Garsington Road, Oxford OX4 2DQ, UK
Blackwell Publishing Asia Pty Ltd, 550 Swanston Street, Carlton, Victoria 3053, Australia

04 05 06 07 5 4 3 2 1

ISBN: 1–4051–0360–4

The natural and modified history of congenital heart disease/edited by Robert M. Freedom . . . [et al.]; medical illustrations by Hawon Yoo; foreword by Andrew N. Redington; epilogue by Jane Somerville.—1st ed.
p. ; cm.
Includes bibliographical references and index.
ISBN 1-4051-0360-4
1. Congenital heart disease.
[DNLM: 1. Heart Defects, Congenital. WG 220 N2845 2004] I. Freedom, Robert M.
RC687.N375 2004
616.1′2043—dc22

2003019455

A catalogue record for this title is available from the British Library
Acquisitions: Steven Korn
Production: Julie Elliott
Typesetter: SNP Best-set Typesetter Ltd., Hong Kong
Printed and bound by CPI Bath, Bath, UK

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www.futuraco.com
www.blackwellpublishing.com

Dedication

For our patients and their caregivers
past, present and future
and
for our families

Foreword

It is with a real sense of poignancy that I write this Foreword, to what Bob Freedom describes in his preface as his last contribution to our field. Having retired due to ill health from his position as Chief of Cardiology here at The Hospital for Sick Children in Toronto, this may well be Bob's last book. In no way, however, will it be his last contribution to the field. The legacy of his enormous contribution will continue for many years to come. With over 370 scientific papers, 120 chapters and 7 books, we will continue to be educated by Bob's written word. We would all do well to learn from Bob Freedom as a man. His dedication to the practice and development of the speciality is reflected in his encyclopedic knowledge of the literature, his desire for continued enquiry, and his nurturing and celebration of the achievements of others, senior and junior, who shared in his obsession. Those of us who have been directly touched by his enthusiasm, humanity, and tangible support, are all the better for it.

In many ways, *The Natural and Modified History of Congenital Heart Disease* is a perfect cameo of Bob Freedom's contributions, and the contribution of The Hospital for Sick Children, Toronto, as a whole. Each of the chapters describes the history and evolution of treatment of an individual lesion, and the experience of "sick kids," in particular. Some of the earlier outcomes will seem shocking to those new to the field, but this was the nature of the early years of congenital heart surgery. We often think of the physicians and surgeons of those times as pioneers, and our heroes. They would be the first to recognize however, that it was the patients and parents that were the true heroes and pioneers. We learn from them today, lessons from the past. While the practice of our speciality in this millennium, is so totally different to that of 40–50 years ago, the outcome of these earlier endeavors continues to guide contemporary practice. Only in the last few years, for example, have we become aware of the negative impact of chronic pulmonary regurgitation after tetralogy repair, and we are now modifying surgical algorithms to address it. Thus, the data presented in this book, detailing the maturation of philosophy, ideas, treatments, and outcomes should not merely be seen as a historical document. Rather, it is a synthesis of contemporary understanding upon which the future of our speciality will develop.

Together with his co-editors, Shi-Joon Yoo, Haverj Mikailian, and Bill Williams, Bob Freedom has put together an extraordinarily timely contribution. There is hardly a lesion described in this book that has not seen major improvements in preoperative care and interventional treatments, surgical mortality and morbidity, and later postoperative outcomes. For example, the last few years at The Hospital for Sick Children have seen surgical mortality for most of the common lesions fall below 1%, and surgical mortality for a prenatally diagnosed infant with hypoplastic left heart syndrome fall below 10%. To some extent however, our previous preoccupation with surgical mortality as an outcome measure, although entirely understandable, is now *passé*. Surgical survival should be considered as an entry criterion into the more detailed study of the quality of surgical outcomes. For example, the late mortality for many lesions will easily surpass the immediate perioperative mortality, and both circulatory and intellectual outcomes must be considered in the context of a lifetime of follow-up. The optimal management of children, in these terms, is the new frontier of our speciality. Not so long ago, I had the privilege of sitting through one of the most inspiring lectures that I have ever heard. Bob Freedom, discussing the future of paediatric cardiology, used as his theme a famous quotation from Sir Isaac Newton: "If I have seen farther than others, it is because I have stood on the shoulders of giants." Bob, you are one of those giants, and by reading and learning from this book, all of us are standing on your shoulders.

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Preface

With so many excellent textbooks devoted to the varied aspects of congenital heart disease, one might ask is yet another work really necessary? Yet there does not appear to be a resource that stresses just several aspects of congenital heart disease: morphology, incidence and genetics, and the outcomes, both natural and modified, of the particular congenital heart malformation under scrutiny. The adjective "natural" is used with caution, acknowledging that "natural" implies virtually no treatment, medical, surgical, catheter-based, etc., and that this situation rarely exists or occurs in contemporary medicine. This book is also not devoted to specific treatment algorithms, nor how to recognize those myriad forms of congenital heart disease. Thus, as one of us (RMF) was completing *Congenital Heart Disease: Textbook of Angiocardiography* (Futura Publishing, Armonk, New York, 1997), I felt that I would like my last contribution to focus on these selected aspects of congenital heart disease, particularly the outcomes. This desire to conclude my career in pediatric cardiology is the impetus for *The Natural and Modified History of Congenital Heart Disease.* I was fortunate to work with Drs Arthur Moss, Forrest Adams, George Emmanoulides, Herbert Ruttenberg, Richard and Stella van Praagh, Alexander S. Nadas, Robert E. Gross, Richard D. Rowe, George A. Trusler, William T. Mustard, all wonderful clinicians, teachers and mentors of pediatric cardiovascular medicine and surgery, and to know the "founding mother" of pediatric cardiology, Dr Helen B. Taussig, during my tenure at Johns Hopkins Hospital. With these wonderful contributers to our specialty in mind, I felt it important to remember and to document the modern history of our specialty, citing some of the relevant literature dating from the mid 1930s, coincident with the publication of Maude Abbott's *Atlas of Congenital Heart Disease*. *The Natural and Modified History of Congenital Heart Disease* is not, however, designed to be a comprehensive history of congenital heart disease, as that will be left to the contributions of the late William J. Rashkind and others who pursue this interest.

The Toronto Hospital for Sick Children's Division of Cardiology has kept its own clinical patient records for more than 50 years, and much of the patient information accumulated over the past 30 years is on a computerized database. The desire to maintain our own clinical records and database began with the first head of the Division of Cardiology, the late John D. Keith, followed by Richard Rowe (1923–88) and continued through my tenure as head of the division (1985–2000) and will continue under the leadership of Andrew Redington. Similarly the Division of Cardiovascular Surgery has created a database in parallel that extends back more than 25 years, and for some conditions nearly 40 years. The surgical database has been largely maintained by Dr Bill Williams and his wife, Gail. These databases provide a history of the contributions to our specialty from a single large institution and allow us to focus on the outcomes of the various treatment algorithms. At the conclusion of many but not all of the chapters, a summary stating some of the important issues is provided. This multi-authored and edited textbook draws heavily from the literature, and we have cited many of the larger and modest-sized published series. While trying to be comprehensive, we acknowledge there will likely be some omissions. As the senior author and editor of *The Natural and Modified History of Congenital Heart Disease*, I will assume responsibility for any of these omissions.

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Acknowledgements

First, I must thank Dr David Naylor, Dean of the Faculty of Medicine of the University of Toronto and Dr Hugh O'Brodovich, Professor and Chair of the Department of Pediatrics, the Hospital for Sick Children and University of Toronto Faculty of Medicine for granting me an academic sabbatical to write much of *The Natural and Modified History of Congenital Heart Disease*. Mr Michael Strofolino, former President and Chief Executive Officer of the Hospital for Sick Children, is a dear friend and was very supportive of the Division of Cardiology's clinical and academic activities during his time as CEO. He supported my application to the Hospital for Sick Children's Foundation for funding to support the cost of graphics and illustrations for this work. In this regard, Dianne Lister, President of the Hospital for Sick Children Foundation, and Claire Fortier, Vice President and Chief Stewardship Officer were both most supportive of this effort and gave freely of their time. We are grateful to Ms Hawon Yoo for preparing many of the illustrations used in this work. We also recognize the support of the Graphics Centre of the Hospital for Sick Children, particularly Tiiu Cask, director of the Graphics Centre and her excellent staff. Mr Diogenes Baena who was so important to the graphics in *Congenital Heart Disease: Textbook of Angiocardiography* (Futura Publishing, Armonk, New York, 1997) was also fundamental to the present work as well. The consistent production of high-quality cineangiographic images requires state of the art cardiac imaging equipment. The images in this book were obtained using Siemens biplane cardiac angiographic units. I especially thank Mr Doug Morton, Vice-President, Medical Solutions Division, Siemens Canada Ltd for his ongoing support of this and other imaging projects carried out by members of the Division of Cardiology, Department of Pediatrics and Section of cardiovascular imaging, Department of Diagnostic Imaging of the Toronto Hospital for Sick Children. Many of the staff of the Divisions of Cardiology and Cardiovascular Surgery contributed to this work and we are most appreciative of their efforts. Much of the patient data used from the Toronto Hospital for Sick Children was analyzed by Dr Brian McCrindle as well as present and former trainees of the Division of Cardiology, and they are acknowledged as authors or co-authors of many of the chapters. The patients' clinical records are retained in the Cardiac Data Center of the Division of Cardiology and we are indebted to the due diligence of Ms Mickey Baldwin and Ms Rooma Vaidya who maintain the records and computerized database for the division. We are particularly pleased that Mr Haverj Mikailian agreed to be a co-editor of *The Natural and Modified History of Congenital Heart Disease*. For so many years he has contributed tirelessly to maintain angiocardiographic excellence at the Hospital for Sick Children. His dedication to our division and to quality and education far exceeds any normal expectation. His co-editor status acknowledges his more than 25 years of service and dedication to pediatric cardiology and angiographic imaging at the Hospital for Sick Children. Furthermore, as I wrote much of this work off site in Granville Ferry, Nova Scotia, most of the images used in this book were selected by Haverj and Dr Shi-Joon Yoo and with Mr Baena were labeled for this publication. The various co-editors acknowledge the contributions and efforts of their secretaries in bringing this work to completion. We are thankful to Ms Katherine McLaren who supported Dr Shi-Joon Yoo tremendously in organizing the figures and figure legends and in getting permissions of the publishers for reproduction of the figures from the published articles. Also, in this regard, I must single out Ms Ruth Taylor and Teresa Angileri, both women who helped me tirelessly to gather material used for this book. As senior secretaries in the Division of Cardiology, they were devoted to me and to this work, and without their unselfish work ethic and meticulous attention to detail this book could not have been completed. I will forever be indebted to them both for their devotion to this task and their friendship. I am pleased to have worked with Mr Steven Korn of Blackwell-Futura and his staff, particularly Joanna Levine, book production editor in the New York office. Steven has been a dear friend for many years, and I appreciate his wisdom and support during the writing and publication of this work. Finally I must also acknowledge Ms Julie Elliott, medical book production deputy manager for Blackwell Publishing in Oxford, and Tom Fryer of Sparks, Oxford, who worked tirelessly to see this project to its conclusion.

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Robert M. Freedom

Historical Overview: a Brief Narrative of the Modern Era of Congenital Heart Disease

Pediatric cardiovascular medicine and surgery are wonderfully exciting and rewarding specialties, and what is so remarkable is how much has been accomplished in these arenas in such a brief time, indeed in less than seven decades, the era in which effective surgery for congenital heart disease began.[1] For patients with congenital heart disease so much is taken for granted today, but of course this can be said, and has been said about so many accomplishments of mankind. It is difficult to convey the excitement that embraces those of us who care for patients with congenital heart disease, patients now including the fetus and adult. Part of this fascination is defined, indeed embraced by the history of our specialties and those events and accomplishments underscoring the successes as well as the disappointments and failures of those who preceded us. Those pioneers of our specialties were certainly imbued with awe as they tackled one challenge after another, forever altering the outcomes for patients with increasingly complex forms of congenital heart disease. With these interventions, medical, surgical, and more recently catheter-based, the natural history of most forms of congenital heart disease has been forever changed. Indeed today the history of many forms of congenital heart disease is not at all natural, but rather a history or outcome that is and has been irrevocably modified by human intervention.

While the recognition of certain forms of congenitally malformed hearts dates back many hundreds of years, likely even more, some would assign the modern era for the study and treatment of congenital heart malformations coincident with the signal contribution of Robert E. Gross of Boston who first successfully ligated the patent arterial duct of a 7-year-old girl on August 26, 1938.[1] In this regard, Acierno has written an interesting history of cardiology.[2] In his chapter devoted to congenital abnormalities he has written:

> Knowledge concerning congenital defects of the heart can be traced as far back as Aristotle in the fourth century BC. Subsequent to this, significant observations were made over the succeeding centuries by a number of people. Among them were Fabricius, von Haller, Morgagni, Senac, Hunter, Spallanzani, Baillie, Rokitansky, Roger, Sandifort, Fallot, Eisenmenger and Mall. The list is by no means complete, and it would serve no purpose to make it so. The important point is that these were isolated descriptions presented by independent observers as part of their other observations, and in an incidental or casual manner. None of these constituted a link, as it were, for forging a panoramic view of the entire spectrum of congenital defects. Moreover, many of these observations remained buried and forgotten in dust-covered manuscripts only to be resurrected or rediscovered when an interest in congenital cardiac defects began to prevail. This did not occur until the 19th century with the publication of two textbooks, one by Farre, and the other by Peacock.

Thus the contributions of Maude Abbott must strongly resonate in the history of congenital heart disease. Abbott, a Canadian, began compiling pathological and then clinical data on patients with congenital heart disease at the beginning of the 20th century, culminating in the publication of her wonderful *Atlas of Congenital Heart Disease* in 1936.[3,3A] Maude Abbott's contributions overlapped with those of Helen Brooke Taussig who developed the first clinic at Johns Hopkins Hospital in Baltimore, Maryland in 1930 to study and care for children with congenital heart disease.[4–8] Taussig in her early publications described the clinical features of many forms of congenital heart disease, all summarized in considerable detail initially in her 1947 *Congenital Malformations of the Heart*[9] and her second edition of *Congenital Malformations of the Heart*, published in 1960, and expanded to two volumes.[10] Taussig stated in the preface to the first edition of her book: "When I first began my work on fluoroscopy and demonstrated that it was possible to make the clinical diagnosis of a non-functioning right ventricle, Dr E. A. Park, then Professor of Pediatrics at the Johns Hopkins Hospital, expressed the hope that some day I would write a book – 'Congenital Malformations of the Heart-Forms that Can Be Recognized Clinically'. This book is in answer to that wish."[9] Taussig lived from the birth of congenital heart surgery (1938) to its near apogee at the time of her death in 1986. Taussig's 100 publications from 1925 to 1988 are listed in reference 6, a lifetime of devotion to the child with congenital heart disease, amongst other important contributions (i.e. the thalidomide story).[6] With the dawn of heart surgery for patients with congenital heart disease, it soon became apparent that these heroic interventions would require a unique and indeed wonderful partnership, the symbiotic relationship between pediatric cardiologist and cardiac surgeon. This partnership is best illustrated by Taussig who convinced Alfred Blalock to construct an arterial duct to treat certain patients with reduced pulmonary blood flow, the shunt now appropriately known around the world as the Blalock–Taussig shunt first performed in Baltimore.[11] With the appointment of an Hungarian immigrant, Alexander Sandor Nadas, as the first pediatric cardiologist at the Children's Hospital in Boston, Nadas and Gross forged a dynamic union that set a benchmark for such programs, a program that soon developed into one of excellence then, and later with Aldo Castaneda who succeeded Gross in 1972, and still.[12,13] Nadas authored one

of the earliest textbooks devoted solely to the clinical recognition and treatment of congenital heart disease, his first edition appearing in 1957, the second in 1963 and the third edition with Donald Fyler in 1972.[12] John Dow Keith (1909–89), pediatric cardiologist, and William Mustard (1914–87), surgeon, developed in the late 1940s and 1950s at the Toronto Hospital for Sick Children a seminal program for the care of children with congenital heart disease. John Keith then recruited Richard D. Rowe (1923–88) and Peter Vlad, and George Trusler joined Bill Mustard (1914–87).[14] The collaboration of Keith, Rowe and Vlad matured into their now famous textbook which eventually went into a third edition.[14A] Such effective partnerships were established in many parts of the world, and these collaborative efforts, old and new, served then and now their patients well. Indeed, reflecting on Taussig's statement in the preface to her 1947 book: "the majority of cyanotic infants do not survive for more than a year and a half."[9] She survived long enough to witness the truly dramatic change in the outcomes of most cyanotic infants.

As stated earlier, the congenitally malformed heart has fascinated physicians for hundreds of years. The names of Farre, Baille, Rokitansky, Holmes and so many others are forever linked with specific cardiac malformations. In this regard, William J. Rashkind (1922–86) who has contributed so importantly to our specialty has edited a book devoted to the benchmark papers in the history of congenital heart disease[15] and has published elsewhere some historical aspects of congenital heart disease.[15A] In Rashkind's 1972 publication, he writes of the earliest observations of cyanosis and the history of tetralogy of Fallot.[15A] Maude Abbott was one of the first to systematically study and compile cases of congenital heart disease, and then many others took up the quest. Paul Dudley White wrote in the preface to her *Atlas*: "Senac, Peacock, Rokitansky and Keith, one after the other, richly advanced our knowledge of congenital heart disease, but it was left to Maude Abbott, fired by the spark from Osler, to make the subject one of general and widespread interest that we no longer regard it with either disdain or awe as a mystery for the autopsy table alone to discover and to solve."[3] Abbott herself wrote in the Introduction to her own *Atlas*: "This volume presents, in a somewhat unusual form, a pictorial retrospect of the author's personal experience in what may be considered a specialized field of clinicopathological research. A first-hand knowledge of the exact morphology of a large range of cardiac anomalies obtained in the first place through an intensive study of the rich material accumulated under the author's care as Curator of the Medical Museum of McGill University, has been continuously applied and amplified through more than three decades of activity, by observations of congenital heart disease in the wards and autopsy rooms of many great hospitals both at home and abroad."[3] Her many and varied publications have been compiled by Waugh[16] (see also Chapter 16 of this text for many references to the life of Maude Abbott). During the last year of her life, Maude Abbott applied for Guggenheim Foundation fellowship for aid in the preparation for a textbook on congenital heart disease. She did not receive this grant, but she was awarded $2500 from the Carnegie Corporation. Sadly, Abbott died on September 2, 1940 from the results of a cerebral hemorrhage she sustained in July 1940, before undertaking this work.[3A]

The descriptive morphology of congenitally malformed hearts was primarily a 20th century interest and so much was accomplished primarily but not exclusively in the last half of the 20th century. The contributions of Drs Maurice Lev of the Hektoen Institute, Jesse Edwards of the Mayo Clinic and the Charles T. Miller Hospital, Maria Victoria de la Cruz, Richard and Stella Van Praagh of Toronto, Chicago and then Boston, Robert H. Anderson of London, Anton Becker of Amsterdam amongst others must be singled out as critically important to the foundation of congenital heart disease: the study and classification of congenitally malformed hearts. With their clinical colleagues they compiled clinico-pathologic correlation, and published extensively on specimens that comprised their cardiac registries. Collectively they described and characterized the entire spectrum of congenitally malformed hearts defining those unifying morphological features. Truex, Lev, Anderson, and Becker, and their respective colleagues also provided detailed information about the specialized conduction tissue in the normal and malformed heart, information critically important if surgical heart block was to be prevented.[17–24] Of the many conundrums facing those caring for patients with congenital heat disease was the issue of classification and thus communication. In an attempt to provide clarity from chaos, Richard van Praagh and his colleagues in a series of important papers initially characterizing hearts with either dextrocardia or single ventricle beginning in the early 1960s from Toronto and then from Boston over the next four decades provided the framework for the segmental analysis of congenital heart disease.[25–28] Three segments were identified: the atria; the ventricular loop (d- or l-), and the great arteries. Using deductive morphology, the various segments could be connected. Eschewing a "deductive" approach to segmental analysis, Dr Robert Anderson and his colleagues from the United Kingdom, also using a segmental approach, advocated beginning in the early 1970s a sequential "connections" approach.[29–31] This approach did not focus on infundibular anatomy as had the Van Praaghs' and their devotees. Neither did Anderson and his colleagues utilize the concept of ventricular loops, nor did their approach incorporate the bracketed short-cut alphabet nomenclature. These two schools of cardiac nomenclature were initially quite polarized, and while both share many similarities, their differences have not been completely resolved. Thus these two schools of cardiac nomenclature are now widely employed by the loyal "disciples" of each of them. As yet the "Esperanta" of congenital heart disease has not been fully unified, but many employ an amalgam of the two schools.[32] An extensive bibliography and discussion of cardiac nomenclature can be found in reference 32.

Throughout this work we will attempt to document the available information on the natural history of some forms of congenital heart disease as well as the modified history of most forms of congenital heart malformations. We will discuss those risk factors that have influenced and continue to influence the outcomes of the various malformations, placing the many medical and interventional experiences of each condition into a historical sequence and perspective. As we write in many of the chapters the ability to define the natural history of any particular condition rests in part on the methodology of surveillance. In this regard there has been a remarkable evolution in those tools used to evaluate patients with congenital heart disease. From clinical examination with standard chest radiography and electrocardiography in the 1930s, this was then complemented by chest fluoroscopic examination. Standard 12-lead electrocardiography was then complemented by vectorcardiography, the latter tool being considerably utilized in the 1960s and early 1970s. But just as silent films were replaced by the "talkies," vector-

cardiography was soon relegated, with rare exception, to the historical archives. Cardiac catheterization with angiocardiography evolved from its infancy in the late 1940s, reaching its apogee in the late 1970s with the benchmark publications on the techniques, advantages, and applications of axial angiography.[33–37] Bargeron became the "Fellini" of cardiac angiography and his images served as the "gold standard."[38] We, too, published large volumes dedicated to the angiographic definition of the entire range of congenital heart disease.[39,40] The early experience of Kjellberg and his colleagues with cardiac angiography now dating back nearly 50 years must also be acknowledged and recognized for their excellence.[41] But with the introduction of cross-sectional echocardiography in the late 1970s, most units experienced over the next decade a dramatic drop in the numbers of so-called diagnostic cardiac catheterizations, with surgery for many of the more simple and even complex cardiac conditions based on echocardiography. Indeed, the introduction in the 1980s of cross-sectional echocardiography and then color flow mapping has provided a unique tool to study noninvasively the change in form and function of congenitally malformed hearts, the response and sequelae of intervention, from the fetus to the adult. Like a sine-wave, pediatric cardiology experienced for many of its tools, great initial interest and enthusiasm, only to have these wax then later wane and become replaced by more sophisticated innovations. Thus interest in all aspects of cardiac angiocardiography initially surged, then waned, with imaging modalities and catheter-based physiological monitoring replaced by cross-sectional echocardiography, color flow Doppler, MR-imaging, etc. The interventional role for the pediatric cardiologist was firmly established by Rashkind and Miller with their balloon atrial septostomy for patients with complete transposition of the great arteries.[42] There was a pause in these innovative catheter-based interventional procedures until 1982 when Kan and her associates published their early experience with pulmonary valve balloon angioplasty,[43] remembering the even earlier experience of Rubio-Alvarez and coworkers with static balloon dilatation of the pulmonary valve.[44] Subsequent to Kan *et al*.'s publication the next two decades witnessed an explosion in these catheter-based therapeutics, with valvuloplasty techniques extended to the four cardiac valves, devices positioned to close the arterial duct, the secundum atrial septal defect, and muscular and then the perimembranous ventricular septal defects. The entire cascade of anomalies, congenital and acquired, that could be treated by catheter-based modalities was so treated. The balloon, blades, various devices to plug holes and vascular channels, endovascular stents all became the therapeutic tools of the interventional pediatric cardiologist. The impact of the interventional pediatric cardiologist on congenital heart surgery has been dramatic. For the heart surgeon there are fewer and fewer so-called easier cases, an issue that impacts on outcome analysis and training programs.

But evolution in pediatric cardiology did not occur in isolation. The rich tapestry and mosaic of pediatric cardiology and cardiovascular surgery are closely interwoven. With Gross's closure of the arterial duct in August of 1938,[1] the accomplishment of Blalock–Taussig in 1944,[11] the repair of aortic coarctation in 1945 reported by Crafoord and Nylin,[45] the early experiences with closed surgical procedures to treat certain congenital heart malformations were rapidly accumulating.[46] Then Brock in 1948 popularized the closed valvotomy for patients with pulmonary stenosis, extending this technique to some patients with tetralogy of Fallot.[47] C. Rollins Hanlon working with Vivien Thomas in the laboratory of Alfred Blalock in 1950 developed a surgical clamp that permitted a closed atrial septostomy, thus facilitating mixing at atrial level for the patient with complete transposition of the great arteries.[48,49] This began the formal era of effective palliation of the baby with complete transposition of the great arteries. In 1952 Muller and Dammann published their technique of surgical pulmonary artery banding to treat patients with excessive pulmonary blood flow and pulmonary artery hypertension, hoping to prevent pulmonary vascular disease.[50] In this regard, more than a decade ago, Nolan reviewed the origins of pulmonary artery banding, a procedure with fewer and fewer applications.[50A]

Cohn reminds us that on May 6, 2003, we celebrate the 50th anniversary of the first successful open-heart operation performed with the use of the heart-lung machine, a development pioneered by John H. Gibbon Jr of the Jefferson University Medical Center.[51] A brief capsule of Gibbon's accomplishment is provided in this commentary.[51] Also in the early 1950s, techniques of open heart surgery initially using the technique of cross circulation were pioneered by C. Walton Lillehei and his colleagues to close atrial and ventricular septal defects, to repair patients with tetralogy of Fallot, and atrioventricular septal defect, and so on.[51A] This signal accomplishment required the development, indeed the platform of cardiopulmonary support, etc.[51B] We will discuss in successive chapters the evolution in surgical techniques extended to patients with complete transposition of the great arteries. These procedures vastly changed and remarkably improved the outcomes of these patients (see Chapters 25A, 25B, and 25C). The saga of the patient with complete transposition of the great arteries is indeed a wonderful drama, and for the most part, a drama with a happy ending. This drama can be summarized in six acts, a drama extending >three decades to completely unfold:

1 1950: the Blalock–Hanlon atrial septectomy[49]

2 1959: the first atrial repair, the Senning procedure,[52] Ake Senning, MD (1915–2000)

3 1963: the second atrial repair, the Mustard procedure,[53] William Thornton Mustard, MD (1914–87)

4 1966: balloon atrial septostomy of Rashkind and Miller[42]

5 1975: the successful arterial switch operation of Jatene of Sao Paulo, Brazil[54]

6 1983: neonatal arterial repair of transposition pioneered by Aldo Castaneda and his colleagues at Boston Children's Hospital.[55]

But there are so many rich dramas that will be fully explored including the evolution of staged repair for many forms of congenital heart disease to primary repair in the neonate and young infant, an approach advocated by Barratt-Boyes of Auckland and Castaneda of Boston, and others.[56–58] The evolution of the cavopulmonary shunt (see also Chapter 35) performed in the 1950s to palliate certain forms of complex heart malformations with reduced pulmonary blood flow to the Fontan procedure in 1971 (see also Chapter 36) has changed the outcomes of patients with congenital heart malformations not amenable to a biventricular repair.[59–65] When Francis Fontan of Bordeaux successfully performed atrial separation and an atriopulmonary connection for the patient with tricuspid atresia, his wisdom and courage paved the way to a treatment algorithm for a wide panorama of congenitally malformed hearts.[66,67] These now include all kinds of single ventricle malformation, the hypoplastic left heart syndrome, and many others. Who would have believed 25 years ago that babies with the hypoplastic left heart

syndrome, the malformation complex once designated "the worst heart disease"[68] would now routinely undergo staged repair, beginning with the palliation conceived by William Norwood, and bearing his name,[69] concluding (hopefully) in a Fontan-type operation[70] (see also Chapter 31)? The Fontan procedure has evolved considerably from the operation conceived and performed by Fontan to variations on the theme, important themes and concepts implemented and published by De Leval and others.[71] Who could have conceived that babies with the hypoplastic left heart syndrome amongst many other forms of complex heart malformations could be treated by cardiac replacement even as newborns, indeed not infrequently listed for organ replacement as a fetus?[72] Shumacker has provided an interesting account of the evolution of cardiac surgery.[72A]

Several years ago, we listed and reviewed some of the more important clinical contributions to pediatric cardiology and cardiovascular surgery from 1950 to 2000.[73] These included:

- perinatal cardiac physiology
- cardiac anatomy and the nosology of congenital heart disease
- cardiac catheterization and the calculation of pulmonary vascular resistance
- diagnosis of congenital heart disease
- open heart surgery
- the prostaglandin story
- right heart bypass and the Fontan experience
- catheter-based therapy in congenital heart disease
- preventive pediatric cardiology
- outcome analysis in congenital heart disease.

There is no doubt that some would dispute this list, deleting some items, adding and modifying others. Yet many items on this list are the threads, indeed the framework that contributes to the tapestry of pediatric cardiovascular medicine and surgery, providing the infrastructure for so many successive and exponential extraordinary accomplishments. Much of what is written in this work is predicated on these many observations and accomplishments which continue to be modified and refined and reflected upon.

An author of mystery novels once said that before you begin writing such a novel you must know how the novel begins and in the final chapter how it concludes. He went on to say that you might take any number of diversions, but you must know the beginning and the end. There is certainly a reasonable consensus when the modern era of treatment for congenital heart disease began with the surgical ligation of the arterial duct in 1938 by Gross.[1] The end is far from clear however. In the ongoing evolution of one's understanding of congenital heart disease, certainly one of the fundamental chapters or themes is the understanding of the fetal circulation and the transitional circulation.[74–87] Abraham Rudolph amongst others contributed so importantly to one's understanding of the fetal circulation and the complex journey to the transitional circulation. As well he was a tremendous mentor and teacher of our discipline. Appreciation of the role of the arterial duct in the fetal circulation and its role in the transitional circulation is fundamental to our understanding of fetal cardiac function and physiology.[74–86] The observation of transient myocardial ischemia of the newborn as a manifestation of a stressed and disturbed transitional circulation had ramifications for the newborn with and without structural heart disease.[88–91] In this regard, the late Richard Desmond Rowe (1923–88), my dear friend, was one of the earliest to focus attention on the newborn with congenital heart disease. Dick was a wonderful teacher, dedicated scholar and mentor for many of us. He was a role model for all with whom he came into contact.[92] The prostaglandin story is certainly more than a diversion and its introduction into the treatment algorithm of patients, usually neonates or very young infants, with duct-dependent pulmonary or systemic pulmonary blood flow radically altered the outlook for these babies.[93–97] This medical therapy for babies with duct-dependent congenital heart disease stands out as one of the benchmarks of the latter half of the 20th century.[93–97] Other diversions resulted from unraveling the etiology of complications of innovative cardiac surgery, and one such is example is the recognition of pulmonary arteriovenous malformations developing after a cavopulmonary shunt. This potentially egregious complication was fully documented just over a quarter of a century ago by McFaul and colleagues.[98] The development of pulmonary arteriovenous malformations following a classic cavopulmonary or Glenn anastomosis was attributed for many years to lack of pulsatile pulmonary blood flow in the dependent segment of the lung isolated from forward ventricular flow.[99] However, in 1995 Srivastava and his colleagues at the Boston Children's Hospital provided compelling clinical evidence that exclusion of hepatic venous blood flow from the lungs was likely causal to the development of pulmonary arteriovenous malformations.[100] Subsequent to their report many other clinical observations support the role of hepatic venous exclusion in the development of pulmonary arteriovenous malformations (see also Chapters 35 and 37). These observations were derived not only from patients with congenital heart disease but from patients with hepatic cirrhosis and cyanosis who improved after liver replacement.[101–103] The paradigm from bed-to-bench is well illustrated by those ongoing investigations as to the nature of this elusive hepatic factor and those factors regulating angiogenesis[104–113] (see also Chapters 35 and 37). There are indeed any number of examples of congenital heart disease that wonderfully illustrate our evolution in knowledge and therapy. Another such example involves one of the relatively more common malformations; namely the persistent arterial duct. The following and overlapping chronology illustrates this point.

1 Anatomic recognition of the arterial duct as a component of the fetal circulation[77,114,115]

2 Recognition of the clinical impact of the large arterial duct in postnatal life[3]

3 Successful surgical ligation of the arterial duct[1]

4 Recognition by Taussig of the role of the arterial duct in patients with duct-dependent pulmonary blood flow[11]

5 Surgical creation of an "artificial" arterial duct: the Blalock–Taussig shunt[11]

6 Definition of the fetal function of the arterial duct and those physiological factors responsible for functional and anatomic closure of the duct postnatally (discussed in reference 77)

7 Pharmacological manipulation of the arterial duct to promote closure: the indomethacin story[114,116]

8 Pharmacological manipulation of the arterial duct to maintain patency: prostaglandin therapy[93–97]

9 Catheter-based closure of the arterial duct beginning with the experience of Portsmann[117–119]

10 Providing a scaffold, the endovascular stent, to maintain ductal patency[120]

11 Definition of the histology of the arterial duct and those histological features (i.e. intimal cushions) responsible for closure of the arterial duct[77,121,122,123]

12 Bioenginering the mechanisms responsible for intimal

cushion formation. Intimal cushion formation requires fibronectin-dependent smooth muscle migration. Mason and her colleagues from the laboratory of Dr Marlene Rabinovitch in Toronto have shown that in the fetal lamb, by sequestering the fibronectin mRNA binding protein, fibronectin translation was inhibited and intimal cushion formation prevented, thus promoting persistent patency of the arterial duct.[124]

Much of this present work is devoted to outcomes and those myriad of factors influencing outcomes. The first and second Joint Studies of the natural history of congenital heart defects were formidable studies that addressed the outcomes of patients with aortic stenosis, pulmonary stenosis and ventricular septal defect.[125,126] These were and remain seminal studies in the natural and modified history of congenital heart disease, and these were complemented by the New England Regional Infant Cardiac Program[127] and the Baltimore-Washington Infant Study.[128,129] Major population studies addressing incidence of congenital heart disease been conducted for many decades, including publications from Mitchell, Samanek and dozens of others.[130–132] Hoffman[133,134] and more recently Hoffman and Kaplan[135] have provided comprehensive reviews of those many studies contributing to the large database on the incidence of congenital heart disease. Because their studies review those reports extending back a number of decades, the influence of non-invasive imaging on diagnosis and thus incidence of the milder lesions can be gleaned from their extensive compilations.

How we look at data, manipulate and analyze it also importantly contributes to one's appreciation and enhancements of outcomes. In this regard, our specialties, indeed our patients are forever indebted to John W. Kirklin and Eugene Blackstone who critically analyzed their institutional results, provided important insights into data analysis and presentation and then organized and implemented the Congenital Heart Surgeons Study.[136,137] Studies from this group provide important insights into the outcomes of many congenital heart malformations including coarctation of the aorta, tetralogy of Fallot, critical pulmonary stenosis, pulmonary atresia and intact ventricular septum, interruption of the aortic arch, atrial and arterial repair of transposition of the great arteries, and the hypoplastic left heart syndrome (cited throughout reference 136). Many are now analyzing their data according to methodologies prescribed by the group at the University of Alabama at Birmingham. Kirklin, Blackstone, and their many colleagues were among the first to evaluate outcomes by institution and patient volume, this latter a particularly thorny issue (again cited throughout reference 136). Since then many others, with Jenkins and her colleagues also amongst the first, took a critical look at congenital heart surgery outcomes stratified by caseload and complexity.[138–145] Such issues are indeed complex, and an institutional volume is but one issue that may impact on outcomes.[144,145] Yet, at least one country, Sweden, has centralized pediatric heart surgery, largely on this type of outcome analysis.[146] Similarly the province of Ontario, Canada, its country's largest province in terms of population with 10 084 885 (based on the 1991 census) inhabitants, began in 2001 to centralize its children's heart surgery from three centers to one institution, the Toronto Hospital for Sick Children.[146A] Furthermore, two pediatric cardiac units in disparate parts of the world have undergone extensive scrutiny of their surgical results because of undue mortality rates. These include the Children's Heart Center in Winnipeg, Manitoba, Canada and Bristol, United Kingdom. The Winnipeg group underwent a review of their surgical results by a Royal Commission and their surgical program has been permanently closed down. Chang and Klitzner have also provided some interesting thoughts about the effect of regionalization of congenital cardiac care.[141] Using abstracted statewide hospital discharge data from California from 1995 to 1997, case volume and in-hospital mortality for pediatric cardiac surgeries at each hospital were calculated. In this theoretical model reducing the number of low volume institutions and reduced surgical mortality.[141] These issues are clearly complex as summarized by Spiegelhalter, although his data also support the volume–outcome relationship in the United Kingdom.[143] Powell states quite forcefully in his letter to the Chang and Klitzner paper that "Volume alone is not the sine qua non of oucome."[141B] De Leval and his colleagues in a very thoughtful and provocative way have addressed those human factors that impact on cardiac surgery, factors that can be modified to enhance outcomes.[147,148] Boneva and her colleagues have provided compelling data showing that mortality in the years between 1979 and 1997 associated with congenital heart defects in the United States is declining, with age at death increasing.[149] This latter finding indicates that affected persons are now living to adolescence and adulthood. The scope of the adult with congenital heart disease has been discussed in detail by Webb and Connelly, and clearly this is an ever increasing population requiring ever expanding resources.[150] In this regard, Joseph Perloff and Jane Somerville began advocating for the adult with congenital heart disease, long before it became a more fashionable interest. Indeed, Jane Somerville established her first unit at the National Heart Hospital in London, UK, in 1975 (personal communication, October 2002) and Joseph Perloff established his first unit at UCLA in 1977 (personal communication, October 2002). With the increasing numbers of patients with repaired and palliated congenital heart disease surviving to adulthood, special units, GUCH (grown-up congenital heart) units as designated by Somerville will continue to contribute to improved outcomes. The study of Boneva and coworkers also found that mortality was 19% higher among blacks than whites and over the duration of the years examined this gap did not seem to close.[149] Finding the cause of this racial disparity may also improve outcomes. Another interesting observation on outcomes in children undergoing heart surgery has been provided by Chang and colleagues.[151] They found that female sex was associated with a 51% higher odds at death than male sex, but the reason for this disparity was unclear. In this study based on statewide hospital discharge data from California between 1995 and 1997, they also found that low volume hospitals had higher mortality rates than the high volume institutions (OR 1,67, $P < 0.01$). These observations again confirmed the findings of Jenkins *et al.*, Stark *et al.*, Hannan *et al.*, and Lundstrom *et al.*, amongst others.[138–143] In my Mannheimer lecture of 1997 I urged that surgical results should address the fate of the entire cohort of patients, the denominator, not just those undergoing the surgery, the numerator,[152] strongly supporting the commentary of Spodick who more than a quarter of a century ago addressed the issue of numerators without denominators.[152A] This critical look at cohorts might identify those factors excluding patients from the orthoterminal procedure, and by addressing those factors improve outcomes. Others have also urged this approach.[153] Also in my Mannheimer lecture I wondered whether certification in the subspecialty of pediatric cardiology is important, or potentially so, in improving outcomes of patients with congeni-

tal heart disease.[152] The American Sub-board of Pediatric Cardiology was established in 1960–61 and 2 years of formal training followed by an examination were required for certification in this specialty.[154] The mandatory length of training for American certification was extended from 2 to 3 years in 1988, reflecting the ever-increasing sophistication and technology of pediatric cardiology. The Royal College of Physicians and Surgeons of Canada has certified the specialty of pediatric cardiology for >30 years and in 1996 extended the mandatory length of training from 2 to 3 years. Whether or not certification itself enhances outcomes is of course speculative, but a formal educational program is probably important. The care of the patient with congenital heart disease is now a global specialty with excellent units established in many parts of the world, and most of those countries with these units have already or are now in the process of establishing specific training criteria.

If bioengineering the closure of the arterial duct brings us into yet another era in congenital heart disease,[124] so too will the identification of the genetic "mistakes" responsible for congenital heart malformations. Perhaps these fundamental approaches will bring us close to the last chapter, a chapter yet to be written. We will see. The frantic rhythm of surgical accomplishments in congenital heart disease is somewhat quieter at this time. For now, the following is a brief and at times overlapping chronology of the modern era of congenital heart disease as reflected by various clinical observations and medical and surgical accomplishments (obviously the author's personal view):

- 1930: Establishment of a pediatric cardiology clinic at Johns Hopkins Hospital. Dr Helen Taussig (considered the "mother" of pediatric cardiology) was appointed by Dr Edward Albert Park to head the clinic. Dr Taussig directed this department until 1963
- 1936: Abbott's *Atlas of Congenital Heart Disease*
- 1938*: Gross and Hubbard – ligation of the arterial duct (* published 1939; performed August 26, 1938) (see Chapter 9)
- 1944*: The Blalock–Taussig shunt (published 1945; first performed on November 29, 1944) (see Chapter 16)
- 1945: Crafoord and Nylin – repair of thoracic coarctation (see Chapter 22)
- 1946: The Potts shunt (see Chapter 16)
- 1948: Brock's closed pulmonary valvotomy (see Chapters 13A and 16)
- 1949: Establishment of the cardiology service at Boston Children's Hospital. Dr Alexander S. Nadas considered the "father" of pediatric cardiology was appointed by Dr Charles A. Janeway to head this service. Dr Nadas headed this department until 1982
- 1950: Blalock and Hanlon's closed atrial septectomy for transposition (see Chapter 25A)
- 1950–1980s: Descriptive morphology of most kinds of congenital heart disease
- 1950s–1980s: Understanding of the fetal and transitional circulation
- Late 1940s–1980s: Cardiac catheterization and angiocardiography of congenital heart disease
- Early to mid 1950s: Partial venous switch operations for transposition (see Chapter 25A)
- 1952: Muller and Dammann's pulmonary artery banding (see Chapter 3)
- 1953: Gibbon's heart-lung machine for cardiopulmonary bypass
- 1954: Open heart surgery to repair intracardiac defects initially using cross circulation (the first such operation by Lillehei and colleagues, March 26, 1954)
- 1955 (May 13): the application of the bubble oxygenator by DeWall and colleagues[51B]
- 1958: The classic Glenn cavopulmonary shunt (see Chapter 35)
- 1959: The Senning procedure for transposition of the great arteries (see Chapter 25A)
- 1960: Formation of the Sub-Board of Pediatric Cardiology, American Board of Pediatrics. Certification of a 2-year course of specialized training in pediatric cardiology. Required training extended to 3 years in 1988
- 1960–80: Nomenclature of congenital heart disease – the development of a segmental, then sequential and segmental approach to congenital heart disease
- 1962: the Waterston shunt (see Chapter 16)
- 1963: The Mustard procedure for transposition of the great arteries (see Chapter 25A)
- 1966: Rashkind and Miller's balloon atrial septostomy for transposition (see Chapter 25A)
- 1966: The use of a pulmonary homograft to repair pulmonary atresia and ventricular septal defect (Ross and Somerville, 1966)[154A] (see Chapter 18)
- 1968: Rowe and Mehrizi's *The Neonate with Congenital Heart Disease*[155]
- 1969: The Rastelli Procedure for transposition, ventricular septal defect and left ventricular outflow tract obstruction[156,157] (see Chapter 25C)
- 1971: Congenital heart surgery performed using profound hypothermia and limited cardiopulmonary bypass[158]
- 1971: The Fontan Procedure (see Chapter 36)
- 1972: The segmental approach to congenital heart disease[25–28]
- 1972: Septation of a common ventricle[159] (see Chapter 32)
- 1973: Hoffman and Rowe's description of transient myocardial ischemia of the newborn
- 1975: Jatene's successful arterial switch for transposition and ventricular septal defect (see Chapter 25A)
- 1976: Prostaglandin introduced to maintain ductal patency (see Chapter 9)
- 1976: Sequential aspect added to segmental approach for cardiac nosology[29–31]
- 1977: Publication of the *First Joint Study on the Natural History of Congenital Heart Disease* (see Chapters 3, 13A, and 14A)
- 1977: Publications on the methodology and application of axial angiocardiography
- 1975 and 1977: The birth of units specializing in patients with grown-up congenital heart disease.
- 1978: The era of palliation of the hypoplastic left heart syndrome begins: the Norwood experience (see Chapter 31)
- 1980: Publication of the *New England Regional Infant Cardiac Program*
- 1980: Application of cross-sectional echocardiography and its successive refinements
- 1982 to the present: Balloon pulmonary valvuloplasty and the subsequent explosion of catheter-based therapy
- 1983: Neonatal arterial repair of transposition of the great arteries and intact ventricular septum (see Chapter 25A)
- 1983: first report of successful Fontan operation for the hypoplastic left heart syndrome (see Chapters 31 and 36)
- 1980s: Neonatal cardiac transplantation (see Chapter 47)

- 1988: Total cavopulmonary bypass
- 1993: Publication of the *Second Joint Study on the Natural History of Congenital Heart Disease* (see Chapters 3, 13A, and 14A)
- 1995: Outcome analysis based on volume caseload and complexity. Regionalization of congenital cardiac care
- 2002: Percutaneous insertion of a pulmonary valve[160]

Though clearly not germane to congenital heart disease, Gutgesell and Lindsey mention in their review of major advances in pediatric cardiology in the 20th century, that unraveling the cause of rheumatic fever warrants mention.[161] Gersony in a similar discussion mentions the origins of atherosclerosis and the development of preventative cardiology and cardiac transplantation.[162]

As a final thought, one would hope that outcomes would improve for all patients with congenital heart disease, independent of race and ethnic differences, and type of medical insurance.[163,164]

All references can be found at the end of the book. See pp. 601–5 for Chapter 1.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

2

Brian W. McCrindle

The Prevalence of Congenital Cardiac Lesions

Prevalence is often the starting point in the discussion of congenital cardiac lesions. It underlies the estimation of disease burden, and helps us to begin to answer the question, "How big or important is this problem?" It also opens a field of epidemiologic study aimed at defining causal or etiologic associations with various genetic and environmental risk factors.

The definition of prevalence

Ratios, proportions, rates

There are many aspects to looking at the question, "How many people have a congenital cardiac lesion?" The first issue is that of definition, in that in much of the published literature there is considerable misuse and confusion related to the terms prevalence and incidence. This has prompted several commentaries.[1–4] One must first consider if the estimate provided is a ratio, proportion or rate.[1] Ratios are the result of dividing one quantity by another, more specifically where the numerator and the denominator are separate and mutually exclusive subgroups from usually the same population. A typical example would be the ratio of persons who died in a given time period vs. those that survived. This is different from a proportion (or a fraction), whereby the numerator is a subgroup of the denominator, such as the proportion of persons who died during a given time period vs. the number of person-years at risk in the population. Rates are indicators of the rapidity of change in one variable as related to another variable, most often time. Rates can be instantaneous or averaged over a defined period of time. Mortality can be expressed as a rate, and underlying the calculation of survival curves are instantaneous rates of death that often vary over time and act on a diminishing population.

Definition of prevalence

Prevalence is defined as the proportion of people with any or a specific congenital cardiac lesion from a defined population at risk at a given point in time.[4] When given a prevalence estimate, one must know the characteristics of both the numerator and the denominator and how they relate to one another. Time is only indirectly included in the calculation. The most commonly used prevalence estimate is determined from a denominator consisting of the number of live births over a defined period of time from which is derived a numerator consisting of the number of those newborns who subsequently have a confirmed and reported diagnosis of a congenital cardiac lesion. The prevalence of a lesion at live birth is affected by the incidence of the lesion from cardiogenesis and the survival characteristics of the fetus with the lesion. Therefore, lesions associated with an important risk of fetal demise may be under-represented in birth prevalence estimates.

Definition of incidence

Incidence is strictly defined as the number of new cases of a given condition developing over a defined period of time for a population at risk.[4] It can be either a rate or a proportion, depending on the denominator. An incidence rate is the number of new cases developing in a given time period divided by the number of person-years at risk in that time period. An incidence proportion has the same numerator as the rate, but the denominator consists of the number of persons at risk at the beginning of the time period. Given this definition, it is difficult to determine the true incidence of congenital cardiac lesions. One would have to be able to begin with all embryos at the time of onset of cardiac development and follow them *in utero* to detect all abnormalities, regardless of viability. For example, one would not discuss the "annual attack rate for ventricular septal defects." Many authors refer to the proportion of children born with a particular congenital cardiac lesion as the incidence or the "birth defect rate," when in fact it refers to the prevalence proportion.[4] While determining the incidence of congenital cardiac lesions from the time of cardiogenesis is not feasible, ideally this is what is needed for accurate studies aimed at determining factors associated with etiology.

The relevance of prevalence estimates

There are many reasons why knowing the prevalence of congenital cardiac lesions is important. The most direct use of prevalence estimates occurs when counseling families as to their risk or likelihood of having a child with a congenital heart lesion. Any information we might have regarding factors that increase or decrease that likelihood would greatly help us to refine that estimate when counseling families before pregnancy or delivery.

Disease burden

Perhaps the greatest use of prevalence estimates is as an indicator of disease burden relevant to congenital cardiac lesions in the population. Congenital cardiac lesions continue to be the

greatest contributor to infant mortality related to congenital defects. In an analysis of death certificate data from 1979 to 1988 in the United States, congenital cardiac lesions accounted for 71.2 deaths in the first year of life per 100 000 live births.[5] In a similar study extending the observation up to 1997, mortality related to congenital cardiac lesions was shown to have decreased for all ages at a rate of 2.7% per year, with a trend towards increasing age at death.[6] Death rates were noted to be higher in black people vs. white people, with no significant change in this trend over time. These trends in mortality have a direct bearing on the point prevalence, which is the estimate of the proportion of the population who are current survivors with congenital cardiac lesions at a set point in time. Point prevalence reflects the interaction of the birth prevalence over consecutive birth cohorts together with cohort-specific, time-related mortality as influenced by the lesion-specific natural history and management. Point prevalence is the best indicator of disease burden in the population, and when combined with estimates of morbidity reflects the resource and economic costs or burden. When health-related quality of life and productive years of life lost are also considered, this indicates the burden to society.

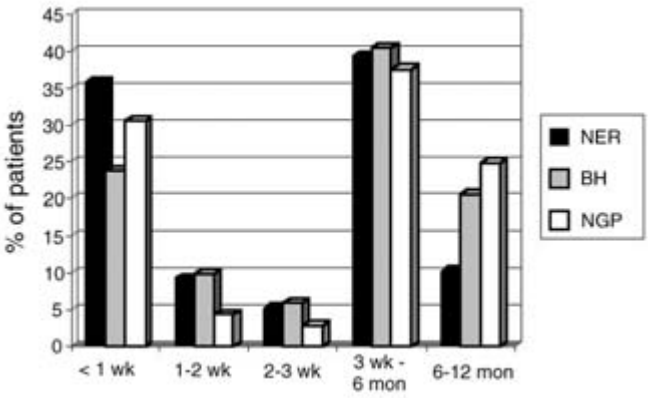


Fig. 2-1 Distribution of age at first hospitalization for infants with major congenital cardiac lesions, as noted in three studies: BH, Brompton Hospital (1973–82); NER, New England Regional Infant Cardiac Program (1980); NGP, Northern Great Plains Regional Cardiac Program (1982–87); mo, months; wk, weeks. (Reprinted from Moller *et al*.,[9] *Pediatrics*, Col. 65, Page(s) S377–S461, Table 15, Copyright 1980.)

Resource requirements

Knowledge of the types of lesions presenting and prevalent at different ages in the population is critical information for planning and allocating health care resources. Minor or mild lesions may undergo spontaneous regression or remain stable, below the threshold for therapeutic intervention. In contrast, several lesions once considered lethal, such as hypoplastic left heart syndrome, are now associated with excellent short- and intermediate-term survival, albeit with intensive use of medical resources. While prevalence estimates provide the basis for anticipating resource requirements, additional information regarding cohort-specific, time-related survival and morbidity is needed.

Increasing numbers of adult survivors are the result of improved survival related to innovations in medical and surgical management. There have been no studies, however, that have focused on defining the point prevalence of congenital cardiac lesions in adults. This has become a particular problem when attempting to define and anticipate the requirements of the health care system to care for this growing population.[7,8] Attempts to provide estimates and projections of point prevalence have relied on calculations incorporating the prevalence and time-related survival associated with specific lesions across various birth cohorts.

Diagnostic likelihood

Prevalence studies that provide breakdowns of the specific types of lesions by their age at presentation provide the clinician with an initial differential diagnosis, which can guide diagnostic and stabilization efforts. Commoner lesions can then be considered before more rare ones. Moller *et al.* compared the distribution of lesions in three consecutive studies of hospitalized infants, including the New England Regional Infant Cardiac Program (1980), the Brompton Hospital (1973–82) and the Northern Great Plains Regional Cardiac Program (1982–87).[9] The distributions of lesions and age at presentation were similar but not identical between studies (Fig. 2-1). However, the distribution of major lesions was significantly related to the age at presentation. In the first week of life, transposition of the great arteries was the most common lesion, followed by hypoplastic left ventricle, tetralogy of Fallot and coarctation of the aorta. In the second week, coarctation of the aorta was the most common diagnosis. This is in contrast to patients hospitalized at age 6–12 months, with ventricular septal defect as the most common diagnosis. Ventricular septal defect was the most common defect overall in the first year of life in all three studies. This variation in the distribution of lesions by age at presentation has important implications for case ascertainment in determining prevalence estimates. If one relies on routine medical care to detect cases, then clearly the prevalence and distribution of lesions will depend on the length of ascertainment after birth.

Surveillance and trends over time

There has always been a great deal of interest as to whether the overall and lesion-specific prevalence has been changing over time, and what factors might have contributed to any change. The necessity for ongoing surveillance has become particularly acute following the epidemic of birth defects associated with the use of thalidomide during pregnancy. When an apparent trend is noted, it is often difficult to determine if the trend is related to actual changes or differences in the incidence or development of congenital cardiac lesions, survival to birth and the impact of fetal detection and elective terminations, access to medical care and the precision of diagnostic modalities, or to changes in definitions and classification schemes.[10] Surveillance of prevalence is also important when making comparisons based on geography or ethnicity.

Etiologic associations

An increased prevalence in a subgroup of the population with a particular characteristic, whether it is environmental or genetic, provides the opportunity to explore hypotheses related to etiology. The classic prevalence study does not often provide this opportunity, as often the frequency of both the lesion and the risk factor is rare in the population. However, recent studies

have been able to focus on differences related to race.[11] Case–control studies are most often used to explore etiologic hypotheses in a more efficient manner.

Aspects of critical appraisal of prevalence studies

Usually when a study reports an estimate of prevalence, it is the focus of the study. Given the importance of having accurate estimates of prevalence, it is necessary to have the skills to appraise such studies critically. Proper critical appraisal allows one to judge the accuracy and relevance of the study, its applicability, and the degree to which it can be reliably compared to similar studies or studies performed in other populations. Critical appraisal is aimed at assessing the source, validity and accuracy of both the numerator or cases, the denominator or source population, and the way the two are related to each other, the reliability of the estimate and its applicability (Table 2-1).

Definition of cases

The first aspect to consider when evaluating the numerator is to determine what things were included or excluded as congenital cardiac lesions. Congenital cardiac lesions have been defined as the presence of "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance."[12] An isolated structural abnormality of no functional consequence, such as persistent left superior vena cava, variants of aortic arch branching and some coronary artery anomalies may be considered normal variants or anomalies, and therefore might be excluded. Sometimes these anomalies, however, contribute to abnormality, such as with total anomalous pulmonary venous return draining into a left superior vena cava, or they may complicate management, such as with bilateral superior vena cava when performing a bidirectional cavopulmonary anastomosis. Some abnormalities that are typically excluded are the congenital arrhythmias, such as prolonged QT syndrome and pre-excitation pathways, as well as isolated cardiomyopathies. Most studies exclude abnormalities of the fetal transition, particularly in the presence of prematurity, such as patent ductus arteriosus, patent foramen ovale and physiologic branch pulmonary artery stenoses. Cardiovascular lesions not present at birth but with an inherent predisposition to develop over time, such as with genetic conditions like Marfan or William syndrome, are not included. Structural lesions associated with acquired diseases, such as patent ductus arteriosus with congenital rubella, or coronary artery aneurysms associated with Kawasaki disease, are excluded. There is debate as to whether many clinically silent abnormalities detected incidentally on echocardiography should be included, such as silent patent ductus arteriosus, non-stenotic bicuspid aortic valve, some ventricular septal defects and very mild thickening or prolapse of intracardiac valves.

The second aspect to consider relates to nomenclature and classification. This becomes particularly important when a study reports lesion-specific prevalence proportions, and importantly impairs the comparison of different studies. There have always been problems regarding uniform nomenclature or coding schemes, which is beginning to be resolved with the international development and publication of common nomenclature.[13–15] These schemes have been developed independently, and efforts are underway to cross-map them. They have not yet been applied in prevalence studies. Additionally, studies may differ in the way in which patients with multiple lesions are handled. Patients are usually classified according to the dominant lesion, often based on its physiologic importance. For example, a patient with transposition of the great arteries with ventricular septal defect would be classified with transposition of the great arteries as the dominant lesion. This may become problematic for some very complex lesions. Some studies report the prevalence of each lesion, regardless of whether its occurrence is in isolation or combination; thus the sum of the estimates of lesion-specific prevalence may exceed the total number of cases.

A final aspect relates to whether cases that are diagnosed before delivery but succumb to spontaneous abortion, elective termination or death before delivery (stillborn) are included. Inclusion of these cases may be important when one wishes to determine the prenatal prevalence, or to explore etiologic associations. Cases that do not reach live birth may be different regarding important characteristics from those liveborn, and may in particular include a greater proportion of cases with chromosomal abnormalities and more severe lesions. Ascertainment can be a major problem. Many early spontaneous abortions may be missed, and often pathologic material is either not available or not submitted to anatomic examination specific to defining cardiac lesions. Fetal echocardiography is not broadly and consistently applied, is associated with varying degrees of accuracy, and is most often used only later in gesta-

Table 2-1 Aspects regarding the critical appraisal of prevalence studies

1 What is the purpose of the study?
2 How accurate and valid is the prevalence estimate?
  a How valid and accurate was the definition of the numerator?
    i What forms of congenital heart disease were included?
    ii What nomenclature and classification scheme was used?
    iii How completely were all possible cases ascertained?
      – How were cases detected or reported in the study population?
      – Was detection affected by health system factors, such as access to medical care or patterns of referral, or adequacy of available technology and expertise?
      – How were diagnoses confirmed or verified?
      – Was the follow-up sufficiently long?
  b How valid and accurate was the definition of the denominator?
    i What was the definition of the study population?
    ii What and how valid and reliable were the sources of data used to enumerate the denominator?
  c Are the cases completely derived from the source population enumerated in the denominator, and not from other sources?
    i Were the cases and population characterized as part of the same study using the same methodology?
    ii How accurately and completely does the study population reflect the target population or population at large?
3 How reliable is the prevalence estimate? Are confidence intervals given?
4 How comparable is the prevalence estimate to that reported by similar studies?
5 How does the setting of the study in terms of time, geography, population characteristics and methodology relate to the population from which your patients are derived? How useful is this estimate to your clinical or research question?

tion.[16,17] Given the high rates for elective termination of fetuses with serious lesions, however, the increasing accuracy and use of fetal echocardiography may impact on the prevalence of major lesions at livebirth. The study of the prenatal prevalence of congenital cardiac lesions has focused largely on determining their association with chromosomal abnormalities as detected by amniocentesis, chorionic villus sampling or examination of the abortus.[18]

Ascertainment of cases

Perhaps the most important aspect to consider when evaluating the numerator is the degree to which or level of confidence that all persons with congenital cardiac lesions as defined have been identified and included. Usually one either defines the denominator and then attempts to ascertain all cases within that population, or one takes what cases are available and then attempts to relate them to a known denominator. Methods to ascertain cases range from passive to intensively active surveillance and reporting to population-based screening. Sources of data for ascertaining cases are shown in Table 2-2.

Death registrations and autopsy reports

Death registries and autopsy reports are one source of information about cases. The cases ascertained from this source include only those cases that died and for whom a diagnosis of a congenital cardiac lesion was noted on the death certificate, or who had confirmation of a lesion on autopsy by a qualified individual. Clearly this numerator is best related to a denominator of all deaths occurring in the same age groups, geographic population and time period. This gives the prevalence and distribution of congenital cardiac lesions among persons who died, and may sometimes include stillbirths. Before the advances in diagnosis and therapy, mortality associated with major congenital cardiac lesions was extremely high, and the prevalence at death may have been a reasonable estimate of the prevalence at birth for many lesions. The completeness of ascertainment of all lesions in all deaths depends on the degree of enumeration of all deaths, the accuracy of death certificate reporting, the autopsy rate and the level of expertise of the persons performing the autopsies. Hook *et al.* compared the diagnoses listed on death certificates of 301 individuals previously entered into a registry of a pediatric cardiology practice.[19] Cardiovascular disease was noted on the death certificate in only 82% of cases, and this increased to 90% if cardiovascular disease had been felt to contribute to death. The major cardiac defect present was specifically noted on the death certificate for only 39% of cases.

Table 2-2 Data sources for prevalence studies

Case ascertainment
1 review of autopsy records
2 retrospective review of referrals to tertiary care centers
  – inpatient
  – outpatient
3 prospective surveillance reporting from cardiology care sources within a geographic area or a health care organization, registries
4 prospective population-based screening
5 use of administrative data
  – vital statistics registries (birth, death)
  – hospital discharge abstracts
  – medical claims data

Population data
1 use of administrative data
2 prospective population-based screening

Secondary data

The sole use of secondary data to determine prevalence estimates, while convenient, is fraught with bias. Secondary data are data that were collected for purposes other than the specific research question at hand. Examples of secondary data include mandatory birth and death registries, hospital discharge abstract databases, periodic health surveys and administrative data, such as health claims data. Use of this data for case ascertainment tends to enumerate and classify cases poorly, since the diagnostic data recorded are often reported by non-medical persons and persons not directly involved in the individual case. Diagnostic data reported on birth registrations are often only relevant to lesions presenting and detected at or shortly after birth. Diagnostic data on death registrations usually emphasize those diagnoses that were most likely to have contributed causally to the death. Recorded diagnoses are often not subject to verification. Thus, sole use of secondary data cannot lead to an accurate estimate of prevalence. Secondary data are, however, often used to determine the population denominator for prevalence estimates if the study is not a prospective cohort study, as there is usually greater motivation to report and record all births and deaths, and thus a more complete enumeration is achieved.

Case series

While the use of secondary data yields a poorly validated numerator yet a good denominator, use of case series yields a validated numerator often without a known denominator. Case series usually consist of reports of all confirmed cases of congenital cardiac lesions presenting and diagnosed by a specialized provider or center. While they rarely lead to an estimate of prevalence, they have often been used to describe the spectrum and distribution of lesions presenting to a given point of care. Only cases with access to that point of care are included, and thus cases that aren't suspected or referred, and cases that die before reaching the center are not included. This may bias the distributions determined. In general, these types of studies are now rarely performed or reported, except in developing countries where more formal surveillance systems may not be in place.

Surveillance

The most common means of case ascertainment is to use a combination of passive and active surveillance activities. These range from systems of voluntary or mandatory reporting of all congenital malformations, to complex networks of active surveillance and referral to specialized centers for confirmation. All of these activities are prospective in nature, and often involve continuous and active monitoring to ensure complete ascertainment of all available cases. The majority of contemporary prevalence studies use this methodology. Most commonly, a collaborative group of tertiary care providers (pediatric cardiologists) is formed and maintains active and detailed reporting of all eligible (for such characteristics as date of birth, geographic location or catchment area) cases. This may be supplemented by monitoring of birth and death registrations, frequent surveillance of institutional autopsy records and surveillance of track-

ing records in obstetric, nursery and pathology departments in the community. There may also be surveillance of referring health care providers in the community to ensure that all suspected cases are referred or verified and reported.

Prospective cohort studies

The ideal study for determining prevalence is to apply a screening assessment associated with a high degree of sensitivity and specificity to a defined cohort or population. This enumerates both the numerator and denominator at the same time and with the same methodology. If the screening assessment is used for case detection, but is not accurate enough for diagnostic confirmation, then follow-up testing must be applied. The most common and cost-effective screening assessment would involve a clinical assessment. Several studies have highlighted that this assessment performed by non-pediatric cardiologists has a suboptimal sensitivity and specificity, and even if performed by pediatric cardiologists, has suboptimal accuracy in terms of making a lesion-specific diagnosis.[20,21] Screening with echocardiography is difficult to apply on a large scale. Since congenital cardiac lesions are relatively rare in the general population, huge numbers of persons would have to be screened for sufficient numbers of cases to be diagnosed, and provide reliable estimates of overall prevalence, the distribution of lesions and lesion-specific prevalence. Therefore, this method of case ascertainment has not yet been performed on a large scale.

Importance of diagnostic confirmation or verification

Diagnostic confirmation is an important issue in the definition and characterization of cases. Reliance only on community-based clinical assessment for screening with referral to pediatric cardiologists for confirmation has been shown to be suboptimal in case ascertainment.[20,21] For patients who die, autopsy with attention to cardiac pathology is necessary. As some cases will die either with or without clinical suspicion, most prevalence studies will include some surveillance of death registration data and the results of all autopsies performed within the target population. With the advent of surgical repair and cardiac catheterization, these became the primary methods for diagnostic confirmation, although they tended to be applied only to those cases suspected of having more major types of lesions. This was followed by echocardiography and, with the use of two-dimensional imaging and color Doppler echocardiography performed and interpreted by experienced providers, has led to the complete detection and characterization of lesions, with widespread applicability. Thus, diagnostic confirmation has evolved over time, and has increased the validity and accuracy of contemporary prevalence studies, while creating controversy as to whether contemporary increases in reported prevalence estimates represent true increases in the incidence of congenital cardiac lesions, i.e. more disease, or better case ascertainment.

Types of denominators

Ideally, the denominator should represent the population from which the numerator was derived. It is the key piece of information that tells us to whom the estimate of prevalence applies, and suggests the population to which an extrapolation may be made. Estimates that attempt to enumerate the denominator prospectively at the same time that the cases are being ascertained are much more reliable and valid, but require considerably more effort. Since the most common prevalence estimate provided is the prevalence at livebirth, most studies will rely on denominators derived from birth registrations that correspond to the population or catchment area from which the cases were derived. These data are often readily available from governmental agencies. Some birth denominators include fetal deaths and stillbirths, which are much harder to ascertain, and may not be included in routinely collected registration systems. Studies that focus on the contribution of congenital cardiac lesions to overall or infant mortality use death registration data for the relevant time period and geographic region.[5,6,22,23] If one is using birth or death registration data, then one should be familiar with the reliability and validity of that data. One should note the completeness with which events are enumerated, which is directly related to the importance of reporting to both the person doing the reporting (voluntary vs. mandatory) and to the agency to which the data are being sent. Attention should be paid to the timeliness and accuracy of the data reported. This can be affected by the qualifications of the persons completing and submitting the registration data. This is particularly important if more complex medical information is to be included, such as clinical and anatomic diagnoses, and the scheme for coding and classification should be known.

The prevalence estimate

In addition to ensuring that the cases and the denominator are derived in a credible manner, there are several other aspects to consider before accepting the prevalence estimate that is reported. One must look for evidence that the cases and the denominator relate closely to one another. They should be similar in terms of time period, geography and any other relevant characteristics, as well as in the definitions used. Some measure of certainty should be included, and the most common is a specified confidence interval. This is essential in determining how random error may affect the estimate, and therefore reflect the truth in the target population. This is also particularly important if prevalence estimates are to be compared over time or between populations and studies. While there may be important differences in two reported estimates, examination of the confidence intervals may show overlap, and one may be reluctant to conclude, all other aspects being equivalent, that a true difference exists.

Examples of published prevalence studies

Autopsy studies

Samanek *et al*. retrospectively examined death certificates and autopsy records collected over a 27-year period ending in 1978 for all stillbirths and children who died up to age 15 years in Central Bohemia in Czechoslovakia.[24] All deaths were studied with autopsy, and all malformed hearts were examined by a single specialized pathologist. The number of cases was related to the total number of deaths and associated autopsies, and to the number of stillbirths and childhood deaths (deaths after livebirth). Congenital cardiac lesions at autopsy were noted in 62 of 1000 stillborn or childhood deaths, with a prevalence of 21 per 1000 stillbirths and 74 per 1000 childhood deaths. Regarding the distributions of specific lesions, there were differences in those found in stillborns vs. childhood deaths. Ventricular septal

defect was the most common lesion, accounting for 22.6% of all lesions.

Clinical center case series

In 1970, Wallooppillai & Jayasinghe reported a prospective series of 555 consecutive cases presenting to the Cardiac Investigation Unit, General Hospital, Colombo, Ceylon from May 1967 to July 1969.[25] Diagnoses were confirmed by cardiac catheterization in 496 cases, with the remainder confirmed at surgery. The authors report the frequency of the various lesions, with the commonest lesion being atrial septal defects, followed by ventricular septal defects and patent ductus arteriosus. Distributions by age at presentation and by gender are given. As a denominator was not available, no estimate of prevalence is reported. This type of study is fairly typical of the case series that were reported predominately by developing countries without uniform access to specialized medical care. While providing limited information, these studies were useful for resource planning within these countries, and comparisons of distributions of lesions across studies were useful in determining the differences in spectrum of lesions that might suggest actual differences in incidence and prevalence, or differences in case ascertainment affected by factors in the health care system.

Studies relying only on secondary data

McCrindle *et al.* used administrative data to determine that there was an increased prevalence of total anomalous pulmonary venous drainage among aboriginal Canadians in a defined geographic region.[26] Several unique characteristics of this population and dataset allowed the comparison to be made. Two methodologies used in consecutive cohorts were employed. For the first cohort, traditional surveillance methodologies were used to ascertain all cases, primarily by medical record review, and their aboriginal status. The denominator of livebirths was obtained from census data and a governmental registry of livebirths among aboriginal Canadians. A birth prevalence of 0.282 per 1000 livebirths was noted in aboriginal Canadians vs. 0.062 in non-aboriginals, giving a relative risk of 4.6 overall and 5.8 for the Manitoba region only. For the next cohort, administrative data were used for the province of Manitoba. All residents of Manitoba were covered by a universal health care system administered by the provincial government, with central reporting. The administrative data had been used by numerous investigators, and included several validation studies. Aboriginal status is associated with mandatory reporting, given that this population is awarded special status and administered differently. Cases and their aboriginal status were ascertained from the abstract database of hospital discharge. Livebirths and their aboriginal status were ascertained from the same source. Using this methodology, the relative risk of total anomalous pulmonary venous drainage in aboriginal Canadians was 5.8, identical to the value obtained from the more traditional surveillance methodology. Several unique properties of the data as mentioned, however, allowed them to be used. Additionally, one had to be assured that all cases and livebirths were associated with a mandatory hospitalization at presentation, and that no cases died before presentation. Clearly, the number of instances in which all conditions would be met regarding secondary data is rare.

Registries for surveillance

Carlgren *et al.* (Sweden, 1981) used four different registries to ascertain cases under 1 year of age, including birth and death certificate registries, a congenital malformation registry and a registry designed specifically for collecting congenital cardiac lesion cases and data.[27] They concluded that the birth certificate registry had poor quality data, and that most cases could be detected with the compulsory national congenital malformation registry and the cardiac-specific registry, which consisted of coordinated reporting of verified cases from all five tertiary pediatric cardiology centers. The 853 cases ascertained by any one of the four registries was related to a denominator of all live- and stillbirths during the surveillance period, for a birth prevalence of 9.1 per 1000. However, only 256 cases were noted in the congenital malformation and cardiology registries, with 564 cases noted only in the birth registry by ICD8 codes, with 75 having only a code indicating suspected malformation, and 68 having patent ductus arteriosus in the setting of low birth weight. Thirty-five cases were identified in the death registry, with 17 of these not appearing in the other registries. This study documents some of the limitations of secondary data and registries in determining prevalence estimates.

The New England Regional Infant Cardiac Program was a voluntary association of hospitals providing care to infants with congenital cardiac lesions and was formed to improve care for those infants.[28] Many systems were put in place to improve the detection, referral, diagnosis and management of these infants. In addition, all hospitals reported data relevant to their entire experience during the operation of the program as a form of active surveillance. As a result of the program, the number of cases reported increased, and when this was related to livebirth registration data for the region, prevalence estimates were obtained. Perhaps the most important information arising from the program was data regarding the distributions of various lesions as a function of the age at presentation (Table 2-3).

The Baltimore–Washington Infant Study was primarily designed as a case–control study to determine potential etiologic associations but, because of the high case ascertainment in a relatively well-defined geographic region, was also able to give reasonable estimates of prevalence. Several sources were used to enumerate all confirmed cases diagnosed under 1 year of age, including surveillance of six pediatric cardiology centers, medical examiner records, pathology logbooks in 53 community hospitals, and birth and death registrations. It was one of the first studies to use echocardiography as a source of diagnostic confirmation, and thus eliminated the large number of "suspected" cases either included or excluded in previous prevalence studies. Controls were drawn randomly from the livebirth cohort from which the cases were ascertained. Standardized interviews of the mothers of cases and controls were obtained during home visits. In an analysis of the data focused on racial differences, there seemed to be no difference in the proportion of cases (0.68) vs. controls that were white infants (0.67).[29] However, significant differences existed for some lesions, with an excess of white infants reported for Ebstein's anomaly, aortic stenosis, pulmonary atresia, coarctation of the aorta, and D-transposition of the great arteries, with a deficit of white infants reported for pulmonary stenosis and heterotaxia. Adjustment for socioeconomic status altered some of the associations. This is only one example of the many reports from this important and well-designed study, and provides the best epidemiologic

0–6 days (%)	7–13 days (%)	13–20 days (%)	180–365 days (%)
D-TGA (17)	CoA (19)	VSD(20)	VSD (20)
HLV (12)	VSD (15)	D-TGA (17)	PDA (14)
Lung disease (10)	HLV (11)	CoA (16)	ToF (14)
ToF (9)	D-TGA (9)	ToF (8)	ASD (10)
CoA (7)	ToF (6)	ECD (6)	ECD (7)
VSD (7)	Heterotaxias (4)	Heterotaxias (6)	Myocardial disease (7)
PAIVS (7)	Truncus art (4)	PDA (4)	PS (6)
Heterotaxias (6)	Single ventricle (4)	TAPVR (3)	CoA (4)
Other (25)	Other (28)	Other (20)	Other (18)

Table 2-3 Diagnostic frequencies in infants by age at presentation

ASD, atrial septal defect; CoA, coarctation of the aorta; D-TGA, complete transposition of the great arteries; ECD, endocardial cushion defect; HLV, hypoplastic left ventricle; PAIVS, pulmonary atresia with intact ventricular septum; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TAPVR, total anomalous pulmonary venous return; ToF, tetralogy of Fallot; Truncus art, truncus arteriosus; VSD, ventricular septal defect. (*From Fyler*[28] *with permission.*)

data available relevant to congenital cardiac lesions and possible genetic and environmental risk factors.[30–55]

Population-based screening

Hiraishi *et al.* (Japan, 1989–90) used two-dimensional and color Doppler echocardiography to screen prospectively at 2–10 days after birth 1028 term neonates born at a single hospital.[56] The focus of the study was to determine the birth prevalence and natural history of trabecular or muscular ventricular septal defects.[56] Defects were noted in 21 neonates, for a prevalence at livebirth of 20 per 1000 (other defects detected included four cases of perimembranous and one case of outlet ventricular septal defect). Only 57% of the neonates had an associated murmur before they were discharged from hospital. Hiraishi *et al.* characterized the defects in these and an additional 21 cases diagnosed at the same hospital before the screening study, and performed serial follow-up examinations. They were able to document the rate and factors associated with spontaneous closure. This study documents the high quality of the data from a population-based screening, and the lack of feasibility in detecting enough cases to give reliable estimates for the birth prevalence of other more rare congenital cardiac lesions. In addition, the study demonstrates the predominance of ventricular septal defects in prevalence estimates, many of which may not be diagnosed before undergoing spontaneous closure.

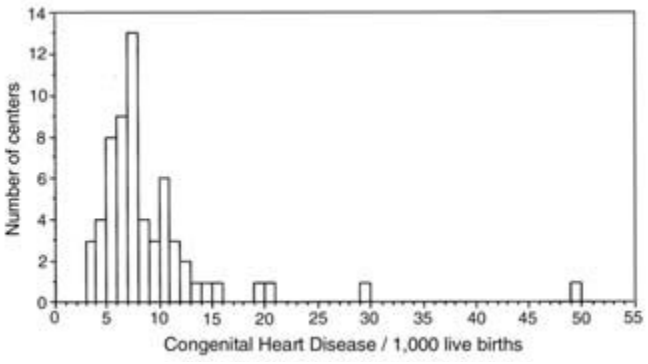


Fig. 2-2 Histogram of the prevalence of congenital cardiac lesions per 1000 live births as noted in 62 reports. (Reprinted from Hoffman & Kaplan[10], Copyright (2002), with permission from The American College of Cardiology Foundation.)

What is the prevalence of congenital cardiac lesions?

Given all of the preceding discussion regarding methodology and specific studies, one may be left wondering if the true prevalence of congenital cardiac lesions can ever be known with certainty. Estimates of prevalence must be viewed in terms of a critical appraisal of the methodology, and put in context with the current state of knowledge and technology at the time the study was performed. Probably no one study will ever give the definitive answer.

There have been several reviews that have attempted to synthesize the information presented in multiple studies to give a more coordinated picture. Ferencz *et al.*, the investigators for the Baltimore–Washington Infant Study, attempted to put their study in the context of eight previous studies that were widely cited in the literature.[12,28,57–62] The purpose of the study was to provide comparisons regarding diagnosis-specific prevalence rates. The studies covered different time periods and geographic populations, different methods of case ascertainment, different intervals of follow-up and different levels of certainty with which diagnoses were confirmed. The New England Regional Infant Cardiac Program limited cases to those with diagnostic confirmation by catheterization, surgery or autopsy,[28] while the Baltimore–Washington Infant Study also included cases confirmed by echocardiography only, which was not yet available for any of the other studies. For the remaining studies, the proportion of cases relying on a clinical diagnosis only ranged from 30% to 52%. Despite the great differences in time, population and methodology, the estimates of overall prevalence per 1000 livebirths for cases with confirmed congenital cardiac lesions only ranged from 3.70 to 4.30, with a prevalence 2.03 from the New England Regional Infant Cardiac Program.

Hoffman and Kaplan provided a critical analysis of available published reports of the prevalence of congenital cardiac lesions to determine the reasons for variability in reported estimates, and to provide a more accurate true estimate of overall and lesion-specific prevalence.[10] A histogram of estimates from 62

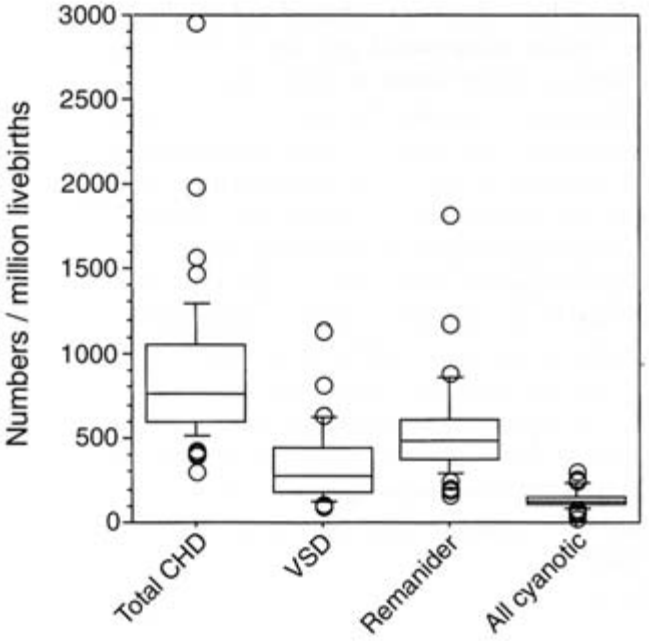


Fig. 2-3 Modified box plots to show the variability of the prevalence per million livebirths. Plots consist of the rectangle enclosing the lower and upper quartiles with the horizontal line in the middle representing the median, with the whiskers showing the 10th and 90th percentiles and open circles giving individual outliers. CHD, congenital heart disease; VSD, ventricular septal defect. (Reprinted from Hoffman & Kaplan,[10] Copyright (2002), with permission from The American College of Cardiology Foundation.)

published reports shows considerable variation and outliers in the reported prevalence at livebirth (Fig. 2-2). In addition, there is a trend towards increasing prevalence. Several previous studies have noted that with the development and widespread use of echocardiography, the overall prevalence of congenital cardiac lesions, and of ventricular septal defect in particular, has risen.[63–65] Hoffman and Kaplan showed that the prevalence of ventricular septal defects dominates estimates of overall prevalence and, together with other trivial lesions, is the major contributor to variation in prevalence estimates (Fig. 2-3). The prospective study by Hiraishi *et al.* clearly supports this assertion, and points to the high prevalence of ventricular septal defects when all defects are detected and included.[56] Birth prevalence estimates for major lesions also show variation, but this is more likely to be related to random error, given the small number of cases for rare, specific lesions and the wider confidence limits in individual studies (Fig. 2-4).

Hoffman & Kaplan summarize their findings in that the prevalence of moderate or severe forms of congenital cardiac lesions is approximately 6 per 1000 livebirths, but increases to 19 if bicuspid aortic valve is included, and to 75 per 1000 livebirths if all ventricular septal defects and other trivial lesions present at birth are included. Thus, the answer to the parent asking about the risk of a congenital cardiac lesion in their newborn is not simple, and should include an estimate of the prevalence of lesions based on severity.

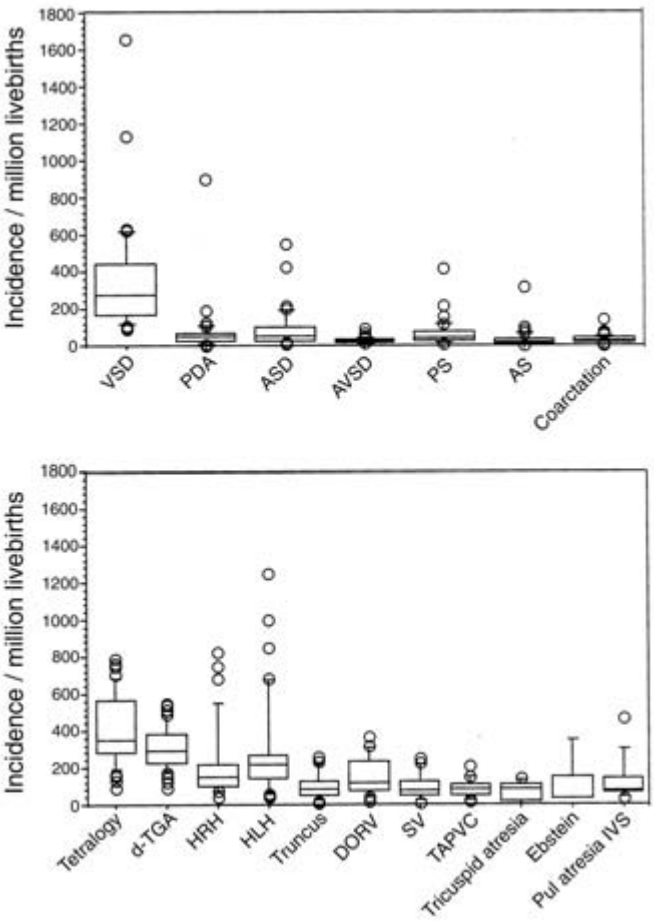


Fig. 2-4 Modified box plots to show the variability of the prevalence per million livebirths for specific congenital cardiac lesions. AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; DORV, double outlet right ventricle; d-TGA, complete transposition of the great arteries; HLH, hypoplastic left heart; HRH, hypoplastic right heart; PDA, patent ductus arteriosus; PS, pulmonary stenosis; Pul atresia IVS, pulmonary atresia with intact ventricular septum; SV, single ventricle; TAPVC, total anomalous pulmonary venous connection; Tetralogy, tetralogy of Fallot; Truncus, truncus arteriosus; VSD, ventricular septal defect. (Reprinted from Hoffman & Kaplan,[10] Copyright (2002), with permission from The American College of Cardiology Foundation.)

All references can be found at the end of the book. See pp. 605–6 for Chapter 2.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

3

Robert M. Freedom, Shi-Joon Yoo, John Coles, and Igor Konstantinov

Ventricular Septal Defect

Ventricular septal defect is the most common of all significant congenital cardiac malformations. Its relative incidence as a proportion of total congenital heart disease has been reported to range from *c*. 16% to 50%.[1–11] Although a functionally normal bicuspid aortic valve and mitral valve prolapse are probably more prevalent in the pediatric age range, both conditions uncommonly produce symptoms in infants and children, and most series do not classify mitral valve prolapse as a congenital defect.[6–8] Ventricular septal defect occurs either as an isolated defect or as a component of a more complex lesion. In this chapter, the discussion will be confined to ventricular septal defects in those hearts with concordant atrioventricular and ventriculoarterial connections.

Incidence and racial variation

Some cardiologists have wondered whether there is another "epidemic" of ventricular septal defects because some recent studies have suggested a prevalence as high as 25.2 per 1000 livebirths.[12] The answer is no, but as Dickinson has stated, the increased ascertainment mainly of small defects resulting from the application of cross-sectional echocardiography with Doppler color flow mapping is probably responsible for this apparent increased prevalence.[12] Hoffman has summarized those factors affecting the accuracy of ascertainment of congenital heart disease.[6,9,13] The incidence has been shown to be much higher in fetuses dying prenatally, and in addition there is some variation depending on the time of fetal death. Furthermore, pregnancy wastage has been shown to be relatively common. These factors must be integrated into any meaningful data on the prevalence of congenital heart disease from the fetus to the liveborn. The reported incidence of isolated ventricular septal defect ranges from *c.* 0.4 to 3.3 per 1000 livebirths.[1,2] The variations in the reported incidence relate mainly to the case finding methodology, and the reporting system, both of which have been ever changing and improving. A recent study reported an overall incidence of 4.68 per 1000 livebirths, which is the highest rate of all.[14] The increased incidence of this study has been attributed to the high risk population of the study. Hoffman has summarized the literature addressing the percentage distribution of congenital cardiac defects.[6] From 22 series, the median percentage distribution of ventricular septal defect was 31%.[6] The prospective Bohemia Survival study identified 2092 patients with ventricular septal defect from a total of 5030 patients with congenital heart disease.[15] This provided a prevalence of 2.56 per 1000 livebirths, accounting for 41.6% of all heart malformations. The fact that ventricular septal defects often close spontaneously in either fetal or postnatal life also accounts for the differences in incidence between the studies that certainly are based on the populations being of different age groups.[1–11] Note that ventricular septal defects are more common in the premature and low birthweight infants.[1–11,16–21] The incidence rates, however, are not related significantly to race, sex, maternal age, birth order, or socioeconomic status. Roguin and his colleagues documented 56 small trabecular, mostly silent ventricular septal defects from a cohort of 1053 asymptomatic neonates.[18]

While there does not seem to be a genetic bias towards the incidence of ventricular septal defects, genetics certainly influences the type of defect. The doubly-commited subarterial or juxta-arterial defect is more common in Asian populations, whereas muscular and multiple defects are less common in the same population. According to Wilkinson, the frequency of the doubly-commited subarterial or juxta-arterial defect requiring repair is at least 30% in an Asian population compared with an incidence of *c.* 5% of occidental patients requiring surgery in western societies.[10] Furthermore, Wilkinson states that while muscular defects account for *c.* 30% of operated defects in the western world, these are uncommon in the Asian surgical population. He further mentions that amongst the Asians, multiple ventricular septal defects are rare, compared to an incidence of *c.* 10% in the West.[10]

Classification and morphology

The classification of ventricular septal defects remains contentious. More than a dozen different systems of classification have been introduced and these have been summarized elsewhere.[22–37] In a previous publication[37] we have supported the classification proposed by Soto and his colleagues[32] and revised subsequently by Anderson *et al.*,[11,34,35] feeling that this system is most useful in clinical diagnosis, treatment and communication. The criteria for this classification system are:

1 the relation of the defect to the atrioventricular conduction axis, i.e. the membranous septum
2 the relation of the defect to the atrioventricular valves
3 the relation of the defect to the arterial valves
4 the position of the defect within the ventricular septum, i.e. the inlet, trabecular or outlet part of the septum.

According to the first three criteria, ventricular septal defects are then classified into four types: perimembranous, juxtatricuspid (and non-perimembranous), doubly committed juxta-

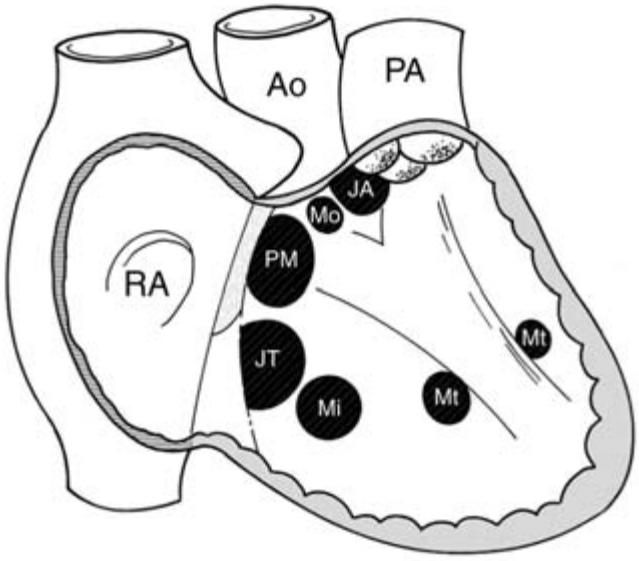


Fig. 3-1 Modified Soto's classification of ventricular septal defects as seen from right ventricular aspect. Defects are classified into: perimembranous (PM); juxtatricuspid but non-perimembranous (JT); doubly committed juxta-arterial (JA); muscular (Mi, Mt and Mo). Ao, aorta; Mi, muscular inlet defect; Mo, muscular outlet defect; Mt, muscular trabecular defect; PA, pulmonary artery; RA, right atrium.

arterial, and muscular defects (Fig. 3-1). The perimembranous defect involves the interventricular membranous septum and the adjacent muscular septum. The aortic and tricuspid valves are virtually in direct contact through the defect. The mitral valve is usually separated from the defect by the intervening atrioventricular membranous septum. On rare occasions with a perimembranous defect that extends extensively toward the ventricular inlet to the crux cordis, i.e. so-called "ventricular septal defect of the persistent common atrioventricular canal type," the mitral and tricuspid are in direct contact through the defect.[38] In all perimembranous defects, the atrioventricular conduction axis is intimately related to the posteroinferior margin of the defect, regardless of its subtype.[39] The juxtatricuspid (and non-perimembranous) defect involves the inlet muscular septum along the tricuspid annulus without direct contact with the membranous septum.[32] In this particular defect, the conduction axis is located at the anterior aspect of the defect along the posteroinferior margin of the intact membranous septum. The doubly committed juxta-arterial defect involves the most cranial part of the outlet septum. The aortic and pulmonary valves are in direct contact above the defect. The muscular defect is surrounded completely by a muscular rim when it is seen from the right ventricle. Defects that are not perimembranous have no direct contact with the atrioventricular conduction axis. Among these four types, perimembranous and muscular defects need further categorization according to the last criterion, i.e. the position of the defect within the ventricular septum. Defining the position of the defect within the ventricular septum should be carried out as seen from the right ventricle. This is because the septal boundaries seen from the right ventricle are not necessarily identical to those seen from the left ventricle.[34,35] The so-called Gerbode-type of ventricular septal defect[36] rarely results from deficiency of the membranous atrioventricular septum, but rather results from tricuspid valve abnormalities, including clefts or perforations of the septal leaflet, deformity or adherence of valve tissue to the margins of the septal defect, and widening of the anteroseptal commissure[36A,36B,37] The morphology and classification of the various types of ventricular septal defect have been comprehensively reviewed by Tynan & Anderson.[11]

The malalignment type of ventricular septal defect

Ventricular septal defect is most commonly a simple punched-out hole. Less commonly, the defect is associated and indeed results from the malalignment of a part of the interventricular septum.[3,10,11,28,37] Malalignment usually involves the outlet or infundibular septum. The malalignment of the outlet septum may occur either anteriorly toward the right ventricle or posteriorly toward the left ventricle (Fig. 3-2). Malalignment occurs as if there is a door that moves round on a hinge.[37] The anterior malalignment of the outlet septum is the most common type of malalignment. In this situation, the outlet septum, which is supported by a hinge along its left anterior aspect, is "pulled" ante-

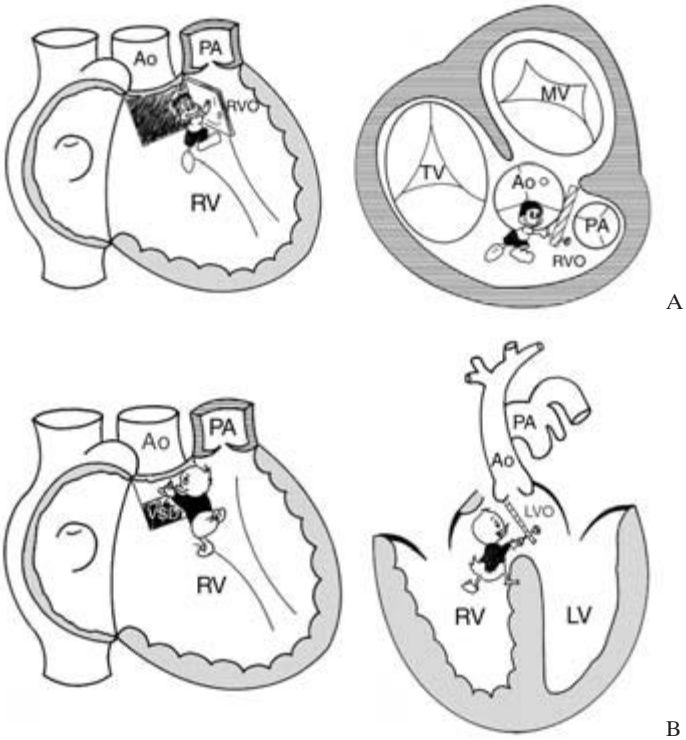


Fig. 3-2 Malaligned ventricular septal defects. **A**. Anterior malalignment type. The trap door of the outlet septum is supported by a hinge along its left anterior margin. The door is pushed open toward the right ventricle (RV) against the free wall of the outflow tract (RVO), resulting in an anterior malalignment type of ventricular septal defect, overriding aorta (Ao) and subpulmonary stenosis, which characterize the morphology of tetralogy of Fallot. MV, mitral valve; PA, pulmonary artery; TV, tricuspid valve. **B**. Posterior malalignment type. The trap door of the outlet septum is supported by a hinge along its superior margin. The door is pushed back toward the left ventricular outflow tract (LVO), resulting in posterior malalignment type of ventricular septal defect and subaortic stenosis. This type of ventricular septal defect are commonly seen in association with coarctation of aorta or interruption of the aortic arch. Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

riorly toward the right ventricular outflow tract.[3,10,11,28,40,41] This anterior malalignment results in a large ventricular septal defect and overriding of the aortic valve, both of which are seen in the Eisenmenger type of ventricular septal defect. More typically, the anterior malalignment is severe enough to encroach on the subpulmonary outflow tract, and the morphology of tetralogy of Fallot results.[3,10,11,40,41] The posterior malalignment is a less common situation in which the outlet septum is pushed backwards into the left ventricular outflow tract; a hinge being present along the aortic valve.[10,11,42–44] This posterior malalignment results in a ventricular septal defect and muscular subaortic stenosis. When the malalignment is severe, the pulmonary valve may override the ventricular septum. The posterior malalignment defect is frequently associated with the obstructive lesion of the aortic arch, and deserves the name, "coarctation type" of ventricular septal defect. This type of ventricular septal defect is also frequently observed in the patient with interruption of the aortic arch.[3,10,11,42,44] Rarely, the malalignment occurs between the atrial and the muscular ventricular septal structures, resulting in straddling and overriding atrioventricular valves. This aspect will not be examined in this chapter.

Size of the defect

How does one ascertain the size of the ventricular septal defect, as it is so often the size of the defect that in large part determines the outcome and requirement for intervention?[1,3,7,8,10,11] This determination evolved from a purely clinical perspective to one based on cardiac catheterization with angiography, and today this determination is mainly based on clinical and echocardiographic findings.[1,3,10,11] Rowe suggested almost three decades ago that the diameter of the ventricular septal defect compared to the diameter of the ascending aorta could be used in determining the prognosis.[45] When the ratio was ≥ 0.8, this defect was considered large, was unlikely to spontaneously close, and the infant would have a large pulmonary blood flow and pulmonary artery hypertension,[45] all features necessitating surgical intervention. Today cross-sectional echocardiography allows the estimation of right ventricular pressure and clearly images the defect and its size, also showing whether there is any tissue limiting flow through the defect (i.e. suggesting the potential for spontaneous diminution in size or closure).[1,7,8,10,11]

Outcome analysis

The outcome and natural history of the patient with ventricular septal defect is influenced by many factors.[1,3,6–14,17–21,45–65] These include the position of the ventricular septal defect, its size, the number of defects, the anatomic structure or structures in the vicinity of the defect, and the association of other malformation. Other factors include the age at which the defect is recognized, the method of ascertainment, and there are some data to suggest that the sex of the patient may have some influence over spontaneous closure. For those patients undergoing surgical intervention, the results are influenced by the anatomic type of the ventricular septal defect, the era during which surgery took place, the effect of previous palliation, the surgical approach to the ventricular septal defect, preoperative pulmonary vascular resistance, etc.

The natural history of the patient with ventricular septal defect may take any of a number of paths, including:

- spontaneous diminution in size or closure
- development of right ventricular outflow tract obstruction
- development of aortic regurgitation
- development of left ventricular outflow tract obstruction
- development of pulmonary vascular obstructive disease
- infective endocarditis.

Spontaneous diminution in size or closure

Spontaneous change in the size of the ventricular septal defect with diminution or closure of the defect has been exhaustively documented and is now recognized as a common phenomenon. Perhaps the first clinical report was that of French who described in 1918 the clinical findings in a young boy whose heart murmur and thrill disappeared at 5 years of age.[66] Spontaneous closure is now recognized as a common phenomenon, affecting both perimembranous and muscular trabecular defects, with closure documented in the fetus as well as in the adult.[1,3,7,8,10,11,14,17,20,21,37,46,48,50,51,53–65] In this regard, there is some information on the outcomes of ventricular septal defect in the fetus.[67–69] The study of Paladini *et al.* showed that *c.* 46% of ventricular septal defects diagnosed in the fetus closed *in utero* and that 23.1% closed during the first year of life, while only 30.8% remained patent.[68] In this study, only 15.8% of defects < 3 mm remained patent in comparison to 71.4% > 3 mm. As one would expect, none of the malalignment defects closed in comparison to 69% of the perimembranous defects and 60% of muscular trabecular defects.[68]

Spontaneous closure seems more frequent in children <10 years of age, but this event has been observed in patients in their third and fourth decades of life.[10,11,17,46,54–57,60,70–74] Moe & Guntheroth suggest that the rate of spontaneous closure decreases substantially after 1 year of age.[14] Alpert and his colleagues found that by 10 years of age, 75% of small ventricular septal defects close spontaneously, and that this is even higher for muscular defects at 83%.[75,76] Krovetz's clinical study was in agreement with that of Alpert, finding that by 10 years of age 71% of ventricular septal defects had spontaneously closed.[77] Krovetz reported on the outcome of 692 patients followed for ≥ 3 years.[77] The ventricular septal defect closed spontaneously in 490 patients (70.8%) with the earliest case of spontaneous closure at 12 days of age, whereas the oldest patient in his series was 19 years. Krovetz's data also showed that the rate of spontaneous closure seemingly followed an exponential decay curve.[77] This finding of an increased rate of spontaneous closure of the trabecular muscular defects has been confirmed by others.[21,58] Mehta and colleagues have studied the natural history of isolated ventricular septal defect in 124 patients seen in the first 5 years of life.[78,79] They found that spontaneous closure of ventricular septal defect was 34% at 1 year and 67% at 5 years. Twenty-five per cent of patients with perimembranous and 4% of muscular ventricular septal defects required surgery by 5 years. This is in contrast to the study of Krovetz who found that only 5.6% of his patients required surgery.[77] The spontaneous closure rate of the muscular defect of patients in the Mehta study was twice that of the perimembranous type, though the relative distribution of both types was almost equal. Overall, 22% of children with a ventricular septal defect from this survey required follow-up after the fifth year of life. Similar findings comparing the rates of closure of muscular to perimembranous defects were reported by Turner and col-

leagues.[57A] Farina & Hook have observed an apparent sex difference in the spontaneous closure of ventricular septal defects.[80] Their observations suggested a predominance of females among children whose ventricular septal defect underwent spontaneous closure.[80] These observations were not wholly supported by the findings of Cook and his colleagues at the Toronto Hospital for Sick Children and Johns Hopkins Hospital.[81] Onat and colleagues have studied the natural course of isolated ventricular septal defect during adolescence.[82] Their study showed that even during adolescence there can be further diminution in size of the ventricular septal defect in > 20%. They also found that *c.* 10% of the patients developed aortic regurgitation.[82] The ventricular septal defect can even close in the adult.[10,11,17,46,54–57,60,70–74] Most of the published studies have indicated that the malalignment ventricular septal defect rarely undergoes spontaneous closure or diminution in size. Tomita and colleagues have studied the incidence of spontaneous closure of the outlet ventricular septal defect, finding spontaneous closure in only *c.* 4% of patients.[83] All of the defects that underwent spontaneous closure were initially < 4 mm in diameter.[83] Some defects with associated so-called aneurysms of the membranous septum have been identified in individuals in their eighth decade of life.[84]

The mechanisms responsible for closure differ if the ventricular septal defect is perimembranous or if the defect is primarily muscular (Fig. 3-3).[3,10,11,57,85–88] When the defect is perimembranous, the most common mechanism responsible for closure is either reduplication of tricuspid valve tissue or progressive adherence of the septal leaflet of the tricuspid valve about the margins of the ventricular septal defect.[87] This latter process has been likened to so-called aneurysmal transformation of the membranous septum, an appearance based on the angiocardiographic features of the ventricular septal defect.[3,7,10,11,37,48,50,51,54–56,70–72,74] It is now clear that the tissue closing the perimembranous ventricular septal defect is neither aneurysmal, nor is it usually derived primarily from the membranous septum. While spontaneous closure of the very small perimembranous ventricular septal defect has been documented in the fetus and neonate, most of the large clinical studies have addressed this phenomenon in older patients. There has been considerable evolution in the methodologies used to define the change in the size of the ventricular septal defect. The auscultatory findings of the typical small ventricular septal defect were described by Roger in 1879.[88A] The auscultatory findings of the closing perimembranous defect have been characterized elsewhere with the early systolic click and late crescendo of the systolic murmur, as has the pertinent angiographic findings.[51,89] There is a substantial amount of information derived from serial echocardiographic studies addressing the mechanism and incidence of spontaneous closure of the ventricular septal defect.[7,10,11,18–21,57–59,61,62,90–93] Most studies have confirmed that the appearance of the so-called aneurysm of the membranous septum is indicative of the tendency to spontaneous diminution or closure of the perimembranous ventricular septal defect.[7,10,11,18–21,57–59,61,62,90–93] Thus while there is the strong tendency for the small ventricular septal defect to close, the moderate-sized defect, and rarely the large defect, can also become smaller or even close. Thus, some infants experiencing congestive heart failure will demonstrate improvement coincident with spontaneous diminution or closure of the ventricular septal defect. Muscular defects close by direct apposition of their muscular borders,[10,11,88] and such closing muscular defects can be recognized from their typical auscultatory findings.[94] The large doubly committed subarterial defect does not undergo spontaneous closure. Prolapsing of the right and non-coronary aortic valve cusps may initially reduce the degree of left-to-right shunting, but the development of aortic regurgitation will reveal the underlying substrate. Furthermore, in some patients the prolapsing aortic cusp may obstruct the right ventricular outflow tract. In addition, a large so-called aneurysm of the membranous septum may obstruct the right ventricular outflow tract.[95]

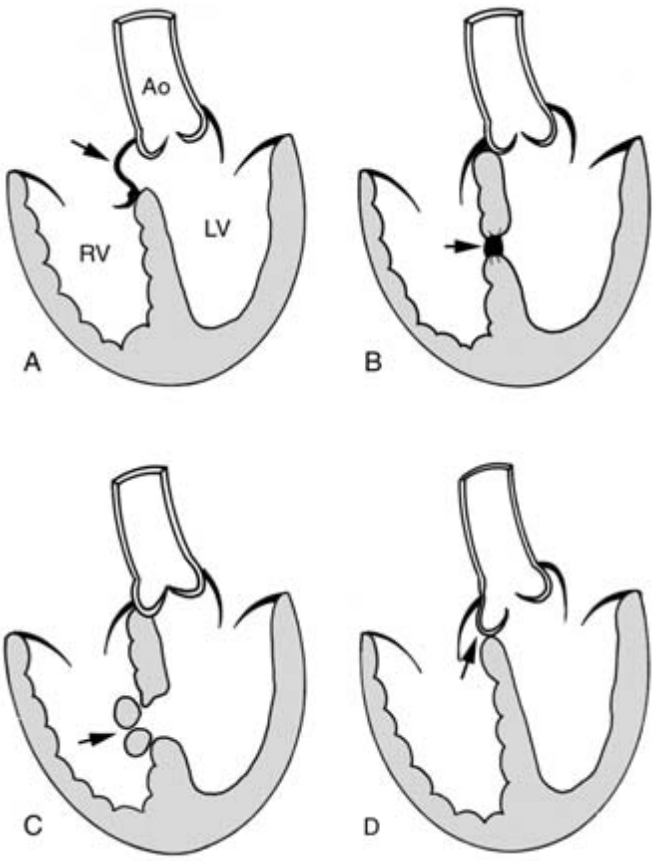


Fig. 3-3 Mechanisms of spontaneous closure of ventricular septal defects. **A.** Closure of a perimembranous defect by adhesion of the tricuspid leaflets to the defect margin. **B.** Closure of a small muscular defect by a fibrous tissue plug. **C.** Closure of a muscular defect by hypertrophied muscle bundles in the right ventricle. **D.** Closure of a defect in subaortic location by adhesion of the prolapsed aortic valve cusp. Ao, aorta; LV, left ventricle; RV, right ventricle.

Although the reports from the First and Second Joint Studies on the Natural History of Congenital Heart Defects are from different eras and use different methodologies in the assessment of the patients with either aortic stenosis, pulmonary stenosis, or ventricular septal defect, these supplements to *Circulation* are far more than just part of our heritage.[96,97] These studies provide a useful, detailed perspective and analysis of the outcomes of patients with these three conditions. From 1958 to 1969, 1280 patients with ventricular septal defect > 2 years of age were admitted to the First Natural History of Congenital Heart Defects after cardiac catheterization.[96] Data published in the first report showed that only 7% of defects had definite

spontaneous closure.[96] This incidence is considerably lower than that presented in many reports, probably reflecting that patients were only enrolled in the study if they were 2 years of age or older, after which age many defects would not have been anticipated to close. Of these 1280 patients, 1099 were alive at the completion of the First Natural History of Congenital Heart Defects, and new data were obtained on 976 (76.3%) of them. The probability of 25-year survival was 87%, and admission severity was the best predictor of survival.[97] The risk of death was influenced by the size of the defect, pulmonary arterial resistance, and clinical status on admission.[97] Patients with trivial, mild or moderate ventricular septal defect (as defined in the study) on admission and who were managed medically, fared well clinically with 94.1% being in New York Heart Association Class I. Even though many of the patients were operated on in an earlier era, most of the patients who underwent surgery were also in a good to excellent status. Those patients admitted to the first study with a large ventricular septal defect and a normal pulmonary vascular resistance had a fourfold higher risk of death when compared to those with a small ventricular septal defect. Somewhat surprising was the observation that nearly 30% of all late deaths were sudden and unexpected, presumably on the basis of a cardiac arrhythmia. Aortic regurgitation is a known event to complicate the course of patients with ventricular septal defect, with the incidence of this complication ranging from 1.4% to 6.3%.[97] The Second Joint Study on the Natural History of Congenital Heart Defects stated that of the 570 full participants, only 12 (2.1%) developed aortic regurgitation.[97] This specific complication is discussed in detail on p. 21.

Most of the patients enrolled in the Second Joint Study on the Natural History of Congenital Heart Defects had medically managed ventricular septal defect, but only *c.* 7% were considered to have clinical or echocardiographic indicators of pulmonary hypertension.[97] This percentage was higher at 13.8% of those requiring surgical intervention, but in whom the ventricular septal defect was considered closed. Many patients considered to have a ventricular septal defect that was clinically small were followed throughout childhood and then into adulthood. The Second Joint Study on the Natural History of Congenital Heart Defects indicated that a number of patients considered by the investigators of the First Joint Study on the Natural History of Congenital Heart Defects not to require surgical intervention, did later require surgery.[96,97] In this regard, Gabriel and colleagues have reported the long-term outcome of 229 patients with ventricular septal defect considered not to require surgical closure during childhood because the defect was considered too small.[98] During childhood, these patients had normal pulmonary artery pressures, < 50% shunt, pulmonary vascular resistance ″ 200 dynes·s·cm^{-5}, and no aortic regurgitation related to ventricular septal defect.[98] Follow-up was completed in 222 patients (97%). The mean age at last visit was 30 ± 10 years. Spontaneous closure of the ventricular septal defect was observed in 14 patients (6%). No patients died, but four patients (1.8%) had an episode of endocarditis, two of whom required aortic valve replacement, and one additional patient (0.4%) had surgical closure for hemodynamic reasons. Of 118 patients entering the study between 1993 and 1996 that were prospectively followed for 7.4 ± 1.2 years, event-free survival with end points defined as death, endocarditis or heart surgery was 99.1 ± 0.8% at 3 years, 96.5 ± 1.7% at 6 years and 95.5 ± 1.9% at 8 years. At last visit, 94.6% of all patients studied were symptom free. Left ventricular (LV) size by echocardiography was normal in 198 (89%) patients, borderline in 23 patients and definitely enlarged in only one patient. None had systolic LV dysfunction, and pulmonary artery pressure (PAP) was normal in all patients. Mean exercise capacity was 92 ± 21% of expected, and 87% of patients had no arrhythmias on Holter monitoring, with the remainder showing benign rhythm disorders. These authors concluded that outcome in well-selected patients with a small ventricular septal defect is good. Surgical closure does not seem to be required during childhood as long as left-to-right shunt is < 50% and signs of LV volume overload are absent, when PAP is not elevated, and no ventricular septal defect-related aortic regurgitation or symptoms are present.

What about the course of the adult patient with a clinically small ventricular septal defect? The data presented by Gabriel *et al.* infer an excellent outlook for the patient with a clinically small ventricular septal defect who transitions from childhood to adulthood.[98] This view is not shared by Neumayer working with Somerville.[74] While the "journey" from childhood to adulthood may be relatively benign, there are some data to suggest that the adult with a small ventricular septal defect is at risk for a number of adverse events. The courses of 188 adults aged 17–72 (mean, 29.2) years with a small ventricular septal defect were reviewed by Neumayer and colleagues.[74] They found that 89 patients (47%) aged 17–44 (mean, 26.8) years had no complications through many years, while spontaneous closure occurred in 19 (10%) during adulthood. However, 46 patients (25%) had serious complications, with infective endocarditis (11%), progressive aortic regurgitation (5%), age-related symptomatic arrhythmias (8.5%), and atrial fibrillation being the commonest. Accepting that there may be a referral bias for those with complications, the course of a small ventricular septal defect is not necessarily benign during adult life. We would agree that these findings reflect that patients were indeed assessed and treated in a referral center, and that the likely outcomes for the majority of such adult patients will be less severe.

Development of right ventricular outflow tract obstruction

Apparent reduction in the magnitude of the left-to-right shunt in ventricular septal defect may reflect acquired right ventricular outflow tract obstruction, a finding firmly established by Gasul and his colleagues *c.* 45 years ago, and then others.[99–101] Data from the First Joint Study on the Natural History of Congenital Heart Disease [70,96] suggest that the incidence of acquired tract obstruction of right ventricular outflow is *c.* 3%, while data from Corone and colleagues[17] suggest a frequency of 7%. The morphological basis for the acquisition of right ventricular outflow tract obstruction in ventricular septal defect has been closely examined.[102] Although hypertrophy and progressive obstruction of a malaligned infundibular septum may result in a narrowed right ventricular outflow tract, usually there is already a substantial pre-existing pressure gradient between right ventricle and pulmonary trunk that progresses over time coincident with changes in the infundibular septum (Fig. 3-4).[102] In patients with a perimembranous ventricular septal defect and only a trivial (< 10 mmHg) pressure gradient between right ventricle and pulmonary artery, hypertrophy of right ventricular muscle bundles is often responsible for the right ventricular outlet obstruction. Coincident with the development of right ventricular anomalous muscle bundles, some patients exhibited

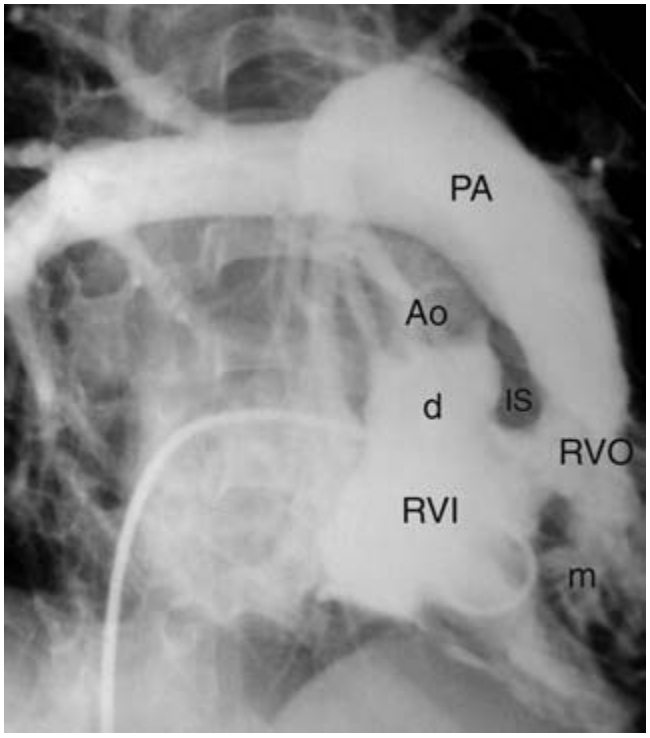


Fig. 3-4 Right ventricular outflow tract obstruction complicating pre-existing matrix. The right ventricle is divided into two parts; right ventricular inlet (RVI) and outlet (RVO) as a result of the hypertrophied infundibular septum (IS) and aberrant muscle bundle (m). Ao, aorta; PA, pulmonary artery; d, ventricular septal defect.

spontaneous diminution in size of the ventricular septal defect.[102] Perhaps one marker of those babies who might acquire right ventricular outflow tract obstruction is a right-sided aortic arch[52] or a more horizontal pulmonary outflow tract.[103] A prolapsing aortic valve leaflet may also obstruct the right ventricular outflow tract (Fig. 3-5).

Aortic valve prolapse

Aortic valve prolapse and subsequent regurgitation are important complications of ventricular septal defects that are in direct contact with the aortic valve, with an incidence ranging from 2% to *c.* 7% in reported series (Figs 3-5 and 3-6).[1,3,7,8,10–11,17,47,49,64,104] Data from the First Joint Study on the Natural History of Congenital Heart Defects suggested that aortic regurgitation was never found during the first year of life.[96] Remembering that these patients were enrolled in the study and with the study published in 1977,[96] the assessment of these patients took place before the era of cross-sectional echocardiography and color flow mapping. Deformity with elongation of the aortic cusp from prolapse is now readily apparent in some patients in the first year of life, and some of these patients may demonstrate with color flow Doppler trivial or more aortic regurgitation. Note that all the perimembranous and doubly committed juxta-arterial defects and most of the muscular outlet defects are virtually in direct contact with the aortic valve.[10,11,47,105–107] Among these subaortic defects, those that have more extensive contact with the aortic valve are the most prone to develop aortic valve prolapse because of the muscular deficiency that inadequately supports the aortic cusps. Aortic valve prolapse usually involves the right coronary cusp, and less frequently the non-coronary cusp (Fig. 3-6). Prolapse of the non-coronary cusp occurs when the defect is a perimembranous type. Involvement of the left coronary cusp is extremely rare. When the muscular support of the valve sinus as well as the valve leaflets is compromised as in cases with a doubly committed juxta-arterial defect or sometimes with a muscular outlet defect, the whole or a part of the valve sinus may prolapse. In its early stage, the prolapse occurs only in the systolic phase because of the "Venturi effect," resulting from the rapid shunt flow through the defect. In later stages, the prolapse also occurs in diastole, as the valve cusp cannot withstand the intraaortic pressure. Eventually the prolapsing aortic valve becomes incompetent because of the significant damage to the valve cusps and annulus. As the prolapsing aortic valve may completely close the ventricular septal defect, the shunt physiology may disappear with the progressive development of aortic regurgitation. Some, or perhaps many, of the cases reported as aneurysms of the sinus of Valsalva might be ventricular septal defects complicated by aortic valve prolapse with complete obliteration of the defect. Rarely, the prolapsed valve cusp may perforate, with resultant aortic regurgitation into the right ventricle.

Left ventricular outflow tract obstruction

Various lesions are responsible for tract obstruction of left ventricular outflow in association with a ventricular septal defect. The obstruction is usually localized above the defect and occasionally below the defect.[108,109] The obstruction may be evident from the immediate postnatal life, may be a progression of the pre-existing lesion that was potentially obstructive, or may be an acquired lesion.[110] The nature of obstruction is either muscular or fibromuscular. Three major structures may be responsible for the muscular subaortic stenosis; the posteriorly malaligned outlet or infundibular septum, the septal deviation or anteroseptal twist, and the anterolateral muscle bundle (see Chapter 14C). The septal deviation or anteroseptal twist is a

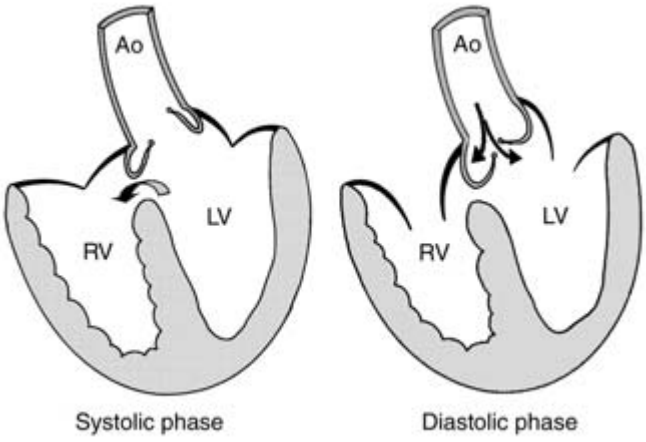


Fig. 3-5 Pathologic mechanism of aortic valve prolapse. The defect in subaortic location is prone to develop prolapse of the adjacent aortic valve cusp because of the Venturi effect, lack of supporting tissue or both. During systole, rapid shunt flow (arrow) through the defect pulls the aortic cusp downward. During diastole, traumatized or unsupported aortic cusp is pushed downward by retrograde flow (arrow) in the aortic root. Malalignment of the aortic valve cusps results in aortic insufficiency. Ao, aorta; LV, left ventricle; RV, right ventricle.

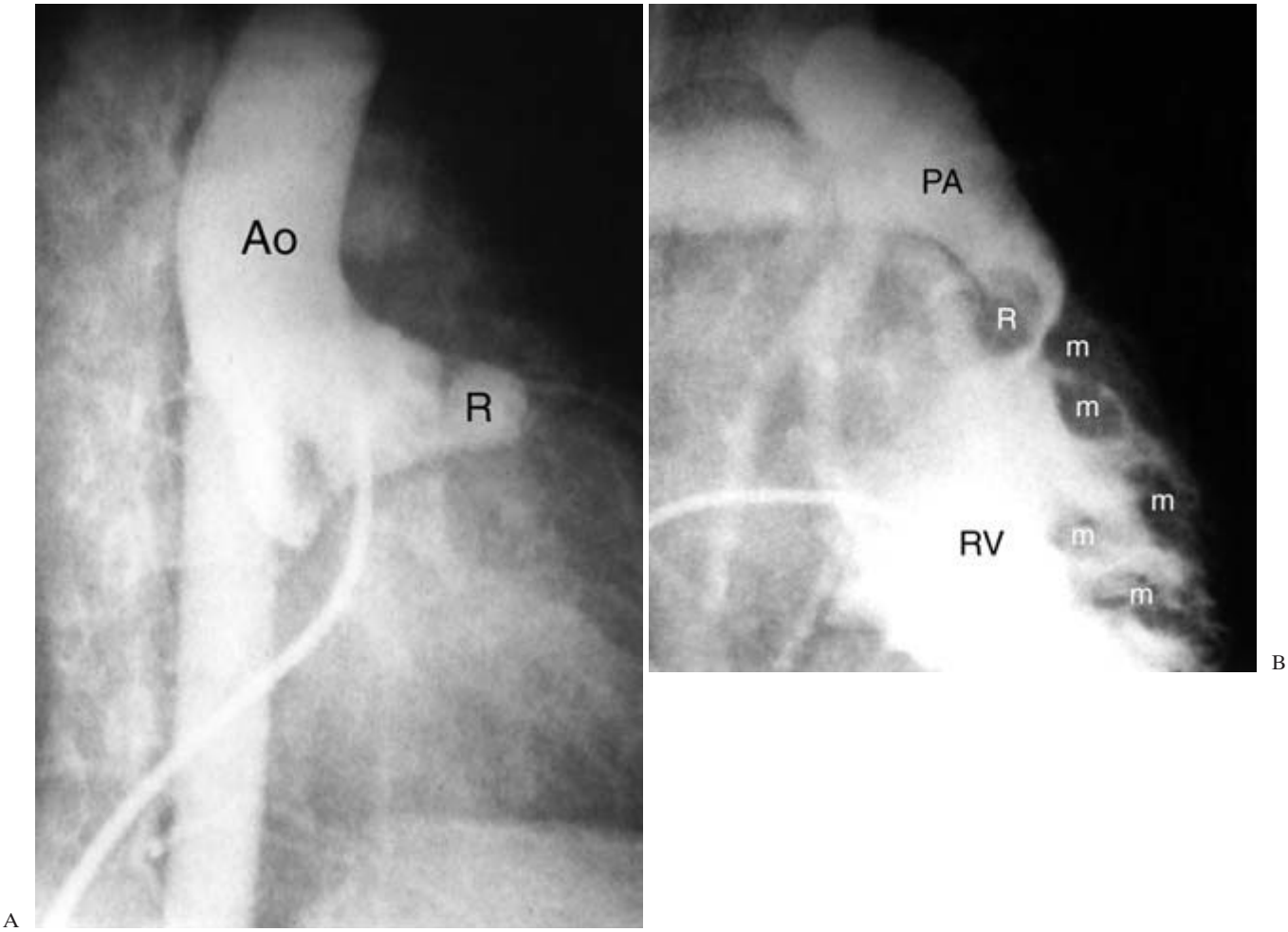


Fig. 3-6 Aortic valve prolapse. Aortogram (**A**) and right ventriculogram (**B**) show the right coronary cusp (R) that is prolapsed into the right ventricular outflow tract through a doubly-committed juxta-arterial ventricular septal defect. The right ventricular outflow tract is narrowed because of a prolapsed aortic cusp and the hypertrophied aberrant muscle bundles (m's) of the right ventricle (RV). Ao, aorta.

muscular protrusion of the left ventricular aspect of the septum along the anterior and superior aspect of the defect.[28,111–113] It is most commonly associated with a central muscular defect and is often associated with additional trabeculae crossing the outflow tract. The anterolateral muscle bundle is a muscular protrusion found between the left coronary cusp of the aortic valve and the anterior leaflet of the mitral valve, extending into the anterolateral wall of the left ventricle.[111–113] It is present in *c.* 40% of normal hearts. When it is unusually prominent in association with a ventricular septal defect, it may cause obstruction of both the left ventricular inflow and outflow tracts. The development or aggravation of muscular subaortic stenosis after pulmonary artery banding has been reported. Rarely, the muscular stenosis is below the ventricular septal defect.[108] The responsible muscle extends along the septal insertion of the anterior mitral valve in a gradual fibromuscular transition, and then the clinical picture simulates a double outlet right ventricle. Very rarely, the abnormal muscular bundle extending from the anterior leaflet of the mitral valve to the septal surface, a kind of the so-called "mitral arcade," is responsible for subaortic obstruction.[114] Discrete subaortic stenosis is most commonly because of a fibrous shelf and less commonly because of a fibromuscular shelf or diaphragm.[115] The fixed short-segment stenosis owing to a fibrous ridge or diaphragm is often associated with spontaneous closure or reduction in size of a perimembranous defect.[109,115,116] It is particularly common when the defect is associated with right ventricular anomalous muscle bundle (see also Chapters 14C and 19A).

Pulmonary vascular obstruction and the Eisenmenger syndrome

A large ventricular septal defect exposes the patient to the risk of developing pulmonary vascular disease, a complex process of vascular remodeling that tends to worsen with age.[10,11,65] This statement assumes survival during infancy. One would hope that pulmonary vascular obstruction and its clinical endpoint, the Eisenmenger syndrome, for the patient with a ventricular septal defect would be relegated to that of a medical curiosity.[117,118] Victor Eisenmenger's signal case description was a 32-year-old man with cyanosis and effort intolerance whose autopsy following an episode of hemoptysis demonstrated a large ventricular septal defect with an overriding aorta.[117] It was Paul Wood who first characterized patients with a wide variety of congenital heart conditions linked together by virtue of pulmonary arterial hypertension and elevated pulmonary vascular resistance,

this constellation being renamed "the Eisenmenger syndrome."[117A] Sadly, the reality is somewhat different, and all large clinical centers will continue to see the rare child with ventricular septal defect and pulmonary vascular obstruction as will the referral center caring for the adult with congenital heart disease.[96,97] It has been well documented that the prognosis for the patient with pulmonary artery hypertension after closure of ventricular septal defect is related to their age at the time of repair and their pulmonary vascular resistance also measured before repair. These two factors relate to outcome and the potential for regression of pulmonary vascular changes.[1,8,10,11,46,65,70–72] Keith, citing his and other earlier publications, estimates the incidence of pulmonary vascular disease in ventricular septal defect to range from 5% to 22%.[146] Again, these observations depend on the age of the patient when first evaluated and the size of the ventricular septal defect.

In the consideration of those indications for operative intervention for the patient with ventricular septal defect is pulmonary artery hypertension and resistance.[10,11,49,65,96,97,119] Also of special concern are those patients whose pulmonary vascular resistance is elevated, but who are still considered operable. This is often a difficult decision, and the pulmonary vascular bed of the patient is challenged pharmacologically to determine its reactivity (nitrous oxide (NO), oxygen, prostacyclin, etc.). Patients with an anatomically small and restrictive ventricular septal defect should not demonstrate important elevations in pulmonary arterial pressures, although several patients have been described with pulmonary vascular obstruction and an unequivocally small ventricular septal defect.[120,121] There is a substantial literature on the mechanisms responsible for causing pulmonary vascular disease in the setting of ventricular septal defect, literature recently summarized by Wilkinson and Tynan & Anderson.[10,11,122–129] As summarized by Wilkinson, the pulmonary vascular changes in children with increased pulmonary blood flow and pulmonary hypertension compose two distinct but overlapping processes.[10] In response to both high pulmonary blood flow and elevated pulmonary artery pressures, pulmonary arterial and venous muscularity increases with extension of muscle more peripherally than normal,[122–128] with the cascade of injury beginning with the endothelial cell.[126] With injury to the endothelial cell, Rabinovitch[126] suggests that this results in an increase in smooth muscle elastase activity. In turn, endogenous vascular elastase releases specific growth factors which induce hypertrophy and proliferation of smooth muscle cells. These stimulate protein synthesis in the connective tissue leading to hypertrophy of the arterial wall.[126] Rabinovitch further suggests that the pulmonary artery hypertension increases elastin and collagen synthesis, and that continued release of elastin leads to smooth muscle migration and further muscularization of the pulmonary vascular bed.[126] In addition, there is a reduction in the size and number of intra-acinar arteries, with occluded alveolar wall arteries, probably reflecting hyperplasia and hypertrophy of differentiating smooth muscle cells in the small, normally thin-walled precapillary segments. These changes result in poor growth and reduced branching in the acinus, and also the total capacity of the pulmonary arteriolar circulation is progressively reduced.[10,122–129] These changes are considered reversible in the first 6 months or so. The second phase or process occurs gradually over many months or years, concluding in the clinical condition of Eisenmenger's syndrome: pulmonary hypertension, pulmonary vascular obstruction and a reversed shunt.[10,117,118,122–128] Progressive intimal thickening with pre-existing medial hypertrophy sets the stage for vascular occlusion, both from intimal thickening and intravascular thrombosis. Intimal proliferation tends to develop towards the end of the first year of life, with fibrosis following. New vessel formation in areas of vascular obstruction leads to the formation of complex so-called plexiform lesions.[10,11,122–129] This process continues to evolve, usually over many years, initially reducing the magnitude of the left-to-right shunt, but with progressive pulmonary vascular obstruction and the increasing pulmonary vascular resistance, the shunt eventually reverses.[117,118] There has been the suggestion that patients with Down syndrome are more likely to develop pulmonary vascular disease at an earlier age than those without Down syndrome (see Chapter 5).

It is unclear what percentage of all patients with ventricular septal defect are potential candidates for pulmonary vascular disease, but it is probably < 10%. Many of those potential candidates if not appropriately treated (i.e. repaired) would succumb in the first year of life with congestive heart failure, failure to thrive, and pneumonia. A considerable literature about the course of patients with Eisenmenger syndrome has accumulated over the years, and with the advent of heart–lung, and double-lung transplants, the life of some of these patients can be extended. Niwa and colleagues have reviewed the outcomes of 47 adult patients with Eisenmenger ventricular septal defect.[118] These patients ranged in age from 23 to 69 years, with a mean 39.5 ± 10.2 years, and the length of follow-up ranged from 5 to 18 years, mean 7.2 ± 4.9 years. Of these 47 patients, 68% had absent or mild pulmonary regurgitation and 32% moderate to severe.[118] Tricuspid regurgitation was absent to mild in 55%, and moderate to severe in 45%; right ventricular wall motion abnormalities were evenly distributed and left ventricular ejection fraction was normal in all.[118] The hematocrits on referral ranged from 49% to 72%, with a mean of 61 ± 7%. Eight patients were iron deficient, and despite platelet counts in the normal range, 55% had cutaneous bleeding; 61% gingival bleeding, and 11% epistaxis. Hemoptysis recurred in 27 patients (57%) and was severe in 17 (36%). Eighteen patients were shown by computerized tomography to have large *in situ* pulmonary thromboses, six of whom had moderate to marked mural calcification. Proximal pulmonary arterial thrombus embolized in two patients, resulting in hemorrhagic pulmonary infarction. Nearly 75% of the patients had proteinuria, 72% had blood urea nitrogen and serum creatinine levels in the normal range, and nearly 60% had elevated uric acid levels. Eight patients (17%) were found to have gallstones, and 23% gouty arthritis. Supraventricular tachyarrhythmias occurred in 13% of these patients. Fourteen patients died at ages 26–69 years, mean age at death 45 ± 5 years. Ten of these 14 (71%) patients died suddenly, and nine of these 10 underwent an autopsy. The causes of the sudden death was massive intrapulmonary hemorrhage in two, rupture of an aneurysmal pulmonary trunk in one, dissection of the ascending aorta in one, and the cause of death was not established in three patients. One other autopsied patient died of a vasospastic cerebral infarct resulting from an intractable migraine headache.[118] Interestingly, infective endocarditis did not occur during the period of surveillance of these patients with ventricular septal defect and Eisenmenger syndrome. Similar findings had been published many years earlier by Clarkson, her colleagues and others.[130,130A]

The outcome of some patients with ventricular septal defect and heart failure was improved by the administration of digi-

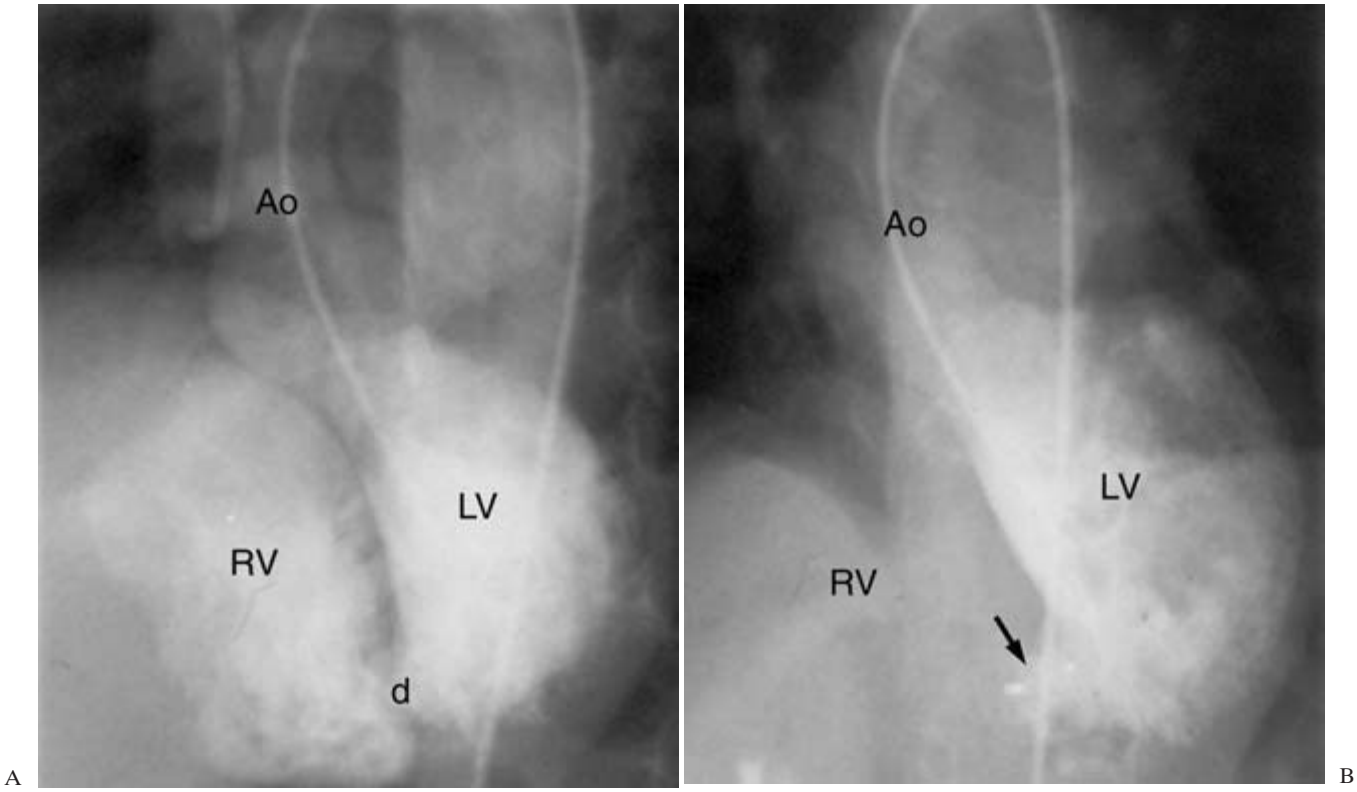
talis and diuretics, although for more than two decades, the role of digitalis has been questioned.[131–137] These therapeutic agents were particularly helpful in those patients with a moderate-sized defect, ones that still had the possibility of spontaneous diminution in size. More recently, there has been interest in the use of systemic afterload reduction.[10,11] In the era before palliation or repair, most babies with large defects succumbed, with a few gradually developing pulmonary vascular obstruction. The signal contribution to the palliation of the patient with a large ventricular septal defect was published just over 50 years ago by Muller & Dammann.[138] They advocated constricting the pulmonary artery. An adequate pulmonary artery band would reduce the pulmonary arterial pressure distal to the band, with a concomitant reduction in pulmonary blood flow. It was often difficult to define the level of constriction to achieve the desirable result, and in the presence of a large interatrial shunt, too tight a band could result in severe hypoxemia. Trusler & Mustard provided some guidelines, depending on whether the great arteries were normally connected or transposed.[139] The pulmonary artery band used in Toronto was radio-opaque. It is marked to a length of 20 mm plus the number of millimeters corresponding to the weight of the child in kilograms. But pulmonary artery banding also had its own deleterious effects, including distal migration and narrowing or occlusion of a pulmonary artery branch, usually the right; infundibular hypertrophy and obstruction; left ventricular outflow tract obstruction; erosion of the band into the pulmonary artery; mycotic aneurysm, etc.[140–145] There was mortality associated with pulmonary artery banding, usually < 10% for patients with isolated ventricular septal defects. Horowitz and his colleagues of the Ochsner Clinic reported a 25-year experience (May 1962 to April 1987) with pulmonary artery banding in 183 patients. This procedure was performed in a heterogeneous group of patients aged from 2 days to 60 months (median, 10 weeks; mean, 21.8 weeks) and weighing 1.4–13.8 kg (mean, 4.2 kg). A ventricular septal defect in isolation was identified in 41.5% of these patients. For the entire group, the mortality was 22.3%.[145] Keith, reviewing the available literature in 1978, stated that reported mortalities for pulmonary artery banding for ventricular septal defect varied from 5% to 35% depending on case selection.[146] Interpreting and extracting data from Weidman *et al.* in 1977, the calculated early and late mortality for pulmonary artery banding was 17%.[70] In 1984, Albus and his colleagues reported the Toronto experience with pulmonary artery banding from 1972 to 1982.[141] The banding mortality for those with a ventricular septal defect was *c.* 3%. Furthermore, in some patients after pulmonary artery banding, the ventricular septal defect went on to spontaneous closure, and still other patients developed pulmonary vascular obstructive disease.[147–152] In this latter situation, the pulmonary artery band may have been inadequate from the start, or banding was carried out in the patient with pulmonary vascular disease already present. In 1955, a few years after Muller & Dammann's publication, a group of surgeons reported the first successful closure of a ventricular septal defect at the University of Minnesota.[153] During the next 15 years, most infants with large ventricular septal defects were palliated with banding, and the method of direct closure was performed in older children. Kirklin and his associates at the Mayo Clinic first closed a ventricular septal defect using a heart–lung machine in 1955,[154] and the surgical approach from a right ventriculotomy to transatrial closure took place in 1957.[155] Okamoto was apparently the first to report in 1969 a routine closure of ventricular septal defects in infancy, using profound hypothermia and total circulatory arrest with rewarming by the pump oxygenator.[156] In 1969, Barratt-Boyes and his colleagues advocated the primary repair of symptomatic infants with large ventricular septal defects with the use of deep hypothermia and circulatory arrest along with cooling and rewarming on cardiopulmonary bypass.[157] Just over 30 years ago in February 1972, the Second International Symposium on Surgical Heart Disease was held at the Green Lane Hospital in Auckland, New Zealand, and the proceedings of this historical symposium published the following year.[158] Thus began the era of primary repair of congenital heart defects in the neonate. But as surgical techniques and indeed the entire "platform" and infrastructure for performing heart surgery continued to evolve and improve, so did the methodologies to evaluate and image congenital heart defects. By 1973, cardiac catheterization with angiography had been routinely used for more than two decades in the investigation of the patient with a ventricular septal defect, but the introduction of axial angiocardiography in 1977 added a new dimension and ability to image complex ventricular septal defects.[159–165] By the mid 1980s, cross-sectional echocardiography and later color flow Doppler imaging had begun to obviate the need for routine angiographic imaging, and patients with ventricular septal defect and other more complex anomalies were referred to surgery on the basis of echocardiographic imaging alone.[166–175] Intraoperative epicardial and transesophageal echocardiography provided even more information, and immediate postoperative transesophageal echocardiography performed in the operating theatre identified important residual ventricular septal defects.[176,177] This latter technique has certainly reduced the requirement for late reoperation.

Thus as one surveys clinical surgical experience and outcome, the results reflect the era in which surgery was conducted, the type and number of ventricular septal defects, the surgical approach to the defect (transatrial, right ventricular, transpulmonary, transaortic, via left ventriculotomy or apical ventriculotomy), the methodologies used in postoperative follow-up, etc. In the late 1960s and early 1970s, those institutions participating in the First Joint Study of Congenital Heart Defects performed pulmonary artery banding in 75% of infants requiring surgery.[96] Today, pulmonary artery banding is used only in exceptional circumstances including some patients with so-called Swiss-cheese type of ventricular septal defect and certain types of apical ventricular septal defect. Primary repair of the isolated ventricular septal defect has been favored for more than two decades, with ever improving results.[10,11,65,178–184] Currently the surgical mortality for repair of an isolated ventricular septal defect is < 1%.[65] Early postoperative deaths from pulmonary vasoconstrictive crises in those patients with some degree of pulmonary vascular disease have been reduced by monitoring of postoperative pulmonary artery pressures and the use of pulmonary vasodilating agents, especially NO.[10,11,65] As indicated earlier in this chapter, most perimembranous defects are closed using a transatrial approach working across the tricuspid valve.[65] In some patients, however, the margins of the defect are obscured by chordal attachments of the tricuspid valve. Hudspeth and his colleagues in 1962 first published the maneuver of detaching the tricuspid valve to improve exposure of the defect.[185] This has proven a safe and effective way to facilitate closure without increasing the risk of heart block, or late tricuspid stenosis or regurgitation as pointed out in a number

of publications.[186–192] Others have reported excellent results of transatrial repair of the ventricular septal defect without tricuspid valve detachment.[188]

There remains considerable discussion about the most appropriate approach to the patient with multiple ventricular septal defects and the patient with some kinds of apical ventricular septal defects, as the repair of these defects is associated with greater mortality and morbidity.[65,184–205] Historically, some have advocated exposure and closure of some muscular defects and multiple and Swiss-cheese defects through a left ventriculotomy.[65,206–211] While there seemed initially some enthusiasm about this approach because of the ease of exposure of the defects, for the most part it has been abandoned because of concerns about late left ventricular dysfunction, arrhythmias, residual shunts, and left ventricular or apical aneurysm formation. Other newer surgical approaches have been described for patients with multiple muscular defects including moderator band resection, oversized patches, a "sandwich" double patch method, a single patch technique with intermediate fixings, septal obliteration technique using cardioscopy, or the use of a right ventricular apical infundibulotomy.[184–204] But as Black has stated, "The myriad of approaches is testimony to the lack of superiority of any one method."[199] Serraf and his colleagues reported in 1992 an experience with the surgical management of 130 patients with isolated multiple ventricular septal defects, an experience encompassing 1980 through September 1990.[197] The perimembranous septum was involved in 102 patients, the trabecular septum in 121, the inlet septum in 12, the infundibular septum in nine and 50 patients had the Swiss-cheese form of the lesion. Using a variety of surgical approaches, the surgical mortality was 7.7% (10 patients). Eighteen patients were found to have residual defects, six requiring reoperation with two deaths. A permanent pacemaker was required in four patients. Low trabecular defects (i.e. those inferior to the moderator band) and a left ventriculotomy were significant risk factors for morbidity including death and residual defects.[197] At 7 years of follow-up, 90% of survivors were in New York Heart Association class I. Actuarial survival and freedom from reoperation at 7 years was 89.6% and 87.5%, respectively. Excellent results have also been reported by Kitagawa and colleagues, who repaired 33 patients with multiple ventricular septal defects between January 1988 and October 1996.[198] In the entire experience of patients with isolated multiple ventricular septal defects including those with complex associated lesions, one hospital death occurred in a patient with double outlet right ventricle and left ventricular hypoplasia, and two patients from the group with complex associated lesions sustained complete heart block.[198] Seddio and his colleagues reported in 1999 an experience with 45 patients from 1992 to 1998 with multiple ventricular septal defects.[193] The mean number of defects was 3.7 and the median age at repair was 86 days. None of their patients required a ventriculotomy and this experience supports their view that most multiple defects can be repaired in infancy, although with a severely Swiss-cheese septum, they wondered whether banding is a safer option.[193] Apical ventricular septal defects are difficult to visualize through the tricuspid valve and to close transatrially.[200–204] There has been considerable interest in this particular type of ventricular septal defect.[200–204] Kumar and colleagues, Stellin and his colleagues, and Van Praagh and her colleagues have fully characterized the morphology of these defects and have shown that excellent exposure of the defects is achieved through a small apical infundibulotomy.[200–202] They have shown that these particular defects occur between the left ventricular and the infundibular apex rather than between the left and right ventricular apices.[200–203] Tsang and his colleagues believe that this defect results from incomplete compaction of the apical muscular septum, leaving a large hole within its apical part.[203] They also suggest that the adherence of the coarse apical trabeculations within the right ventricle to the septal surface serves to provide this solitary defect in the septum with multiple right ventricular orifices.[203] These defects do not lend themselves to transcatheter closure. In this regard some have advocated transcatheter closure of muscular and/or multiple ventricular septal defects in the catheter laboratory using any of a variety of devices, while others have reported intraoperative device closure of muscular ventricular septal defects (Fig. 3-7).[212–215] For the patient with an isolated perimembranous defect or a single defect in the inlet septum or muscular outlet septum, important residual defects are seldom encountered, especially with the almost routine application in many centers of immediate postoperative transesophageal echocardiography. This is a significant departure from the experience recorded more than two decades ago in the First Joint Study of the Natural History of Congenital Heart Defects,[70,96] and that from Johns Hopkins published a few years earlier by Ho and his colleagues.[216] In the former study, about 20% of children had residual shunts, and this increased to 40% in infants.[70,96] We have recently reviewed our experience with the repair of 180 patients with diagnosis of multiple ventricular septal defects and biventricular heart between January 1982 and January 2002.[216A] The effect of potential dichotomized morphological and procedural variables, as well as those indicative of the extent of ventricular septal deficiency, were analyzed with respect to the outcome variable, death at any time, using Cox proportional hazards time-related multivariable regression analysis. The most frequent associated lesions include aortic arch obstruction (n = 32), transposition of the great vessels (n = 20), atrioventricular septal defect (n = 10), double outlet right ventricle (n = 8), tetralogy of Fallot (n = 10), and truncus arteriosus (n = 5). Thirty deaths occurred including six before the index operation directed to surgical repair of the ventricular septum: the actuarial survival rate was 75.3% ± 6.85% at 12 years postoperatively. There were only five reoperations for residual ventricular septal defects (one late death), and the freedom from reoperation for any indication was 90.2% at 10 years postoperatively. Complete heart block (CHB) occurred in 22 (12.6%) eligible patients, and this complication was more common in those patients with highly deficient septa (perimembranous plus two or more muscular defects). In our series, survival following surgical repair of multiple ventricular septal defects is dominated by the effect of major associated cardiovascular lesions rather than the extent of ventricular septal deficiency and the specific technical management *per se*.

In most infants with a large ventricular septal defect, pulmonary artery hypertension, and a large pulmonary blood flow, the pulmonary vascular resistance is usually normal, or just mildly increased. With closure of the defect in this situation, the pulmonary vascular bed gradually remodels in an advantageous way, resulting in normal hemodynamics. Data from the First Joint Study indicated that a few children whose preoperative pulmonary artery resistance was only slightly elevated demonstrated a significant increase in resistance postoperatively, some to the point where they were considered to have Eisenmenger syndrome.[70,96] In this regard, of 564 patients with ventricular



A B

Fig. 3-7 Device closure of the muscular defect in the trabecular ventricular septum. **A**. Left ventriculogram in left anterior oblique view shows a defect (d) in the apical part of the interventricular spetum. **B**. The defect was closed by placing an Amplatzer device (arrow). Ao, aorta; LV, left ventricle; RV, right ventricle.

septal defects treated medically, only 12 children, whose mean pulmonary artery pressure was 50 mmHg on admission, had cardiac catheterization pressures higher than those at the final catheter investigation.[70] In the Second Natural History study, 54% of 98 non-operated patients with ventricular septal defect and Eisenmenger syndrome were alive 20 years after the initial diagnosis.[70,96] From Clarkson's earlier study, the probability of survival 5 years after diagnosis for patients 10–19 years of age was 95%, and for patients > 20 years, it was 56%.[130] Oyo and colleagues have addressed the poor prognosis of adults recognized to have Eisenmenger syndrome as aduts.[130A] The patients were diagnosed as having the Eisenmenger syndrome at a mean age of 35 ± 2 years, ranging from 15 to 68 years. The mean survival time from diagnostic cardiac catheterization to death was 5.4 years. Survival rates of all 106 patients in this study were 98% at 1 year, 77% at 5 years, and 58% at 10 years. The authors found that elevated right atrial pressures and low systemic blood flow were independent predictors of mortality.[130A]

One tries to avoid operation in patients whose pulmonary vascular disease is likely to progress after closure of the defect. As pointed out by Somerville the prognosis for patients with elevated pulmonary vascular resistance who undergo closure of their defects is worse than for Eisenmenger patients without repair but with the same congenital heart condition.[127] This may prove to be a difficult decision, and pulmonary artery wedge angiography as advocated by Rabinovitch and her colleagues[122] or lung biopsy may be used to arbitrate this decision.[123–125,128,217] None the less, there will be some patients with pulmonary vascular disease whose ventricular septal defect has been surgically closed with the hope that the pulmonary vascular disease will regress.[1,10,11,49,65,70–72,218–220] Obviously the results of such actions are variable, but when the patient is older at the time of operation, it is more likely that the vascular obstruction will increase. This is not invariably true as even in some infants and young children with ventricular septal defect, there may be rapidly progressing pulmonary vascular obstructive disease.[221] When one reviews the clinical courses of patients enrolled in the First Joint Study[96] with large ventricular septal defect, elevated pulmonary artery pressures but normal pulmonary resistance who underwent surgical closure, none developed Eisenmenger's syndrome, although 15% had some degree of residual pulmonary artery hypertension. Of 41 patients admitted with large ventricular septal defects and increased pulmonary vascular resistance that was managed surgically, one developed Eisenmenger's syndrome and 17.5% had residual pulmonary artery hypertension.[70] One tends to be more optimistic regarding regression of pulmonary vascular disease in the young infant and child, although such optimism is not always warranted.[221]

There is an exhaustive literature on the morphology of ventricular septal defects associated with aortic valve prolapse and regurgitation, on the morphology of the aortic valve in this situation itself, on the natural history of the ventricular septal defect with aortic valve prolapse, surgical techniques dealing with prolapse and/or regurgitation and late follow-up.[1,3,10,11,17,37,47,49,65,70,104–107,222–245] Numerous reports document the progressive nature of aortic valve deformity and subsequent regurgitation in patients with either a perimembranous or doubly committed subarterial ventricular septal defect.[1,3,10,11,17,37,47,49,65,70,104–107,222–245] Some cardiologists have made the observation that the longer the duration of aortic

regurgitation, the more the morphologic changes to the aortic valve, and this tends to decrease the flexibility of the valve as well. There are many reports on the long-term results of aortic valvuloplasty for ventricular septal defect and aortic regurgitation.[222–245] Most agree that for the patient with the doubly committed subarterial ventricular septal defect, it is best to close the defect before there is frank prolapse or regurgitation. Backer, DeLeval, Komai and their respective colleagues have stated that once the diagnosis of doubly committed subarterial ventricular septal defect is established, the patient should undergo immediate operation.[229,234,246] Komai and his colleagues found that no patient without aortic regurgitation developed regurgitation in the early or late follow-up period.[229] Lun and colleagues have also analyzed the indications for closure of the doubly committed subarterial ventricular septal defect without associated aortic cusp prolapse and aortic regurgitation in 214 patients followed for 8.6 ± 5.2 years between 1975 and 1999.[243] Similar to the experience of Komai,[229] no patient without aortic valve prolapse before operation developed prolapse after operation.[243] Of 139 patients managed conservatively, 102 (73%) developed aortic cusp prolapse, 78% of whom developed aortic regurgitation. The prevalence of aortic valve prolapse and aortic regurgitation at 1, 5, 10, and 15 years old was 8%, 30%, 64%, and 83%, and 3%, 24%, 45%, and 64%, respectively. All patients with aortic valve prolapse had a defect size of ≥ 5 mm. On the basis of these data, they recommended that the doubly committed subarterial ventricular septal defect ≥ 5 mm should be closed as early as possible to prevent aortic valve prolapse and regurgitation. Lun and colleagues felt that the asymptomatic patient with small defects < 5 mm could be managed conservatively.[243] Once there is aortic valve prolapse and regurgitation, a number of techniques have been used to restore the integrity of the valve.[243] Many surgeons use the technique initially published by Trusler and his colleagues in 1973,[224] with their surgical results extended to 1992.[225] In the consideration of those risk factors for failure of aortic valvuloplasty in patients with aortic regurgitation and ventricular septal defect, Elgami and colleagues identified the degree of aortic regurgitation at hospital discharge, direct closure of the ventricular septal defect, smaller size of the defect and plication of more than one end of the prolapsed cusp(s) as possible risk factors for valvuloplasty failure.[238] Hisatomi and colleagues have also addressed the issue of direct closure of the doubly committed subarterial ventricular septal defect, but they concluded that this technique was safe and reliable in improving mild aortic regurgitation.[231] Although either patch closure or direct closure of the doubly committed subarterial ventricular septal defect in the patient without prolapse prevents later aortic valve deformity, once there is aortic regurgitation, simple closure of the defect is unlikely to prevent progressive aortic regurgitation, and also aortic valvuloplasty may not suffice to prevent progressive aortic regurgitation.[231] This view is not shared by all. Cheung and colleagues have reported on the impact of preoperative aortic cusp prolapse on the long-term outcome after surgical closure of the doubly committed subarterial ventricular septal defect.[242] Their clinical experience did not support the need for aortic valvuloplasty for mild to moderate aortic cusp prolapse, with their caveat that close follow-up is warranted.[242] Trusler and his colleagues have reported the late results after repair of aortic insufficiency associated with ventricular septal defect in 70 patients operated on between 1968 and 1988.[225] In this series, the ventricular septal defect was perimembranous in 50 patients and doubly committed subarterial in 20. In this experience, patient survival was 96% at 10 years. Freedom from valvuloplasty failure and freedom from reoperation were 76% and 85%, respectively, at 10 years.[225] There are some as yet unresolved questions regarding certain management issues and these have been summarized by Graham & Kavanaugh-McHugh.[246A] It is well known that since the introduction of color Doppler, some patients without an audible murmur of aortic regurgitation will have echo Doppler evidence of aortic regurgitation. In the asymptomatic patient with a doubly committed subarterial defect and aortic regurgitation noted only by color Doppler, we would agree that surgical repair is probably indicated. There is less evidence for this approach in the patient with a small perimembranous defect, unless there is unequivocal evidence of cusp prolapse or distortion. Thus we would not operate on the patient with a small perimembranous defect, normal pulmonary artery pressures and a Qp/Qs ratio < 1.5/1 with only color Doppler evidence of aortic regurgitation and an aortic valve that seems normal. We would follow this patient carefully with attention focused on the form and function of the aortic valve. Finally, one of the unusual early complications occurring in the patient with residual aortic regurgitation following repair of ventricular septal defect with aortic incompetence is mechanical hemolysis, a type of "waring blender syndrome" (see Chapter 5).[247] The cause of hemolysis was considered to be the result of the aortic insufficiency jet against the VSD patch. The hemolysis ceased after two reoperations to improve and eliminate the aortic regurgitation.[247]

Infective endocarditis

Infective endocarditis is a well-known risk for the patient with a ventricular septal defect, and can also occur after surgery in the patient with a residual defect.[248–256] One population-based study reported an overall bacterial endocarditis incidence rate of 0.38 per 10 000 person years.[250] From the First and Second Joint Studies on the Natural History of Congenital Heart Defects, 32 patients with ventricular septal defect of the 1347 patients admitted to the studies with a diagnosis of ventricular septal defect and followed for a total of 22 077 patient years developed endocarditis.[256] This gave an overall incidence of 14.5 per 10 000 person-years of follow-up. When one attempts to define the incidence of endocarditis stratified by operated vs. non-operated, the findings are interesting. The incidence of endocarditis in patients operated for a ventricular septal defect was 7.3 per 10 000 person-years of follow-up. In contrast, for patients with non-operated ventricular septal defect, the incidence of endocarditis was 18.7 per 10 000 person-years of follow-up.[256] The risk of endocarditis is probably higher in those with a smaller defect, and furthermore the risk is probably lower during childhood, increasing in the adolescent and adult. Patients with a proven episode of endocarditis are considered at increased risk for recurrent infection. Also, many cardiologists would recommend surgical closure of the small ventricular septal defect after a previous episode of proven endocarditis.[252].

We have discussed earlier in this chapter the observations about the development of right ventricular or left ventricular outflow tract obstruction occurring as facets of the natural history of non-operated ventricular septal defect. Occasionally after closure of a ventricular septal defect, late development of right ventricular outflow tract obstruction is documented.[257] The basis for this obstruction is related to the hypertrophy of pre-

existing anomalous muscle bundles in the right ventricule.[102] It is probable that a small pressure gradient across the right ventricular outflow tract preoperatively has been attributed to high flow, rather than to anomalous muscle bundles. After closure of the ventricular septal defect, further hypertrophy of the anomalous muscle bundles continues to divide the right ventricle promoting important obstruction between the inlet and outlet components of the right ventricle. Similarly, late outflow tract obstruction of the left ventricle may occur after ventricular septal defect closure.[258,259] This has been documented in the patient with both the perimembranous and doubly committed subarterial ventricular septal defect.[260,260A] In the former situation a divided right ventricle was also present, and thus one might anticipate a left ventricular fibrous ridge.[261,262] In the latter situation, both subaortic and subpulmonary ridges have been identified, promoting the substrate for outflow tract obstruction.[260] Grunenfelder and colleagues reported severe left ventricular outflow tract obstruction following repair of a subsemilunar conal septal defect, probably resulting from a redundant patch.[260A] From our own experience and from published reports, development of outflow tract obstruction of either the right or the left ventricle following repair of a ventricular septal defect is uncommon.

What are the indications to close a truly restrictive ventricular septal defect? A patient with such an unequivocally restrictive defect should have a normal chest radiograph, normal pulmonary artery pressures, and a left ventricular end diastolic dimension within the normal range. At first, what seems to be a small ventricular septal defect at one age may have more of a clinical impact as the patient ages, perhaps reflecting a change in ventricular compliance. The patient with a small perimembranous ventricular septal defect or the small muscular outlet defect and who develops unequivocal evidence of aortic valve prolapse and aortic regurgitation would probably benefit from surgery, assuming one can exclude a primary commissural abnormality of the aortic valve. We also agree with L'Ecuyer & Embrey that a patient with a small, clearly restrictive ventricular septal defect who has had a proven episode of endocarditis should undergo closure of that defect once the infection has been adequately treated.[252] We question whether the patient with a small, restrictive perimembranous ventricular septal defect with left ventricle to right atrium shunting should be considered for surgical intervention. These patients may demonstrate rather impressive dilation of the right atrium[10,11,36A,37] and we have seen such patients develop atrial flutter/fibrillation, presumably on that basis.

Conduction disturbances after repair of ventricular septal defect

Complete block of the right bundle branch is a known consequence of surgical closure of the ventricular septal defect.[10,11,65,263–267] In some studies,[265] but not all,[263,264,266,267] this complication occurred much more frequently in the era of transventricular repair when compared to the transatrial route. Hobbins and her colleagues found that complete block of the right bundle branch developed in 13 of 39 children (33.3%) undergoing transatrial repair, compared with 15 of 19 children (78.9%) undergoing repair via a right ventricular incision.[265] This was a statistically significant reduction in complete block of the right bundle branch in the former group. The incidence of left axis deviation occurring with complete block of the right bundle branch was similarly statistically reduced. Transient complete heart block and arrhythmias were not statistically different in the two groups. These results were not confirmed by Abe & Komatsu who also studied conduction disturbances after closure of ventricular septal defects by three different surgical approaches.[266] They found that the transpulmonary approach had the lowest incidence of complete block of the right bundle branch postoperatively, but that there was no significant difference in the incidences of complete block of the right bundle branch between the transatrial and transventricular approaches. Complete block of the right bundle branch and left axis deviation occurred in nearly 4% of patients undergoing transatrial repair and in *c.* 11% of those undergoing transventricular repair of ventricular septal defect.[266] Even earlier, Okoroma had found similar incidences of complete block of the right bundle branch in patients whose ventricular septal defect had been closed either transatrially or via a right ventricular incision, acknowledging either more proximal or peripheral injury to the right bundle.[263]

In the early years of surgical closure of ventricular septal defect, complete heart block was not an uncommon complication, although even in that era some had a very low incidence of this complication.[65] Knowledge about the course of the specialized conduction tissue was important in reducing the incidence of this complication. Kirklin & Barratt-Boyes[65] attribute early identification of the specialized conduction tissue in ventricular septal defect to Truex as important to reducing this complication.[268] Other publications followed defining with clarity the nature of the atrioventricular conduction tissue in ventricular septal defect and the results of injury.[269–277] Complete heart block occurred in 2% of the patients repaired by those institutions participating in the First Joint Study on the Natural History of Congenital Heart Defects.[70,96] The contemporary incidence of surgically-induced complete heart block for simple ventricular septal defects is < 1%, but somewhat higher in patients with multiple muscular or Swiss-cheese defects.[65] Many reports note the development of transient complete heart block in the early postoperative period, with reversion to sinus rhythm before hospital discharge.[278–280] In most patients, sinus rhythm is regained. Weindling and colleagues note that in 97% of patients with early onset complete heart block, sinus rhythm returned within 9 days.[279] Unfortunately, some patients develop complete heart block many years after surgery, having been discharged after the initial surgery in sinus rhythm.[281,282]

Cardiopulmonary and exercise testing has been performed in patients with small ventricular septal defects, and in patients with operated ventricular septal defects.[219,220,283–290] Many of these studies show some abnormalities when compared to a control population. Some of the abnormalities have been identified in the individual with a small, non-operated ventricular septal defect, and in the patient repaired during childhood.[283–290] Impaired function and abnormal exercise testing has been attributed to the effects of chronic volume loading on the left ventricle, and perhaps to inadequate myocardial protection.[287,288] The data from Maron and his colleagues lends some support to these observations because their data showed a relation between older age at operation and abnormal reduction of cardiac output.[290] Using equilibrium gated radionuclide angiography, Jablonksky and colleagues studied ventricular function in three groups of patients: group 1, patients with small ventricular septal defects and Qp/Qs < 2-to-1; group 2, previously surgically closed ventricular septal defects; group 3, Eisen-

menger ventricular septal defects.[283] They found that all study groups failed to demonstrate an increase in ejection fraction in either ventricle with exercise. Furthermore, resting left ventricular ejection fraction in groups 2 and 3 was lower than that in the control subjects and resting right ventricular ejection fraction was lower in group 3 vs. control subjects (0.30 ± 0.07 vs. 0.46 ± 0.06; $P < 0.001$). Thus left and right ventricular function on exercise were abnormal in patients with even a small ventricular septal defect when compared to control subjects. Left ventricular ejection fractions during resting and exercise remained abnormal despite surgical closure of the ventricular septal defect in the remote past; and resting left and right ventricular function was abnormal in patients with Eisenmenger's complex. Jablonksky and colleagues suggested that lifelong volume overload could be responsible for these findings and thus detrimental to myocardial function.[283] Otterstad and his colleagues using a standardized ergometer bicycle test also found that patients with small non-operated ventricular septal defects and those who had undergone closure of their defects had impaired left ventricular function based upon hemodynamic studies during moderate supine exercise.[287,288] The poorest results in this study were found in operated patients with residual ventricular septal defects.[287] Driscoll and his colleagues in the report from the Second Joint Study on the Natural History of Congenital Heart Defects found that patients with ventricular septal defects tended to exercise below the predicted levels for age.[289] They also found that the per cent predicted exercise time was related significantly to age and to final clinical status. Also, they found that mean per cent predicted maximum heart rate was less in the ventricular septal defect patients when compared to a control population, as stated in earlier reports.[218] Hallidie-Smith and her colleagues also studied the medium-term postoperative outcomes of patients with large ventricular septal defects whose pulmonary vascular resistance was at least 8 units.[220] While most showed a fall in pulmonary artery pressures and pulmonary vascular resistance, most had some evidence of pulmonary vascular disease with a rise in pulmonary artery pressures with mild exercise.[220] Hallidie-Smith and her colleagues have also reviewed the functional status of patients with large ventricular septal defects and pulmonary artery hypertension 6–16 years after surgical closure of their defects which had taken place at 3–12 years of age.[218] All the patients led normal unrestricted lives and most denied any symptoms. When exercised during the postoperative cardiac catheterization, however, most demonstrated striking pulmonary hypertension when compared to their own resting basal level of systolic pulmonary artery pressures, findings similar to those published a few years earlier by Weidman & DuShane and by Lueker and colleagues.[219A,284,284A] Ikawa and colleagues have also measured pulmonary vascular resistance during exercise late after repair of large ventricular septal defects and have related these findings to age at the time of repair.[286] They found that 85% of patients with a preoperative pulmonary-to-systemic resistance ratio of between 0.15 and 0.50 had a normal pulmonary vascular resistance during exercise when operated on at < 3.8 years old, and 85% of those with a preoperative pulmonary-to-systemic resistance ratio of > 0.50 would have normal pulmonary vascular resistance during exercise when operated on at < 1.1 years.[286] Ikawa and colleagues conclude that it is best to close the large ventricular septal defect in the patient whose Rp/Rs is > 0.5 in the first year of life. Reybrouk and colleagues have measured the ventilatory anaerobic threshold in patients with a variety of congenital heart malformations.[288] They found abnormal levels of ventilatory anaerobic threshold in patients with small, non-operated ventricular septal defects as well as in patients who had undergone surgical closure of the defects. They found the probable explanation to be subnormal levels for their daily level of activity.[288]

We are now approaching 50 years since the first surgical closure of a ventricular septal defect.[153,154,291] As Perloff so eloquently wrote, the majority of patients do not require surgical intervention as they benefit from the "therapeutics of nature – the invisible sutures of 'spontaneous closure'."[292] Just over a decade ago, Moller and his colleagues provided information on the late follow-up (30–35 years) after operative closure of the isolated ventricular septal defect from 1954 to 1960.[293] This survey reviewed the outcomes of all 341 patients who underwent operative closure of the isolated ventricular septal defect during this time.[293] Forty-five patients (13%) died after surgery. Of the 296 patients discharged from the hospital, follow-up information is available on 290. Of the 296 surviving patients, 59 (20%) died from 1 month to 33 years after the operation. These 59 deaths at an average of 26.8 years of follow-up are considerably higher than the 8.64 expected deaths. Thirty-one deaths occurred in the first decade after surgery, 13 in the second, 14 in the third, and one in the fourth. The deaths were related to complete heart block in the era before pacemaker therapy, after reoperation for residual lesions, pulmonary vascular disease, endocarditis, some at the time of accidents, and a few patients without cardiac symptomatology died suddenly and unexpectedly.[293] Moller and his colleagues reported on the outcome of 258 patients stratified by the type of conduction disturbance after surgery.[293] Of 168 patients with complete block of the right bundle branch, 26 died. Of nine patients with complete block of the right bundle branch and left axis deviation, two died. Of 37 patients with transient complete heart block and nine with complete heart block, eight and seven patients, respectively, died. Nine episodes of endocarditis occurred, and in three of these, postoperative cardiac catheterization showed neither a residual shunt nor any other defect. The majority of patients enjoy good health, and of 232 patients, 208 were in class I of the New York Heart Association and 18 were in class II. Infants that were operated on during the past decade or two for their ventricular septal defects should fare even better. Similar findings as to well-being after repair of ventricular septal defect have been published by others.[294] Despite the sense of well-being, exercise tests and assessment of left ventricular function are often abnormal.[10,11,218,283–290] Sudden and unexpected death was noted in patients treated medically and surgically in the report from the First and Second Joint Study on the Natural History of Congenital Heart Defects,[70,72,295,296] and in other reports as well.[297–304] Houyel and colleagues have studied the frequency of ventricular arrhythmias in patients with ventricular septal defects repaired either by the transatrial or transventricular route.[304] While the frequency of complete block of the right bundle branch was higher in those undergoing a ventriculotomy, the incidence of ventricular arrhythmias did not differ significantly between the two groups. The occurrence of ventricular arrhythmias in the patient population as a whole, however, increased significantly with age at surgery and age at evaluation ($P < 0.05$); this increase was also noted in each group ($P = 0.06$). Preoperative right ventricular systolic pressure, severity of intraventricular disorders of conduction or duration of extracorporeal circulation and aortic clamping had no influence on the occurrence of ventricular arrhythmias.[304] The risk of

pulmonary vascular disease is certainly obviated by early intervention, and Graham also suggests that any long-term deleterious effect of chronic volume loading on left ventricular performance is improved or at least lessened by earlier intervention.[305,306] While the prognosis for the patient with an Eisenmenger ventricular septal defect is better than for the patient with primary pulmonary hypertension, the designation of "Eisenmenger" still implies irreversibility of advanced pulmonary vascular disease and inoperability.[307,308] The better solution for this disadvantaged group of patients is earlier recognition and intervention. For more than a decade, there has been some interest in the transcatheter closure of the perimembranous ventricular septal defect (Fig. 3-6),[309–317] but this procedure is not without real and potential complications.[318,319] Whether this technique for the isolated and uncomplicated perimembranous defect will become assimilated into standard therapeutic algorithms is uncertain. Finally, it is at present unclear whether catheter-based intervention will prove the most safe and efficacious method for certain complex muscular and multiple defects.

All references can be found at the end of the book. See pp. 606–14 for Chapter 3.

The Natural and Modified History of Congenital Heart Disease
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4

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Atrial Septal Defect

One of the more common forms of congenital heart malformation is the secundum atrial septal defect.[1,2] Perhaps the first description of a communication between atrial chambers can be attributed to the Renaissance Master Leonardo da Vinci. "I have found from a, left auricle, to b, right auricle, the perforating channel from a to b."[3] The pathologic anatomy and its embryologic origins were described late in the 19th century by Karl von Rokitansky[4] distinguishing the septum primum from septum secundum defects. The radiological characteristics were described by Assman early in the 20th century.[5] In 1934, Roesler reviewing the 62 recorded autopsy cases of secundum atrial septal defect found that only one had been diagnosed during life.[6] The clinical features of the patient presenting with an isolated lesion were elaborated by Bedford *et al*.,[7] while the detailed anatomy was characterized by Hudson[8] and then expanded upon by Sweeney and Rosenquist,[9] and many others.

Like other forms of acyanotic congenital heart malformations, patients with secundum atrial septal defects have the potential for their defects to undergo spontaneous diminution in size, remain stable for many years, operative or catheter-based closure, or go on to develop progressive pulmonary vascular obstruction. This chapter will provide information on the "natural" and modified history of the secundum and sinus venosus types of atrial septal defect. The ostium primum type of atrioventricular septal defect is considered in Chapter 5.

Morphology

Knowledge of the morphology of the secundum atrial septal defect (Figs 4-1, 4-2) and its environs has dramatically increased over the past decade or so commensurate with interest and desire for transcatheter closure. In the context of what does the interventional cardiologist need to know, Ferreira Martins and colleagues have revisited both the structure of the normal atrial septum and defects within the oval fossa, reminding us that only those holes within the oval fossa are true atrial septal defects.[10] These defects often designated secundum atrial septal defect exist because of deficiencies of the flap valve derived from the septum primum.[10] Defects within the oval fossa according to Martins and colleagues can take one of three forms:[10]

- when the flap valve is of insufficient dimension to overlap the rim
- when the flap valve is perforated or filigreed
- when the entirety of the flap valve is virtually or completely absent.

The important morphological questions that need to be answered by the echocardiographer working with the interventional cardiologist include:[10]

- the dimensions, shape and number(s) of the defect
- the adequacy of the superior and inferior rims which will hold the device in place
- the location of the defect relative to the surrounding atrial structures.

The morphology of the so-called coronary sinus defect and sinus venosus atrial septal defect have been discussed elsewhere.[11] Deficiencies in the atrial septum located close to the superior vena cava, and above the fossa ovalis are known as sinus venosus defects, and constitute about 2% to 3% of interatrial communications.[11,12] The superior margin of such defects is absent and there is frequently (80% to 90%) associated anomalous pulmonary venous return from the right lung, usually of the right upper or middle lobe pulmonary veins to either the superior vena cava or right atrium.[11,13–16] In size, the sinus venosus defect may vary from small (and clinically unrecognizable) to nonrestrictive. The superior caval vein tends to override the defect, allowing for a biatrial superior caval connection.[17–25]

Incidence and genetics

Hoffman has thoroughly reviewed the literature addressing postnatal incidence of congenital heart disease and his publication in 1995 stated that the median percentage distribution of atrial septal defect was 7.5%, and for comparison the median percentage distribution for the ventricular septal defect was 31%, and for an arterial duct 7.1%.[1] Hoffman and Kaplan in 2002 extended these observations, and from 43 studies in the literature found the incidence of atrial septal defect to be 941 per million livebirths.[2] It is of interest that the New England Regional Infant Cardiac Program defined an incidence during the years 1975 to 1977 of only 65 per million livebirths.[26] This was in the era before the routine application of cross-sectional echocardiography and color flow mapping. The Prospective Bohemia Survival Study found a prevalence of atrial septal defect of 0.53 per 1000 livebirths and these accounted for 8.67% of all congenital heart malformations encountered in this prospective study.[27] This study surveyed 815 569 children born in central Bohemia between 1980 and 1990, and these children were studied with echocardiography. The disparities in incidence can be partly explained by the methodology used to detect an atrial septal defect, as well as by the age of the patient

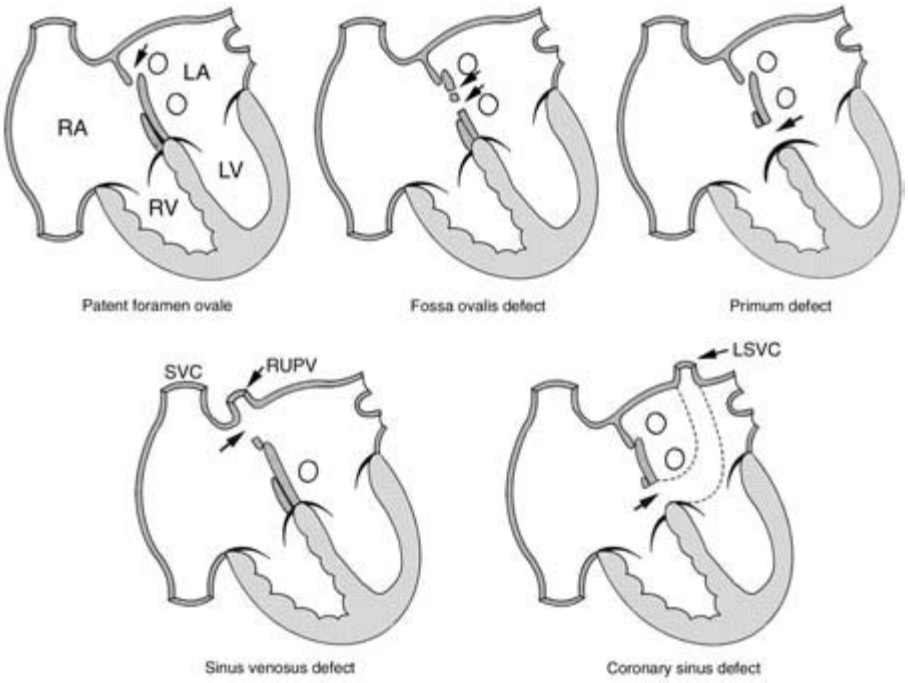


Fig. 4-1 Types of interatrial communications (arrows). LA = left atrium; LSVC = left superior vena cava; LV = left ventricle; RA = right atrium; RUPV = right upper pulmonary vein; RV = right ventricle.

at which the determination is made. This point is firmly confirmed by the Baltimore–Washington Infant Study that defined incidence of an atrial septal defect when the diagnosis was made by either echocardiography, catheterization, surgery, or autopsy of 0.317 per 1000 livebirths, and when established by catheterization, surgery, or autopsy, the incidence was only 0.094.[28]

There is a female predominance of about 2:1 in patients with a secundum atrial septal defect.[11] Atrial septal defect of the ostium secundum type is almost always sporadic, with multifactorial inheritance. But while this form of congenital heart disease is not usually inherited according to Mendelian patterns of inheritance, there are many reports of kindreds with secundum atrial septal defects.[29–38] Some of these patients have associated abnormalities of sinus node function or atrioventricular nodal dysfunction.[31,34–36] The patterns of inheritance have been primarily autosomal dominant.[29–37] There is a particular association with the Holt–Oram syndrome, the syndrome of secundum atrial septal defect and radial limb deformities.[39–49] Holt–Oram syndrome is an autosomal dominant disease with 100% penetrance. No correlation exists between the maternal clinical expression and that of the affected offspring. The syndrome includes a wide range of cardiac and skeletal malformations. Holt–Oram syndrome is a developmental disorder affecting the heart and upper limb, the gene for which was mapped to chromosome 12 in one kindred. The gene (HOS1), responsible for this disorder (TBX5) is a member of the Brachyury (T) family corresponding to the mouse Tbx5 gene.[42–49] Six mutations have been identified, three in HOS families and three in sporadic HOS cases. Each of the mutations introduces a premature stop codon in the TBX5 gene product. Tissue *in situ* hybridization studies on human embryos from days 26 to 52 of gestation reveal expression of TBX5 in heart and limb, consistent with a role in human embryonic development.

Recurrence

We discussed in Chapters 3 (Ventricular Septal Defect) and 16 (Tetralogy of Fallot) the issue of recurrence of congenital heart disease. Nora and colleagues found the frequency of all congenital heart malformations in children with affected parents to be 3%.[50–53] An even higher frequency of recurrence was reported by Whittemore and her colleagues at 16.1%,[54] and Rose *et al.* and others have found a recurrence risk of about 10.4%.[55,56] These findings would lead to the conclusion that the incidence of congenital heart disease should increase in North America, a finding supported by Gold, Sherman, and others.[1,2,38] There are any number of issues responsible for the changing perception and reality of the incidence of congenital heart disease. These include better surveillance with cross-sectional echocardiography, partially offset by parental decision to terminate certain pregnancies and of course the methodologies of ascertainment and the age at which the patient is evaluated. This latter issue is particularly germane for patients with very mild forms of congenital heart disease such as the small atrial septal defect or mild pulmonary stenosis. Gold and his colleagues have shown that the incidence of recurrence of a congenital heart defect with an affected parent with an atrial septal defect is about 10%.[38]

Associated malformations

Those cardiac malformations occurring with the secundum atrial septal defect are numerous, and won't be considered in this chapter.[11,57] One issue that will be discussed is the complication of mitral regurgitation, a finding that may complicate the late course of the unrepaired (surgical or catheter-based) patient with a secundum atrial septal defect.[58–62] The morphology of the mitral valve responsible for mitral regurgitation is usually that of a prolapsing mitral valve. A myxomatous abnormality of the mitral valve occurs in about 25% of patients with a secundum atrial septal defect.[62] Less commonly an isolated

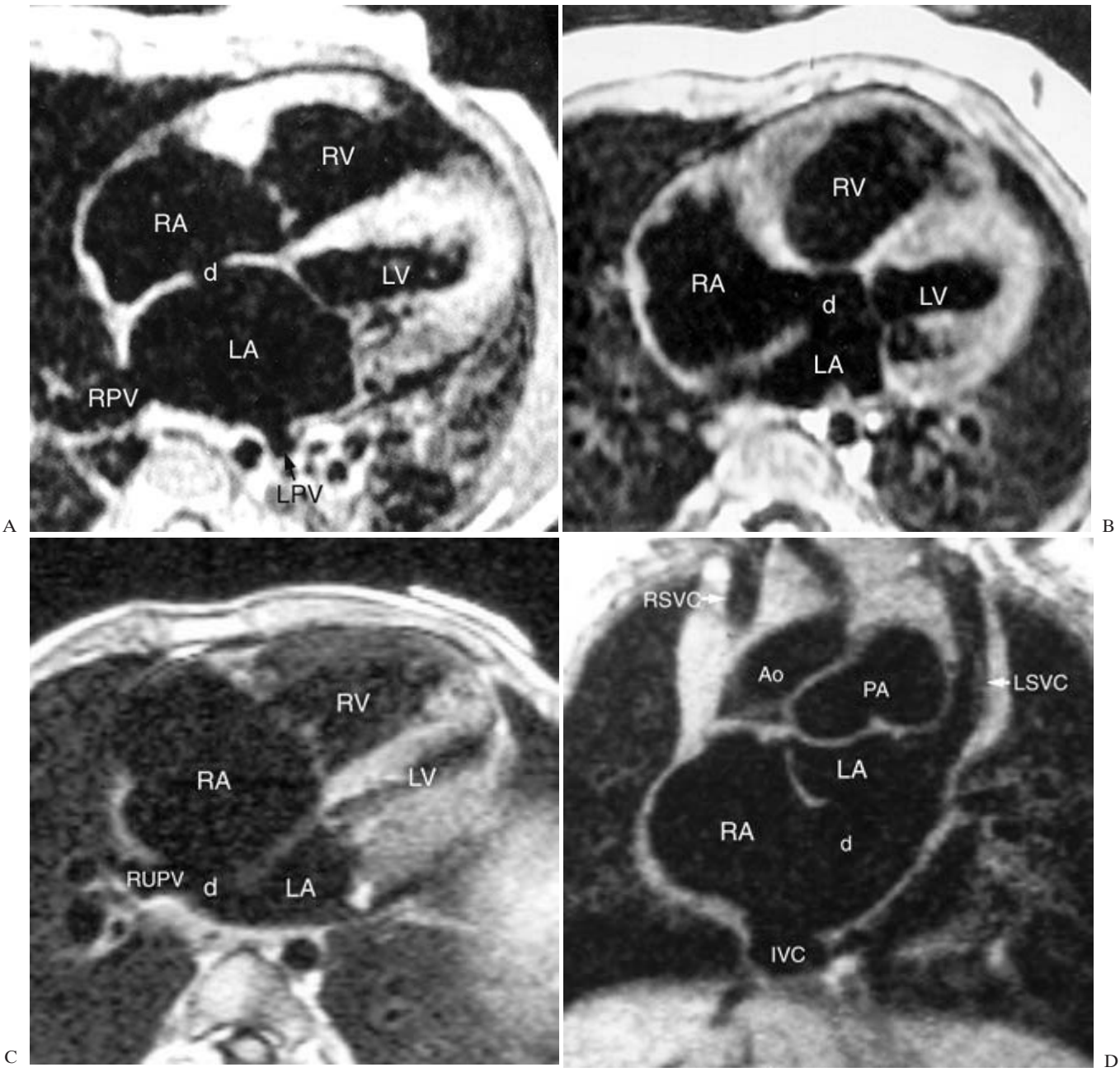


Fig. 4-2 MR images showing fossa ovalis defect (**A**), primum defect (**B**), sinus venosus defect with anomalous connection of the right upper pulmonary vein (RUPV) to the left atrium (LA) (**C**), and coronary sinus defect (**D**). Ao = aorta; IVC = inferior vena cava; LPV = left pulmonary vein; LSVC = left superior vena cava; LV = left ventricle; PA = pulmonary artery; RA = right atrium; RPV = right pulmonary vein; RSVC = right superior vena cava; RV = right ventricle.

cleft of the anterior mitral leaflet will be the causal morphology.[62] Not uncommonly, one or more pulmonary veins may connect to a systemic vein or to the coronary sinus.[11,57] Kirklin and Barratt-Boyes have reviewed in detail this occurrence and its surgical management.[63] We have addressed in a separate chapter the outcomes of patients with partial anomalous pulmonary venous connections (see Chapter 24D).

Outcome analysis

Since a functional defect of the interatrial septum within the oval fossa is an integral part of the normal fetal circulation, it is not the presence of a defect within the oval fossa in the fetus that draws one's attention, but rather its premature closure or severe restriction to flow. This is seen in some patients with the hypoplastic left heart syndrome (see Chapter 31) or transposition of the great arteries (see Chapter 25A). Fetal recognition of the Holt–Oram syndrome might indicate the predisposition for a secundum atrial septal defect.[64–66] The importance of fetal atrial septal aneurysm is discussed later in this chapter.

The physiologic sequelae of an isolated secundum atrial septal defect and thus the natural history (or more appropriately-defined the modified history; modified by medication, not by surgery or catheter-based intervention) depends on the size of

the defect, the relationship between right and left ventricular diastolic compliance, and the ratio of pulmonary-to-systemic vascular resistance.[67–73] The hemodynamic/anatomic abnormalities resulting from a secundum atrial septal defect include right ventricular and atrial volume overload, pulmonary artery hypertension and increased pulmonary vascular resistance, tricuspid valve and/or pulmonary valve regurgitation, and supraventricular tachyarrhythmias.[67–73] The clinical findings of an atrial septal defect may be subtle and thus it was not uncommon for this abnormality to escape recognition for many years. The routine application of m-mode echocardiography in the 1970s and then in the 1980s cross-sectional echocardiography has led to an increased recognition of this anomaly, and often at an earlier age.

Spontaneous closure

There is now considerable information based primarily on serial cross-sectional echocardiography that small to moderate sized defects within the oval fossa tend to undergo complete closure.[74–91] Among the earliest clinical observations on spontaneous closure of the atrial septal defect were those provided by Hoffman and his colleagues in 1965,[70] Timmis and coworkers in 1966,[88] and Cayler in the *New England Journal of Medicine* in 1967,[74] Most defects 5.0 mm in diameter or less when recognized in infancy will undergo spontaneous closure, and many defects approaching 8.0 mm diameter will also become smaller, again when ascertained in infancy.[77,78,82,83,91] In the era before routine application of cross-sectional echocardiography, outcome analyses were obviously biased towards the clinically apparent defect.[74–76,81,86,87] Because the clinical findings of the atrial septal defect tend to be "soft" or subtle, small defects were consistently missed, and many of the patients with even moderate to large defects were not detected until adulthood. Thus the older literature tended to address the outcomes for patients with moderate to large defects, while the more current observations embrace the entire clinical range of these defects. Brassard and her colleagues have reviewed the outcomes of 30 infants with an atrial septal defect considered too small for surgical closure.[79] The mean age at diagnosis was 1.3 years and the mean follow-up duration was 11.5 years. In 17 patients, the atrial septal defect underwent spontaneous closure; and in 7 asymptomatic patients the defect remained patent on echocardiography ranging from 1–6 mm. The remaining 6 patients were considered to require intervention on the basis of an apparent increase in size of the defect, accompanied by secondary clinical and hemodynamic consequences.[79] In some patients an apparent atrial septal aneurysm may have a role in the spontaneous closure of an associated atrial septal defect.[77] Fukuzawa and colleagues have studied the atrial septum of neonates with reference to the timing and mechanism of spontaneous closure of secundum atrial septal defects.[78] This group performed cross-sectional echocardiograms on 102 consecutive neonates. Atrial openings were evident in 24 infants (24%) within the first week of life, in 13 (13%) older than 1 week, in 7 (7%) older than one month, in 5 (5%) older than 6 months, and in 2 (2%) older than one year. The predominant mechanism in this study for closure of the atrial septal defects was fusion of valve-like openings in the oval fossa.[78] The incidence of spontaneous closure of the atrial septal defect continues to be discussed. The methodology used and age at assessment are clearly important in this determination. Ghisla and colleagues found a 14% incidence of spontaneous closure, commenting that this likely underestimates the true incidence of this occurrence.[82] The overall rate of closure of atrial septal defects of 87% as observed by Radzik and his colleagues is likely too optimistic.[91]

Natural history of the clinically significant secundum atrial septal defect

Campbell's publication in 1970 on the natural history of the atrial septal defect stated that the mortality rates for an atrial septal defect are low for the first two decades, 0.6% and 0.7% per annum.[67] In successive decades, they rise from 2.7%, to 4.5%, to 5.4%, and to 7.5% per annum. His analysis goes on to suggest that one-quarter of patients with secundum atrial septal defects have died just before their 27th year, half by their 36th year, three-quarters by 50, and 90% by 60 years of age. The arithmetical mean age at death was 37.5 ± 4.5 years, with the median age at death also 37 years.[67] Dalen and his colleagues found that life expectancy in patients with atrial septal defect is dramatically reduced by pulmonary vascular disease.[67A] Rarely a patient will survive with a large atrial septal defect into the 9th or 10th decade of life.[92–93] Zaver and Nadas state in their study, patients ranged in age from less than 1 year to 96 years.[93] They do not provide any specific information about this 96-year-old patient, cerainly one of the oldest, if not the oldest such patient mentioned in the literature. Craig and Selzer in 1968 reported the natural history and prognosis of 128 adult patients with secundum atrial septal defect.[68] They found that significant pulmonary artery hypertension developed in 22% of the series, of which 15% had high pulmonary vascular resistance, with significant arterial hypoxemia in 14%. They state that the most serious risk factor for the patient with an atrial septal defect is severe pulmonary vascular disease occurring in about 14% of patients.[68] This complication usually develops when the patient is between 20 and 40 years of age, may be rapidly progressive, leading to shunt reversal (the Eisenmenger syndrome), disability and death. Were these early studies of Campbell and Craig and Selzer overly pessimistic?[67,68] Shah and colleagues conducted a historical prospective natural history study in an adult population after medical or surgical treatment.[94] This study published in 1994 argued that in their experience outcome in adults with secundum atrial septal defects is not improved by surgical closure because no patient in their modest-sized series developed pulmonary vascular disease.[94] Their discussion is not terribly persuasive, and most today would likely consider closure of any substantial atrial septal defect without evidence of severe and fixed pulmonary vascular obstructive disease. Hamilton and coworkers retrospectively studied the course of 412 patients with secundum atrial septal defects followed over a 20-year period.[95] They observed that symptoms, heart size, right ventricular hypertrophy, pulmonary artery pressures, systemic desaturation, and atrial arrhythmias increased progressively with age.[95]

Cherian and colleagues have addressed the issue of pulmonary hypertension in isolated secundum atrial septal defect.[96] From a cohort of 709 consecutive patients with isolated secundum atrial septal defect, the pulmonary artery systolic pressure was > 50 mmHg in 118 patients (17%). Pulmonary hypertension was present in 13% of patients under 10 years of age and in 14% of those aged 11 to 20 years. The Eisenmenger reaction or syndrome was identified in 9% of the 709 patients.[96] According to the authors none of the patients with elevated pul-

monary artery pressures lived at high altitude.[96] Their data on the age at which pulmonary hypertension developed is interesting.[96] Using a pulmonary vascular resistance > 5.0 units as the definition of pulmonary hypertension, 12% of those between 0 and 10 years, 10% from 11 to 20 years, 17% between 21 and 30 years, 19% from 31 to 40 years, and 11% above 40 years of age had a pulmonary vascular resistance of that level or higher. The frequency of the Eisenmenger reaction was found to be 7% in the first decade, 8% in the second decade, 10% in the third decade, and 11% in the fourth decade and beyond.[96] Thus, at least in this series, the development of pulmonary vascular disease was independent of the age of the patient. Vogel and his colleagues have provided data suggesting that patients with sinus venosus atrial septal defects have higher pulmonary artery pressures and resistances than patients with secundum defects, and the former group develop these complications at a younger age.[97] Thus while it is uncommon for the child or adolescent with an "uncomplicated atrial septal defect" to have significant pulmonary artery hypertension, this phenomenon is well known.[98–107] These infants and young children behave differently than the overwhelming majority of patients with a secundum atrial septal defect. None the less, according to Borow and Karp most patients with secundum atrial septal defects between 1 and 10 years of age are asymptomatic, but in comparison only 4% of those over 40 years of age deny symptoms.[108]

Surgical repair of the secundum atrial septal defect

Surgical correction of the secundum atrial septal defect became a reality in 1948 when Murray closed an atrial septal defect in a child using an external suture technique.[109] Bailey and his colleagues published in 1954 their experience with atrioseptopexy[110] and in 1954 and 1957, Sondergard reported closure of an atrial septal defect in three patients using a purse-string suture closure.[111,112] About the same time, Gross developed the well technique to close an atrial septal defect.[113] These approaches were basically "blind" and performed without visualization of the atrial septal defect. But with the development of the pump oxygenator, Gibbon in 1953 initiated the era of open heart surgery when he repaired a secundum atrial septal defect in a young woman by a so-called open technique with complete visualization of the defect.[114] According to Kirklin and Barratt-Boyes, by the late 1960s almost all surgeons were using cardiopulmonary bypass for repair of the atrial septal defect.[63] Thus there is now surgical follow-up extending back nearly five decades. Most consider indications for operation or catheter closure a pulmonary/systemic blood flow ratio of 2:1 or evidence of a volume-loaded right ventricle.[11,57] Contemporary surgical mortality for the uncomplicated atrial septal defect with normal or just mildly increased pulmonary vascular resistance is almost zero percent, and this is true for catheter-deployed devices as well.[63] Mortality will be somewhat higher in those patients whose pulmonary vascular resistance is significantly elevated and thus closure in these patients is always debated and contentious. Murphy and his colleagues have reported the 27-to-32 year long-term outcome after surgical repair of isolated atrial septal defect.[115] This study reviewed the outcomes of all 123 patients operated at the Mayo Clinic between 1956 and 1960 for either a secundum atrial septal defect or sinus venosus type of defect. The overall 30-year actuarial survival rate among survivors of the perioperative period was 74% as compared to 85% among controls matched for age and sex.[115] The perioperative mortality in that era was 3.3%. Actuarial 27-year survival rates stratified by age at operation indicates the increased risk for the older patient. These actuarial survival rates for patients ″ 11 years and 12 to 24 years were no different from rates among controls – 97% and 93% respectively. However, for patients operated at ages 25 to 41 years and > 41 years, the actuarial 27-year survival rates were 84% and 40% respectively compared to the controls, 91% and 59%, respectively. Independent predictors of long-term survival were age at operation and preoperative systolic pressure in the main pulmonary artery.[115] Sellers and his colleagues have also provided early and late results using extracorporeal circulation to repair 275 patients with secundum atrial septal defects.[116] These patients were operated on at the University of Minnesota from July, 1955, to May, 1965.[116] The hospital mortality was 3.6%, and the risk in the absence of important pulmonary artery hypertension or mitral valve disease was 1.8%. The causes of death in the early postoperative period included: a neurological complication related to an air embolism in 3 cases, low cardiac output secondary to pulmonary vascular disease in 2 patients; heart block, pulmonary infection, pulmonary embolus and wound infection in one patient each, and in one patient the cause was undetermined.[116] Late deaths occurred in 4 patients, resulting from heart failure due to a residual shunt in one patient, one patient with severe pulmonary artery hypertension, bacterial meningitis in one, and death following mitral valve replacement, 3 years after the initial repair of the atrial septal defect. No late deaths occurred in those patients with normal or near normal pulmonary artery pressures.[116] Others have also reported the impact of pulmonary hypertension on the operative risk.[117]

We have commented earlier that there are a number of infants and young children who develop symptoms earlier, fail to thrive and require intervention.[11,96–107] Some of these patients have significant pulmonary hypertension as well.[96] Mainwaring and his colleagues reported on 6 patients with atrial septal defects and intractable heart failure requiring surgery in the first year of life.[105] These 6 patients were identified from a cohort of 166 patients undergoing repair of an isolated secundum atrial septal defect between 1978 and 1995. While all survived the surgery, five of the six patients showed little or no improvement in symptoms and each of these five eventually showed signs of developmental delay.[105] This finding of developmental delay is not a consistent feature of those infants presenting in infancy. Others have attributed the early presentation to a rapid remodeling and thinning of the pulmonary vascular bed.[96,108] Furthermore a number of reports show that symptomatic infants requiring surgery usually do very well after repair. In this regard, there are instances of spontaneous closure of atrial septal defects even when the patient presented in infancy in heart failure.[80,84–86]

Because many patients present late because of the subtlety of the clinical findings,[93] it was not uncommon to see patients with variable degrees of pulmonary hypertension and pulmonary vascular disease. Some of these patients with obvious right-to-left shunting and clinical evidence of fixed pulmonary vascular disease were inoperable. The caveat of clinical evidence of pulmonary vascular disease is important because a few patients with normal pulmonary vascular resistance also manifest right-to-left shunting.[118–122] This may reflect disadvantageous intracardiac streaming because of a prominent venous valve directing inferior caval blood to the left atrium; ventricular compliance

imbalance, etc. There is not agreement as to the level of pulmonary vascular resistance above which surgery should not be contemplated, or undertaken. Rahimtoola and colleagues have written that the outcome of repair of the patient with secundum atrial septal defect whose pulmonary arterial peak systolic pressure is greater than 60 mmHg is poor.[123] Dave and his colleagues state that a poor outcome is likely when the pulmonary artery mean pressure is greater than 40 mmHg.[124] In terms of pulmonary vascular resistance, Dave *et al.* argue that surgery should not be undertaken when the Rp/Rs is above 0.20[124] while others have stated that operation is contraindicated when the Rp/Rs is above 0.40. Steele and his colleagues suggest that total pulmonary vascular resistance in patients with pulmonary hypertension is the best predictor of outcome.[125] They advise that surgery be undertaken in patients with total pulmonary resistance less than 15 U/m^2.[125] They also suggested that in patients with "borderline" total pulmonary vascular resistance, the systemic arterial oxygen saturation provides a reasonable prediction of surgical outcome with 92% being the cutoff value.[125] Murphy and his colleagues found that the presence of moderate or severe pulmonary hypertension (≥ 40 mmHg) had a markedly adverse effect on survival in patients more than 24 years old at the time of operation.[115] Others have used the open lung biopsy as the arbiter of surgical intervention when the pulmonary vascular resistance is greater than 8 U/m^2.[201] Attempts to manipulate the pulmonary vascular bed with vasodilating agents including NO may prove helpful in determining operability in patients with elevated pulmonary vascular resistance. There is no doubt that pulmonary hypertension and pulmonary vascular disease impacts both on immediate surgical mortality and long-term follow-up. Patients with unoperated atrial septal defect developing the Eisenmenger syndrome may be expected to survive into the third or fourth decades of life, and survival beyond that has been recorded.[125–129] The inexorable course of irreversible pulmonary vascular disease results in progressive clinical deterioration, hypoxemia, pulmonary thrombosis, often hemoptysis, and eventually death.[125–129] Somerville has suggested that those patients with high pulmonary vascular resistance who underwent surgical closure but continue to develop pulmonary vascular obstructive disease do worse than those patients whose defects were not closed.[129] The tragedy of the Eisenmenger syndrome in these patients may be palliated by double lung transplantation. Sadly, most who develop irreversible pulmonary vascular obstruction will die.

Catheter-based closure of the secundum atrial septal defect

Until the last quarter of the 20th century, there was no alternative to surgical closure for patients requiring surgery. However, in 1976, Mills and King reported an experimental device[130,131] for transcatheter therapy and its clinical application, but due to its large size (22F), it was not suitable for percutaneous application, particularly in childhood. It wasn't until 1987, that a multicentre clinical trial was begun with a single, self-expanding umbrella with six stainless steel arms, three of which were fitted with barbed hooks for anchoring within the left atrium.[132,133] The device was successfully deployed in approximately two-thirds of a small number of patients. It was however not felt safe due to inability to reposition the device once deployed, or retrieve upon expansion. Furthermore the barbed hooks frequently engaged a part of the left atrium other than the atrial septum.

By 1989 the first large human trial was undertaken. Lock and colleagues had modified William Rashkind's PDA occluder device by introducing an elbow in the center of each arm and extending the length of the individual arms.[134] This device, known as the "Clamshell Septal Occluder," was successfully implanted in over 800 patients. Preliminary data on 400 patients from five centers (patient age range 21 days to 78 years), demonstrated no device related deaths. Seventeen Clamshells embolized after release, 11 occurring immediately following implantation. These patients remained remarkably stable until either transcatheter or surgical removal. With growing experience in patient selection and echocardiographic monitoring of optimal device positioning, the incidence of these events declined. Systemic thromboembolic phenomena occurred in 3 patients, vessel damage in 2 patients and air embolism in 6 patients. Among those with successful implantation (376 of 400), 33% had small residual leaks**.** Boutin and colleagues demonstrated residual left to right shunts in 91% immediately following device implantation.[135] This incidence decreased to 53% at 10 month follow-up, with only 5% having hemodynamically significant left to right shunting. Residual shunting was not influenced by (1) ASD dimension, location, or position in relation to the device as assessed by transesophageal echocardiography; (2) location of the ASD; or (3) device size relative to the stretched dimension of the defect.[135] Longer-term follow-up of the Clamshell revealed one or more device arm fracture in up to 83% of patients at 1 year.[136,137] Although none of these fractures resulted in patient morbidity or mortality, the device was withdrawn from investigational studies in 1991.

The Clamshell device was redesigned and reintroduced as the CardioSEAL Septal Occluder (Nitinal Medical Technology, Inc, Boston, Mass), eventually achieving FDA approval in September 1999 (Fig. 4-3). Its metal base had been changed to the stress resistant alloy MP35N. The device arms too were modified, and now had two elbow joints to further resist metal fatigue. An additional self-centering mechanism comprised of nitinol

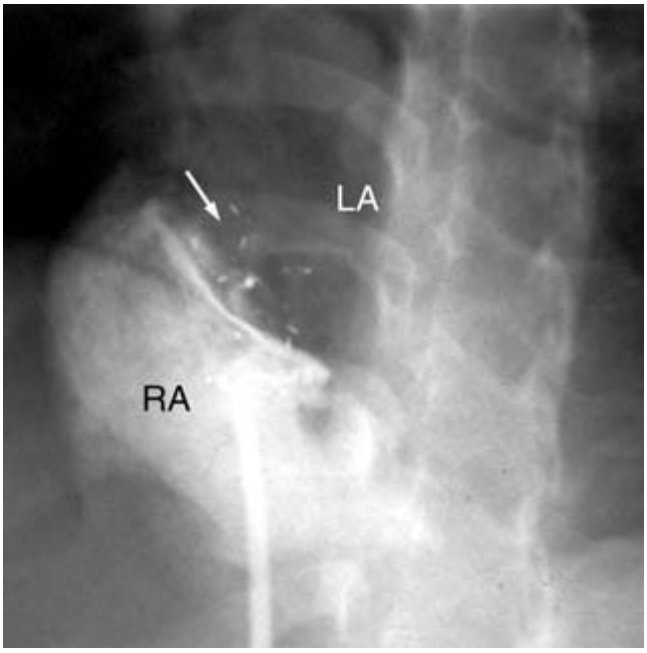
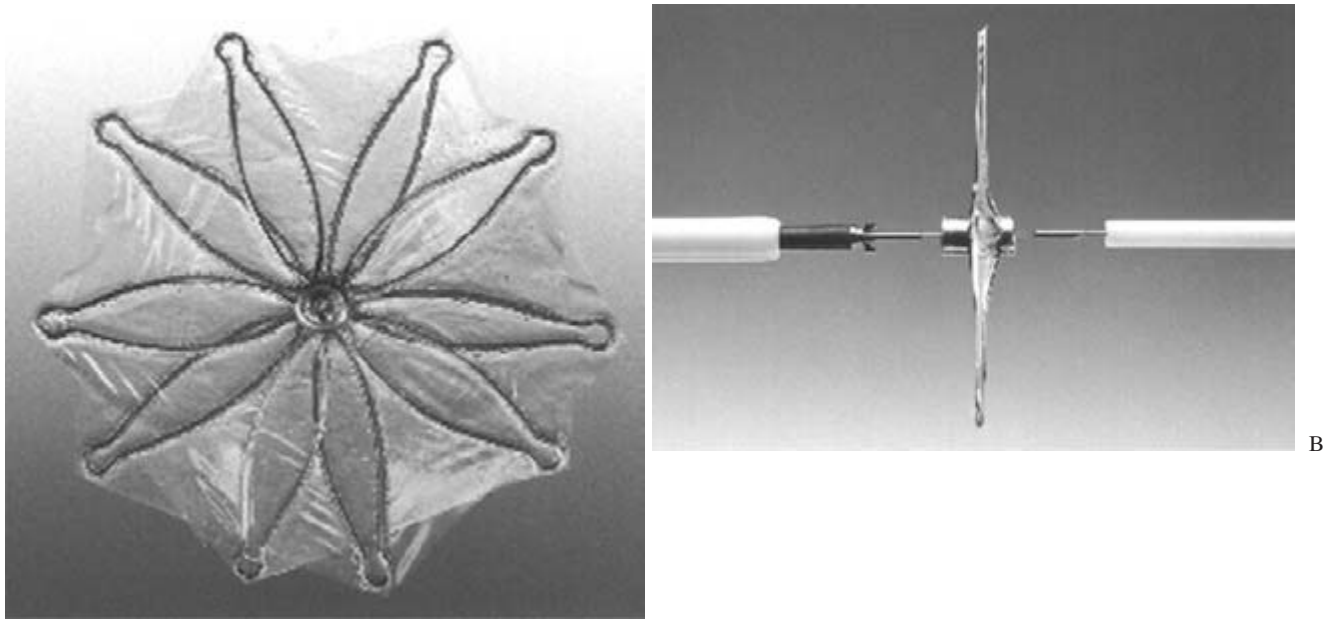


Fig. 4-3 Device closure of a fossa ovalis defect. Closure with a CardioSEAL (arrow). LA = left atrium; RA = right atrium.

springs connected between the two umbrellas and a flexible core wire with a pin-pivoting connection was secured in the STARFlex device. Both the CardioSEAL and STARFlex devices were investigated in a multicentre European trial.[138] The procedure was attempted in 334 patients with a mean age of 12 years. Device implantation was achieved in 325 (97.3%) patients. Of these, the device embolized in 13 patients (4%) early after implantation (within a few hours). Successful transcatheter re-implantation was achieved in 3, and the remaining 10 patients had surgical removal of the device and intraoperative defect closure. Residual shunting was detected immediately after the procedure in 41% of the patients, with the incidence decreasing to 31% at discharge, 24% at 1 month, 21% at 6 months, and 20.5% at one year. During the period of follow-up, elective surgical repair became necessary in two patients, due to malposition of the device in one, and late embolization in the other. Fractures of arms were seen in 6.1%, most commonly with the largest devices. All those with fractured arms of the device were asymptomatic, and no clinical complications related to the fractures were observed. There were no arrhythmias, endocarditis, valvar distortion, thromboembolic events, or other complications. After one year of follow-up, 92.5% had either complete closure of the defect or only a trivial leak.

Other devices currently in use include the ASDOS, the Angel Wing, the Buttoned device and the Amplatzer device. Babic *et al* first described he ASDOS (Atrial Septal Defect Occluder System-Osypka GmbH, Germany) in 1991.[139] The ASDOS consists of two major components: delivery system (Fig. 4-4) and prosthesis consisting of two self-opening umbrellas made of a nitinol wire frame and a thin membrane of polyurethane (Fig. 4-4). Each umbrella has five arms that assume a round shape in the open position. When joined together, the umbrellas assume a discoid shape in profile and a "flower" shape in the frontal view. Feasibility, safety, and efficacy of the ASDOS were investigated in 20 European centers. Two hundred patients were included, 154 with secundum ASD and 46 with patent foramen ovale. There were 62 children and 138 adults. Patients were included in this study if they had a secundum ASD < 20 mm, as determined by echocardiography, or < 25 mm, as measured by balloon sizing, a residual septal rim > 5 mm, or if they had a PFO and repeated neurologic events. Seventy-seven percent of patients initially evaluated for device closure were excluded due to inadequacy of the septum posterior to the aorta. In some patients with hyperdynamic atrial excursions the diameter of the ASD during atrial diastole was bigger than the diameter of the whole atrial septum during the atrial systole, making it unsuitable for device closure. The procedure failed in 26 patients (13%). Complications necessitating surgical removal of the device included device embolization in 2, device entrapment within the Chiari network in 1, frame fracture in 1, and perforation of atrial wall in 2 patients. Additional 11 patients (11%) underwent surgical removal of the device during follow-up. There were 163 patients (81%) with an implanted ASDOS at follow-up (6 to 36 months). Twenty-eight percent of patients had an early residual shunt, and this did not change significantly during follow-up. Only 8% of patients had medium or large residual shunts at late follow-up requiring surgical closure.

The Angel Wing Das device (Microvena Corporation, White Bear Lake, MN) was first described by Das *et al*. in 1993. The original construct consists of two square nitinol wire frames, each supporting a square of stretchy Dacron fabric sewn to the perimeters. The two squares are connected centrally to form a "conjoint ring." The four corners of the device can be approximated and thereby the device can be drawn into a delivery system. Once the distal disk has been expanded, the device is not designed to be removed easily. The Angel Wing Das device has been tested in phase I and II trials in the USA. Implantation success rates vary between 92% and 94% for secundum ASDs and 97–100% for patent foramen ovale. There were no device related deaths, episodes of endocarditis, or device embolizations. For patients with ASDs 86% of patients have no or less than 1 mm shunts, and 14% have 1–2 mm residual shunts. None of the patients had large residual shunts. None of the patients with patent oval foramens had significant residual



A B

Fig. 4-4 The ASDOS™ device. **A**. Frontal photograph of connected ASDOS umbrellas showing a "flower" shape. **B**. Lateral photograph of connected ASDOS umbrellas with the loading system.

shunts. The Angel Wings has now been modified to have two circular disks (Angel Wings II). It is retrievable into the delivery system and is repositionable. It is anticipated to be released for clinical use in the near future.

Sideris *et al* in 1990 introduced the so-called Buttoned device after experimental work in a dog model.[140] The device consists of a square sheet of polyurethane foam supported by two independent, diagonally situated wire arms (the occluder) and a separate counter occluder. This device has the least rigidity of all devices. The foam occluder can easily be folded into the delivery system by compressing the four sides of the square so that the support wires are parallel to each other. The foam resumes a square shape once advanced and exposed in the left atrium. It remains attached centrally to a nylon thread looped through a hollow loading wire that extends out of the end of the delivery catheter, providing flexible control of the occluder. Once the occluder has been expanded, it can be removed from the body only with difficulty. Once an acceptable size and position of the occluder has been achieved, the counter-occluder is then advanced over the loading wire and buttoned on to a knotted loop attached to the center of the occluder. The device was investigated during a multi-institutional USA trial in 1994. Occlusion was attempted in 57 patients aged 1 to 62 years (median 5). The procedure was abandoned in 7 after one or more unsuccessful attempts, and devices were released in 50 patients. Urgent retrieval was necessary in 4 patients because of unstable device position: three devices had unbuttoned with migration of the counter-occluder to the pulmonary artery or the inferior caval vein. The patients remained stable until surgical retrieval. Successful device implantation was achieved in 46 patients (81%). At 1–20 month follow-up 45 of 46 patients (98%) had either no or only trivial residual shunt. Since its initial description, the buttoned device has undergone a number of design changes. These include radiopacity in the button, making visualization easier, introducing a second button (which has essentially eliminated the potential for unbuttoning), and inclusion of a centering device. The latter has permitted occlusion of larger defects with smaller sized devices. Outcomes with the newer modifications of the device as are yet still unknown.

The Amplatzer septal occluder (AGA Medical Corp., Golden Valley, MN) (Fig 4-5) was introduced in 1997. At this time most existing devices, apart from the Das device, were not truly self-centering. There were also significant technical difficulties with large delivery systems, complicated implantation techniques, late fractures and perforation, lack of retrievability once expanded, and the need for a septal rim on the antero-superior portion of the interatrial septum below the level of the ascending aorta. The Amplatzer device was designed to bridge many of these shortcomings. It is constructed of super-elastic Nitinol, which allows the device to rapidly regain its preformed shape. The basic design is that of a double saucer, with a central connecting cylinder. The device is formed from 72 Nitinol wires braided into a cylindrical mesh. It employs the concept of closing the ASD by stenting the defect with its central connecting cylinder thereby also achieving true self-centering and fixation and stability. Thrombosis is induced by three polyester patches sewn into three portions of the device. Important advantages compared to other devices are the lack of need for an antero-superior atrial septal rim below the level of the ascending aorta, relative ease of implantation with a rapid learning curve, and easy retrievability until the device is released from the delivery wire. In the light of these advantages, the

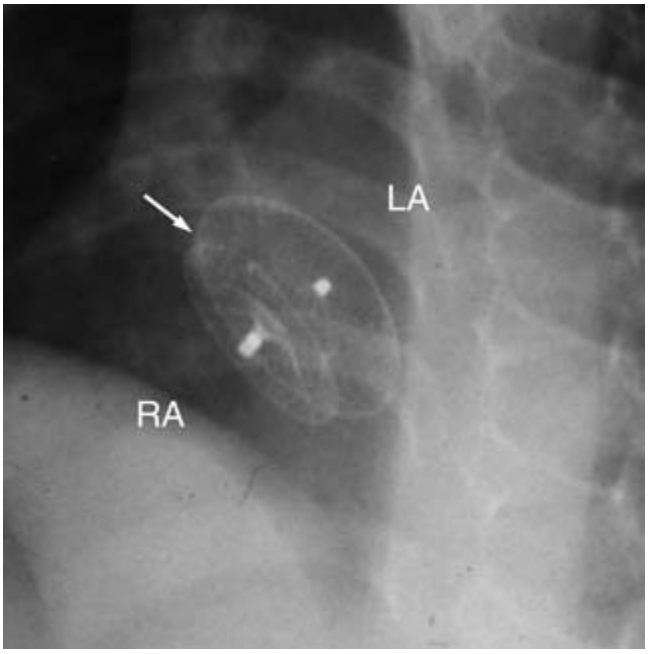


Fig. 4-5 Device closure of a fossa ovalis defect. Arrow indicates Amplatzer ™ device. LA = left atrium; RA = right atrium.

Amplatzer has become the preferred device for closure of single secundum ASDs. The larger left atrial disk (7 mm radius from the stenting cylindrical portion) also permits simultaneous occlusion of fenestrations close to the primary defect**.** Early experience with device was reported by Chan *et al.* in a multi-institutional investigation in the UK.[141] One hundred and one procedures were performed in 100 patients aged 1.7 to 64.3 years. There were 7 device failures and 1 embolization requiring surgical removal. Immediate total occlusion rate was 20%, 85% at 24 hours, 93% at 1 month and 99% at 3 months. Complications of the procedure included transient ST-elevation in 1 patient, transient atrioventricular block in 1 patient, deep vein thrombosis in 1 patient and transient ischemic attack in 1 patient. The Amplatzer device is suitable for the occlusion of larger defects. Berger *et al*. reported their experience in 45 patients with defect larger than 25 mm.[142] Device sizes 2–4 mm larger than the stretched diameters were used. A complete occlusion rate of 91% was achieved at 0.82 years (range 0.1 to 2.6 years). The remaining 95% of patients all had hemodynamically insignificant shunts. The device has been modified for patent oval foramens and multifenestrated aneurysmal atrial septums omitting the central connecting cylinder.

No comparative studies are available for the various devices, and published results make direct comparisons difficult. The complications inventory of the Association for Paediatric Cardiology in 1999 revealed an embolization rate of 10% for the buttoned device, Angel Wings and ASDOS devices, 6% for the CardioSEAL, and 0% for the Amplatzer device. No contemporary data are however available with the newer generations of the devices.

There are currently a number of new devices under investigation including the Helex, Centring on demand (a modification of the Buttoned device), and balloon deliverable wireless devices. Alongside these developments has been the introduction and evolving application of intracardiac phased-array ultra-

sound probes to device implantation. This permits the direct vision of structures which are sometimes difficult to see on TEE, and importantly permits the operator to perform defect closure without general anaesthesia. In considering surgical vs. catheter-based intervention, it is reassuring that cardiopulmonary bypass to repair an atrial septal defect in otherwise normal children does not affect cognitive function.[142A]

Patent ovale foramen and atrial septal aneurysm

As placed into perspective by Hanley and his colleagues, atrial septal aneurysms have been related (either by association or as potential causes) to systolic clicks, atrial arrhythmias, systemic and pulmonary embolism, atrioventricular valve prolapse and atrial septal defect.[143] This Mayo Clinic study found a prevalence of 0.22% for the atrial septal aneurysm.[143] As we discussed earlier, these aneurysmal bulgings of septum primum may participate in the mechanism of closure of the secundum defect.[77] There is considerable information about the pathology and echocardiographic appearances of atrial septal aneurysms.[144–145] Of concern is that PFO has been consistently demonstrated to be associated with cerebral and systemic embolism, giving rise to so-called cryptogenic stroke particularly in the presence of atrial septal aneurysm.[145–156] Lechat *et al.* investigated a population of 60 adult patients under 55 years with ischemic stroke, and compared them to a control group of 100 patients.[157] The prevalence of PFO (detected by transthoracic echocardiography) was 40% among the study population compared to 10% in the control group ($P < 0.001$). Among those patients with no identifiable cause for their stroke (15 patients), PFO prevalence was 40% compared to 21% in patients with identifiable causes such as mitral prolapse, endocarditis, or oral contraceptive use. This association between PFO and cryptogenic stroke has been confirmed in a number of subsequent studies.[146–159] Petty *et al.* investigated 116 consecutive patients with cerebral infarction and used transesophageal echocardiography to detect right to left interatrial shunting.[160] Their findings were remarkably similar to those of Lechat *et al*,[159] in that PFO was found in 40% of 55 patients with cryptogenic infarcts, and in 25% in infarcts with a known cause. When their analysis was restricted to patients who had performed a Valsalva maneuver during the transesophageal echocardiogaphy, 50% of patients with cryptogenic stroke were found to have PFO.

Atrial septal aneurysm in addition to PFO has now also been firmly implicated in the genesis of cryptogenic stroke. Cabanes *et al*. elegantly demonstrated in their series of 100 consecutive patients < 55 years with cryptogenic ischemic stroke, that PFO and atrial septal aneurysm were significantly associated with stroke, odds ratio 4.3, confidence intervals 1.3 to 14.6, $P = 0.01$.[161] Overell and colleagues further defined the incremental risk of cryptogenic ischemic stroke in patients with PFO compared to those with atrial septal aneurysm, and those with a combination of both PFO and atrial septal aneurysm.[162] They demonstrated the following odds ratios: 1.83 (95% CI, 1.25 to 2.66) for PFO alone, 2.35 (95% CI, 1.46 to 3.77) for atrial septal aneurysm and 5.09 (95% CI, 1.25 to 20.74) for patients PFO and atrial septal aneurysm.

The exact mechanisms of stroke in PFO patients remain unclear. Thrombotic and or vasoactive substances may be shunted paradoxically from the venous circulation to the systemic circulation, allowing cerebral ischemia or infarction. Atrial septal aneurysm may also be associated with a higher frequency of atrial arrhythmia. Various therapeutic strategies have been applied based on the presumption of a causal relationship. Mas *et al*. investigated 581 patients (age 18 to 55 years) who had ischemic stroke of unknown origin. All patients were treated with aspirin 300 mg per day. After 4 years the recurrence of stroke was 2.3% (95% CI, 0.3 to 4.3) among PFO only patients, and 15.2% in patients with both atrial septal aneurysm and PFO.[151,154] There were no recurrences among patients with only atrial septal aneurysm. A multi-institutional centre (42 centres) investigating the effect of medical therapy on stroke recurrence randomized 630 stroke patients to either warfarin, or aspirin. Endpoints were recurrent ischemic stroke or death. The investigators found no difference in time to primary endpoints between the warfarin and aspirin group, 2-year event rate 16.5% vs. 13.2%. Recurrence risks were similar between patients with PFO and those without PFO. In this particular cohort the presence of atrial septal aneurysm did not affect recurrence risk.

A number of investigators have evaluated the role of closure of the interatrial communication either by transcatheter means or via the surgical approach. Early transcatheter results look promising. Bruch and colleagues evaluated recurrence risks among 66 patients (mean age 47.8 ± 12.7 years) with presumed paradoxical thromboembolic events.[163] Twelve patients had atrial septal defect and the remaining 54 had a PFO. Successful transcatheter device deployment was achieved in all patients, with only 2 patients demonstrating residual shunting after 3 months. After 112.2 patient-years' follow-up, no patients had recurrent thromboembolic events. Hung *et al.* reported on 63 patients who too had transcatheter closure of PFOs, with a total of 164 patient years. They found recurrent events among 4 patients (6.3%).[164] In 2 of the 4 patients with recurrent events, there were residual leaks across the device, one associated with device fracture and left atrial thrombus.

Shunichi Homma and colleagues reported their experience with surgical closure of PFOs after cryptogenic stroke.[165] Of their 28 patients who underwent surgical closure, the actuarial recurrence rate was 19.5% (95% CI, 2.2–36.8%). All those with recurrence (4 in total) were older than 45 years, and 2 of the 4 had small residual leaks across the atrial septum. In the Mayo Clinic series reported by Joseph Dearani and colleagues 91 patients had surgical closure of a PFO after a cerebral infarct in 59 and transient ischemic attacks in 32.[166] Deep vein thrombosis was documented in 9 patients, and a hypercoagulable state in 10. During follow-up no one had a recurrent cerebral infarct, but 8 had transient ischemic attacks during 176.3 patient-years. The actuarial recurrence rate was 7% at 1 year and 16.6 at 4 years.

The jury is still out on the most effective therapy of cryptogenic stroke. Current options include antiplatelet therapy (aspirin, and ADP mediated platelet aggregation blockers), warfarin or mechanical closure of the PFO (surgery or device closure). It is apparent from the above results that cryptogenic stroke is undoubtedly associated with right to left shunting at atrial level, and in many cases may be causative to the stroke. The effectiveness of PFO closure in preventing recurrent systemic thromboembolic events depends largely on how accurately other sources of thrombosis, thromboembolism and or vasomotor disturbance can be identified and treated separately from the PFO.

Interesting work has recently emerged from Wilmshurst and Nightingale.[167] They noted a high prevalence of migraine with

aura in divers with decompressions illness and a large right to left shunt at atrial level. In their investigation of 200 individuals referred for decompression illness, migraine with aura in everyday life occurred in 38 of 80 (47.5%) patients with a large right to left shunt at rest, as compared to those with a smaller shunt or only visible during the Valsalva maneuver (5 of 40, i.e. 12.5%). A similar association has been noted between transient global amnesia and PFO. Closure of the right to left shunt in a group of 40 consecutive migraine patients, resulted in complete resolution of the migraine in 50% of the group, and significant improvement in frequency and severity of migraine in the remainder.[168] Meier and Lock have recently provided a review of those issues to be considered in the contemporary management of patent foramen ovale.[168A]

Atrial arrhythmias

Atrial arrhythmias form part of the late natural history of ASD and are associated with important morbidity and mortality especially in the older adult patient. It is associated with the onset of congestive heart failure and systemic embolization, the most important of which is stroke. Atrial flutter or fibrillation is uncommon before the age of 40 years with a reported incidence of 1%.[169] After the age 40 years its prevalence increases disproportionately as compared to that of the general population. Berger *et al*. reported an atrial fibrillation prevalence of 15% in those 40–60 years of age, and 61% among those older than 60 years.[169] Similar statistics have been reported by other authors[94,115,170–174] for the development of atrial fibrillation including age (with a RR of 1.9 per decade of age, 95% CI, 1.3 to 2.7), left atrial dimension (RR 2.8 for each 10 mm increase in LA dimension, CI, 1.5 to 5.2), mitral regurgitation (RR 3.0 for each degree of mitral regurgitation, 95% CI, 1.6 to 5.8) and tricuspid regurgitation (RR 1.9 for each degree of tricuspid regurgitation, 95% CI, 1.0 to 3.7). Gatzoulis *et al.* found that patients with atrial fibrillation or flutter were also more likely to have higher pulmonary arterial pressures and were more likely to have a worse NYHA functional class.[71]

These observations yield important clues with regard to the multifactorial nature of atrial fibrillation in ASD. Longstanding volume loading, pulmonary hypertension, ventricular dysfunction, atrioventricular valve regurgitation conspire to increase atrial pre- and afterload, and thereby the degree of atrial myocardial stretch. Right atrial enlargement occurs long before left atrial enlargement, the latter usually marking the onset of atrial fibrillation. Atrial stretch prolongs atrial refractoriness in a heterogeneous manner, making the atria vulnerable to the induction of fibrillation. Morillo *et al*., using a dog model of atrial fibrillation, demonstrated that an increase in right atrial area of 40% or more was strongly associated with inducibility of sustained atrial fibrillation, $r = 0.87$.[175] Henry and colleagues have demonstrated atrial fibrillation was common among patients with left atrial dimensions in excess of 40 mm (as documented on the parasternal long axis echocardiographic view).[176]

Anatomic closure of ASD has been associated with progressive normalization of right ventricular and right atrial sizes.[177] Kort *et al.* demonstrated progressive decline in right atrial area from baseline to 6 and again to 24 months following percutaneous ASD closure, with right atrial area indexes of 15.2 to 12.1 to 10.6 cm^2/m^2.[178] This remodeling of the atrial myocardium seems to be best in the youngest patients. Shaheen *et al*. demonstrated similar findings in a young adult population (mean age 37 ± 19 years) with decline in atrial area from 21 ± 6 cm^2 to 14 ± 5 cm^2 after surgical ASD closure.[179] A subsection of patients with anatomic closure of their ASD appear to have incomplete remodeling of the right ventricle and right atrium. In the series reported by Meijboom and coworkers 26% of patients had persistent right ventricular dilation in the absence of residual atrial shunting.[180] In our own series 29% of patients had persistent right ventricular dilation at 1 year of follow-up.[177]

The impact of anatomic ASD closure on atrial arrhythmias has been previously explored. Of the 213 patients in Gatzoulis *et al*. cohort, 19% (40 patients) had atrial fibrillation or flutter before surgery.[71] This group were older (mean [±SD] age, 59 ± 11, vs. 37±13 years) and had higher mean pulmonary artery pressures (25 ± 9.7 vs. 19.7 ± 8.2 mmHg). Following surgical closure of the defect (mean follow-up period 3.8 ± 2.5 years) 24 of the 40 continued to have atrial fibrillation or flutter. The mean age of these patients was older than those whose atrial arrhythmia resolved. Patients older than 40 years at the time of ASD closure were more likely to new onset atrial flutter or fibrillation than their younger counterparts, and patients who had atrial arrhythmia either before surgery or immediately after surgery were more likely to have unresolved atrial arrhythmia. Oliver *et al*., in their cohort of 192 surgically treated patients, demonstrated that age at surgical repair was 47.7 ± 19 years among those patients with persistent atrial fibrillation vs. 22.9 ± 18 years among those who have had resolution of their atrial arrhythmia following surgery. Incomplete atrial remodeling despite correction of the volume loading clearly may be an important factor in the lack of arrhythmia resolution. Possible factors contributing to these irreversible changes within the atrial myocardium may be related to longstanding volume loading, and the degenerative effects of age may be accelerated inducing permanent structural changes within the extracellular matrix and microfibrillar proteins.

Paroxysmal supraventricular tachycardia also forms part of the spectrum of arrhythmia seen late in ASD. Meijboom *et al*., in their series of 104 repaired adults, reported a prevalence of 45%.[180] Thirty-nine percent of these subjects also had sinus node dysfunction by traditional criteria. Brandenburg and colleagues reported a supraventricular tachycardia prevalence of only 5% in their 188 adults over the age of 44 years (all of whom had previous surgical repair).[170] Supraventricular tachycardia, in contrast to atrial fibrillation, is usually more homogeneous, is often reentrant, but may also be secondary to atrial myocardial automaticity.[181] As with atrial fibrillation, atrial enlargement with distention, or increased atrial pressure may contribute to inducibility of paroxysmal supraventricular tachycardia.

Follow-up issues

Whether closed surgically or in the catheter laboratory, a number of post-closure issues need to be addressed.

Freedom from re-intervention

For patients with normal or only mildly elevated pulmonary vascular resistance operative mortality approaches zero, and there is little morbidity and requirement for re-intervention.[11,63,182–184] Re-operation was occasionally required in the early eras of operative repair. One reason was a residual left-to-right shunt. A less common reason was inadvertent diversion of the inferior

caval vein into the left atrium producing a right-to-left shunt. Rarely, a Budd–Chiari syndrome will occur may years after repair of *n* atrial septal defect as in the case reported by Diegeler and colleagues.[185] A young adult patient, in whom 20 years previously a secundum atrial septal defect had been closed surgically, presented with symptoms of a Budd–Chiari syndrome, cirrhosis of the liver, ascites, and edema of the lower legs. The inferior vena cava–right atrial junction was obstructed by a calcified Teflon patch and shrinkage of the surrounding tissue. Augmentation of the inferior vena cava–right atrial junction with a Gore-Tex patch resulted in unobstructed inflow into the right atrium alleviating the situation. Mitral regurgitation is also known to develop after otherwise successful repair of the secundum atrial septal defect.[58–63,186–201] The etiology is considered multifactorial, but the morphology of the valve is often myxomatous with prolapse.[58–63,186–201] The majority of patients following closure of the secundum atrial septal defect, especially those repaired as children or adolescents, enjoy excellent health, regain somatic growth, have normal or near normal exercise tolerance, and are free from important rhythm disturbances.[201A–F] Brochu and colleagues have provided data showing improvement in exercise capacity in asymptomatic and mildly symptomatic adults after percutaneous closure of the atrial septal defect.[201F] On the basis of these findings, they suggest that closure of the atrial septal defect should be considered in the adult, even in the absence of symptoms.

Regression of right ventricular volume loading and hypertrophy

Many studies have shown that after surgical closure of the atrial septal defect indices of right heart enlargement tend to normalize. Resolution of cardiomegaly on the chest radiograph and right ventricular hypertrophy on the electrocardiogram occur in the majority of operated patients. Young found, however, that about one-third of such postoperative patients persisted with cardiac enlargement on the chest radiograph.[202] Berger and his colleagues compared the acute effects on right ventricular hemodynamics of surgical vs. catheter-closure of the secundum atrial septal defect.[203] They found no difference in right ventricular volumes or function early after closure of atrial septal defects, irrespective of whether this was achieved surgically or via transcatheter closure. Kort and his colleagues have studied the resolution of right heart enlargement after closure of secundum atrial septal defect with transcatheter technique.[178] They found that closure of a secundum atrial septal defect results in decreased indexed right ventricular volume comparable to that in control subjects at 24 months following closure. The indexed right atrial area remained increased compared to that of the control subjects but did decrease over time. The decrease in right atrial area was inversely proportional to age at time of atrial septal defect closure. size. Hanseus and colleagues have also studied the cross-sectional echocardiographic measurement of right atrial and right ventricular size in children with atrial septal defect before and after surgery.[204] After surgery, there was a significant decrease in all of the parameters studied, except for right ventricular length. The mean postoperative values of right atrial measurements in the apical four-chamber view and of RVOT were still significantly larger than normal. The right ventricular four-chamber measurements except the apical four-chamber length were not significantly enlarged. The greatest decrease in right atrial and right ventricular size occurred in the first postoperative year. Longer follow-up periods did not change the measurements significantly. There tends to be less normalization of right heart size in the older patient.[204] Furthermore, for patients with increased pulmonary vascular resistance surviving operation, there is less remodeling of the right ventricle and the pulmonary vascular bed, and indices of right heart size tend to remain enlarged.[204]

Bacterial endocarditis

Bacterial endocarditis is extremely rare after repair of an uncomplicated atrial septal defect, and antibiotic prophylaxis is generally only carried out during the first 6 months of surgical closure.[200] There are fewer data on the incidence of endocarditis after catheter-closure, but many tend to recommend prophylaxis for at least a 6 month period or longer. There have thus far been two reported cases of endocarditis involving a transcatheter device after ASD closure. In both instances there was a history of bacteremia, followed by clinical features of endocarditis, at 8 weeks and the other at 10 to 14 weeks after device implantation.[205,206] In both cases there was a large vegetation on the device (1 CardioSEAL and 1 Amplatzer Septal Occluder), one on the right atrial surface and in the other case on the left atrial surface. Endothelialization was incomplete in both instances. These reports underscore the importance of early recognition and prompt treatment of bacteremia, continued antibiotic prophylaxis during the period of endothelialization of the device (i.e. the first 6 months), and the merits of antibiotic prophylaxis during the device implantation.

The fate of elevated pulmonary vascular resistance

Elevated pulmonary pressures, i.e. in excess of 32 mmHg, occur frequently in pediatric and adult patients with ASD. Cherian *et al*. studied 709 consecutive patients with isolated ASD, and the incidence of raised pulmonary arterial pressures they found are shown in Table 4-1.[90]

Evans JR *et al*. from our institution demonstrated SPAP > 50 mmHg in patients < 16 years to occur at a frequency of 5%.[207] In older patients the incidence may be more frequent. Attie *et al*. described a 32% prevalence of mean pulmonary artery pressure ≥ 35 mmHg in adult patients > 40 years.[208] Among patients over the age of 18 years (range (18 to 67 years), Craig *et al*. described elevation of SPAP > 50 mmHg to occur in 22% of patients.[68] Severe pulmonary hypertension and elevated pulmonary vascular resistance is uncommon in ASD. Incidences range in frequency from 4% to 14% across all ages.[96,97,125] As shown in Table 4-2, Cherian and colleagues elegantly demonstrated that elevated pulmonary vascular resistance might occur equally among younger and older patients.[96]

Table 4-1

Age group (yr)	SPAP > 32 mmHg
0–10	71/175 (40%)
11–20	96/248 (39%)
21–30	83/177 (47%)
31–40	41/81 (50%)
Above 40	16/28 (57%)

Table 4-2

Age group (yr)	N	%
0–10	21/175	12
11–20	24/248	10
21–30	30/177	17
31–40	15/81	19
Above 40	3/28	11

Pediatric patients with pulmonary arterial hypertension, although not clearly defined in the above study, have been characterized by other authors. These patients usually present during infancy with heart failure and have coexistent severely elevated pulmonary hypertension. In the small cohorts described by Haworth[98] and Andrews and colleagues,[209] significant concurrent extracardiac anomalies existed in 83% and 20% respectively. Steele *et al*. further demonstrated that elevated PVR might also occur in young adults aged 20–40 years.[125] Although there is an association between age and raised pulmonary vascular disease, this association is certainly not linear, and may be multifactorial in nature giving rise to a rather complex grouping.

The fate of elevated pulmonary vascular resistance, after anatomic closure of the ASD is as yet incompletely defined as are the specific indications for surgical or transcatheter intervention when the PVR is elevated > 10 U/m^2. Steele *et al*. examined 40 patients (mean age 44 years) with PVR > 7 U/m^2 over a follow-up period of at least 4 years and a median follow-up interval of 12 years.[125] At their most recent follow-up, 43% of the cohort was dead. Of their 22 surgically treated patients with a total pulmonary arteriolar resistance of less than 15 U/m^2, 19 were alive with significant regression of symptoms. All 4 of the surgically treated patients with pulmonary resistance in excess of 15 U/m^2 were dead and of the 9 medically treated patients with similar pulmonary resistance, 6 had died, and the surviving 3 patients had progression of their symptoms. From their multivariate analyses they determine that total pulmonary resistance ($P < 0.00001$), systemic arteriolar resistance ($P < 0.00001$), pulmonary-to-systemic resistance ratio ($P = 0.004$), systemic arterial saturation ($P = 0.005$) and pulmonary arterial oxygen saturation ($P = 0.007$) were correlated with survival. Similarly Murphy *et al.* demonstrated that patients older than 24 years with pulmonary arterial systolic pressures in excess of 40 mmHg, were less likely to survive than those patients who were younger or had lower pulmonary arterial pressures.[115]

These data denote heterogeneity of outcome and presumably of pathophysiology in patients with elevated pulmonary vascular resistance. Yamaki *et al.* and others have defined the histological changes seen in raised PVR including plexogenic pulmonary arteriopathy, thromboembolism, musculoelastosis with intimal proliferation of longitudinal smooth muscle bundles and elastic fibers, and various combinations of these histological phenomena.[98,100,101] The distribution throughout the lung fields of these abnormalities also varies considerably within an affected individual, and this has inspired Yamaki and coworkers to develop an index of pulmonary vascular disease which has been used to predict likely outcome after anatomic closure.[210]

Yamauchi and coworkers have recently reported the case of a 35-year-old woman with ASD and severe pulmonary vascular disease.[211] On open lung biopsy she had complete occlusion of 70% of the small pulmonary arteries and arterioles due to musculoelastosis. Following surgical closure of the ASD, long-term oral prostacyclin therapy was initiated. Pulmonary arterial peak pressures decreased from 80/40 (mean 52 mmHg) to 65/35 (mean 48 mmHg) during 2 years of follow-up. These findings resembles those in patients with primary pulmonary hypertension in whom prostacyclin therapy has been associated with improved survival, decreased PVR, longer 6 minute walk-tests and better quality of life.[212,213]

Some have expressed concern about the long-term fate of individuals such as the above patient. Barst in her comments on the above case, denotes that patients such as the above individual may deteriorate in the long term (after 5 years) despite initial clinical improvement following defect closure. She recommends only partially closing the defect leaving a small residual "pop-off" safety valve for the patient. In our experience of nine patients with raised pulmonary vascular resistance and ASD who have been operated on with complete closure of the defect, mean length of follow-up was 13.3 years (range 4–25 years). Before surgery mean PVR was 9 U/m^2 (range 3 to 12.7). At most recently follow-up, there were 2 deaths (1 perioperatively) and the other at late follow-up. One patient had deteriorated clinically with worsening functional capacity, and now awaits heart/lung transplantation. The remainder of the group either remained the same or had improvement in symptoms and or pulmonary arterial pressures (unpublished data). These preliminary observations have paved the way for extending the spectrum of patients who have physiology that is amenable to anatomic closure. Additionally, vasodilator therapy and newer drugs affecting pulmonary arteriolar matrix composition and smooth muscle tone are likely to play an important role in the treatment of patients with pulmonary hypertension and ASD or other associated congenital heart disease.[214]

Specific problems

Sinus venosus atrial septal defects

Patients with uncomplicated secundum atrial septal defects as well as those with sinus venosus atrial septal defects and partial anomalous pulmonary venous return have been shown to have some degree of sinus node dysfunction.[215–226] Walker and her colleagues have found a paucity of sinus node dysfunction following repair of sinus venosus defects in children.[218] Others have reduced the incidence of atrial arrhythmias by modifying the approach to repair of the secundum atrial septal defect.[216] While many of the follow-up issues for the patient with a sinus venosus atrial septal defect are similar to those with an uncomplicated secundum atrial septal defect, there are some differences, related primarily to surgical management of the anomalously connected right pulmonary veins.[19–24,215–226] In most of the series cited there has been a low incidence of superior vena caval narrowing or residual left-to-right shunting. Rarely as in the case of Weber *et al*. superior caval stenosis may be severe with formation of significant pulmonary venous collateralization with right-to-left shunting.[222] In the evolution of the surgical treatment of the secundum atrial septal defect or the sinus venosus defect, most now utilize echocardiography as the imaging modality of choice.[227–229]

Lutembacher syndrome

This is a relatively uncommon syndrome, the syndrome of a secundum atrial septal defect in association with mitral stenosis.[230] The name of Lutembacher has been irrevocably linked with this syndrome since his description of this association in 1916.[230] Hans-Rudolf Wiedemann has found correspondence that reveals that Johonn Friedrich Meckel Senior provided a description in 1750 of what is known today as the Lutembacher syndrome.[231] Perloff provided in 1970 a then contemporary reappraisal of Lutembacher's syndrome.[232] As Perloff discusses in this review,[231] most consider the mitral stenosis to be of rheumatic origin, despite the fact that Lutembacher considered the origin of the mitral valve disease in his 61-year-old patient to be of congenital origin.[230] There are now a number of clinical and interventional reports about the Lutembacher syndrome,[233–236] but as Cheng has stated, this association lends itself ideally to catheter-based intervention: balloon dilatation of the mitral valve and device-closure of the atrial septal defect.[237]

Fetal atrial septal aneurysms

We have discussed elsewhere in this chapter that atrial septal aneurysms may be responsible for anatomic closure of the secundum atrial septal defect, and that these protuberances may participate in the etiology of the cryptogenic stroke. There is a considerable literature addressing the relationship in infants and children between atrial arrhythmia and atrial septal aneurysm.[238–240] Shiraishi and coworkers have also shown that such aneurysms may promote spontaneous closure of secundum atrial septal defects and that they have a tendency to regress as the patient grows up.[240] Rice and her colleagues provided in 1988 a comprehensive review to that time addressing the history and clinical implications of the atrial septal aneurysm, commenting specifically on the association of the atrial septal aneurysm in the child or adult with atrial arrhythmias.[241] There is now considerable literature defining the relationship between fetal atrial septal aneurysm and fetal atrial arrhythmia.[242–247] Data provided by Pappa and his colleagues showed that among high risk fetuses, the incidence of atrial septal aneurysms is 7.6%.[247] Their observations showed an important correlation between the degree of bulging and the presence of arrhythmias, supporting the hypothesis of a mechanical stimulus. However, the observed arrhythmias were not prone to degeneration. In their study they concluded that atrial septal aneurysm observed during fetal life is often associated with premature atrial beats, which are apparently in direct relation to the degree of bulging of the atrial septum. Yet they also found that atrial septal aneurysms almost invariably disappear at birth and are not associated with major arrhythmias.[247]

Cosmetic issues

Perhaps indirectly related to outcome of intervention for the atrial septal defect is the issue of the cosmetic result for those patients undergoing surgery. With the approximate 2:1 female-to-male ratio, it is not surprising that the appearance of the median sternotomy scar is an issue. In order to minimize this standard incision, some have advocated a right anterolateral thoracotomy, while others have used a limited midline sternotomy.[248–258] With the ever-increasing cost constraints on western health care, reducing length of stay has become a widespread challenge. Most centers continue to reduce the length of stay, and same-day-discharge or next day discharge has become a reality for many patients undergoing surgical repair of the secundum atrial septal defect. Whether these less invasive approaches for congenital heart surgery routinely lessen hospital length-of-stay is uncertain.[257]

All references can be found at the end of the book. See pp. 614–20 for Chapter 4.

The Natural and Modified History of Congenital Heart Disease
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Atrioventricular Septal Defect

Patients with so-called endocardial cushion defect, common atrioventricular canal defect, or atrioventricular septal defect comprise a group of hearts unified by absence of the muscular and membranous atrioventricular septum.[1] These terminologies all refer to the same basic forms of congenital heart malformations despite the various designations. Some years ago, Becker and Anderson asked in a provocative editorial: "What's in a name?" when they suggested that "atrioventricular septal defect" is an appropriate designation for those hearts whose diverse morphology is unified by a deficiency of the atrioventricular muscular and membranous septa.[2] We agree and choose to use this terminology, acknowledging that some prefer to use other designations. In this chapter we will consider the outcomes of patients with the complete and partial (ostium primum) forms of atrioventricular septal defect.

Incidence

Data from the New England Regional Infant Cardiac Program provides a frequency of "endocardial cushion defect" of 0.118/1000 livebirths,[3] while the data from the Baltimore–Washington Infant study defined a prevalence of 0.362.[4] The New England Regional Infant Cardiac Program was carried out before the era of cross-sectional echocardiography in the diagnosis of this malformation, and this might account for some of the difference in prevalence. The Alberta Heritage study defined the prevalence of atrioventricular septal defect using invasive methodology for the diagnosis as 0.203 and non-invasive methodology as 0.242 per 1000 livebirths.[5] The prospective Bohemia Survival study identified a total of 201 children with a complete or partial form of atrioventricular septal defect from the 815 569 children born between 1980 and 1990, giving a prevalence of 0.25 per 1000 livebirths and these 201 children accounted for 4% of all congenital heart malformations.[6] Data from Malta found a birth prevalence of 0.31/1000 livebirths.[6A]

The genetics of atrioventricular septal defect

Formation of the atrioventricular canal results from complex interactions of components of the extracellular matrix.[7] In response to signaling molecules, endothelial/mesenchymal transformations are crucial to normal development of the atrioventricular canal. Atrioventricular septal defects can result from arrest or interruption of normal endocardial cushion development. Atrioventricular septal defects have been associated with chromosome abnormalities, laterality or left–right axis abnormalities, and a variety of syndromes. An atrioventricular septal defects susceptibility gene has been identified in a large kindred with many affected members. Studies of transcription factors and signaling molecules in heart development over the past decade are paving the way for our understanding of the heterogeneous mechanisms of causation of atrioventricular septal defects.[7] Down syndrome (DS) is a major cause of congenital heart disease (CHD) and the most frequent known cause of atrioventricular septal defects (AVSDs). Molecular studies of rare individuals with CHD and partial duplications of chromosome 21 established a candidate region that included D21S55 through the telomere. Barlow and colleagues report human molecular and cardiac data that narrow the DS-CHD region, excluding two candidate regions, and propose DSCAM (Down syndrome cell adhesion molecule) as a candidate gene.[8] They studied a panel of 19 individuals with partial trisomy 21 using quantitative Southern blot dosage analysis and Fluorescence *in situ* hybridization (FISH) with subsets of 32 BACs spanning the region defined by D21S16 (21q11.2) through the telomere. These BACs span the molecular markers D21S55, ERG, ETS2, MX1/2, collagenXVIII and collagen VI A1/A2. Fourteen individuals are duplicated for the candidate region, of whom eight (57%) have the characteristic spectrum of DS-CHD. Combining the results from these eight individuals suggests the candidate region for DS-CHD is demarcated by D21S3 (defined by ventricular septal defect), through PFKL (defined by tetralogy of Fallot). These data suggest that the presence of three copies of gene(s) from the region is sufficient for the production of subsets of DS-CHD. This region does not include genes located near D21S55, previously proposed as a "DS critical region," or the genes encoding collagens VI and XVIII. Of the potential gene candidates in the narrowed DS-CHD region, DSCAM is notable in that it encodes a cell adhesion molecule, spans more than 840 kb of the candidate region, and is expressed in the heart during cardiac development. Given these properties, they propose DSCAM as a candidate for DS-CHD.[8]

Thus the management of patients with atrioventricular septal defect is often complicated by Down syndrome.[9–34] Down syndrome was present in 114 of 142 (80%) infants under one year of age with the complete form of atrioventricular septal defect undergoing surgery in this institution.[21] Similar associations have been recorded elsewhere. When viewed from the reverse perspective, between 35% and 40% of patients with Down syndrome have an atrioventricular septal defect, and in most of these this takes the form of a common rather than a partitioned

atrioventricular orifice. Rosenquist and his colleagues have suggested that an enlarged membranous ventricular septum may be an internal stigma of Down syndrome.[11] Minich and colleagues have studied the relation between ventricular structure size and surgical outcome in Down vs. non-Down syndrome infants with an atrioventricular septal defect.[35] They reviewed the charts and echocardiograms of 44 consecutive infants (34 with Down syndrome) who underwent atrioventricular septal defect repair. Children with Down syndrome had significantly greater aortic valve diameters, left ventricular valve areas, and left/right atrioventricular valve area ratios as well as fewer adverse outcomes than non-Down syndrome children.[35] As well, De Biase and colleagues suggest that there is an increased prevalence of left-sided obstructive lesions in patients with atrioventricular septal defect without Down syndrome.[35] Marino and his colleagues have assessed the prevalence of associated cardiac malformations in a large cohort of patients with atrioventricular septal defect compared with patients without Down syndrome.[15–18] Among 220 patients with atrioventricular septal defect, 130 had a complete form of atrioventricular septal defect; 80 of these had Down syndrome (61.5%) and 50 without Down syndrome (38.5%). Of the 90 patients with a partial form of atrioventricular septal defect, 25 (28%) had Down syndrome and 65 (72%) without Down syndrome. Thus Down syndrome was most commonly associated with a complete form of atrioventricular septal defect ($P < 0.01$), and the patients without Down syndrome tended to have the partial form of the defect. Addressing the entire spectrum of associated cardiac malformations in these 220 patients, 112 had a total of 137 associated malformations. The associated cardiac malformations were significantly more frequent ($P < 0.0001$) in patients without Down syndrome. Amongst those patients with Down syndrome and the complete form of atrioventricular septal defect, tetralogy of Fallot was more prevalent. In patients without Down syndrome, the hypoplastic left ventricle and coarctation were more common. Marino has also found that patients without Down syndrome and atrioventricular septal defect have a higher risk of left-sided obstructive lesions.[16] Interestingly, Marino and his colleagues documented the rarity of additional ventricular septal defects in the apical muscular septum of patients with atrioventricular septal defect and Down syndrome.[17] Surgical results for atrioventricular septal defect have been stratified against patients with and without Down syndrome.[14,15,25–27] Again, there is not unanimity of opinion that Down syndrome disadvantages surgical outcome. Data provided by Morris suggested a trend towards higher mortality and poorer postoperative hemodynamics in children with Down syndrome,[25] though this was not the conclusion found by Vet and Ottenkamp,[27] and data from Castaneda and Clapp both indicate an improvement in hemodynamic status after surgical repair.[28–30] Similarly data from Rizzoli did not support the position that surgical outcome was poorer in the patient with Down syndrome.[26]

Bull and her colleagues forwarded the suggestion some time ago that patients with Down syndrome and atrioventricular septal defect might do better without surgery because of the inherent risks of surgery.[31] This suggestion provoked considerable discussion[33,34] and clearly in many centers today repair of the complete form of atrioventricular septal defect can be accomplished with a risk of less than 5%, considerably lower than the data provided by Bull (see Outcome analysis below). Shinebourne and Carvalho have recently provided an overview of atrioventricular septal defect and Down syndrome.[32]

Morphology of the atrioventricular septal defect

As we have stated earlier, the group of hearts designated as "atrioventricular septal defects" are united by their absence of the membranous and muscular atrioventricular septa (Fig. 5-1).[2] An extensive literature has accumulated documenting the anatomic heterogeneity of and the disposition of the specialized conduction tissue in these hearts.[36–69] One can further categorize or subclassify hearts with atrioventricular septal defects by the presence of a partitioned or common valve orifice; whether a ventricular septal defect is present and the size of the defect; the presence and size of the ostium primum atrial septal defect; and whether the defect is balanced or unbalanced (i.e. dominant right or left ventricular forms) (Fig. 5-2).[41,63] There is today relatively less emphasis on Rastelli's classification.[53,54] The atrioventricular septal defect includes a spectrum of abnormalities, ranging at one end the patient with intact or nearly so atrial and ventricular septa and at the other end, the patient with large and usually confluent atrial and ventricular septal defects with a common atrioventricular orifice.[36–65,70] This spectrum thus includes the ostium primum atrial septal defect with cleft left atrioventricular valve to the large defect that is divided into the interatrial and interventricular components by the free-floating common atrioventricular valve leaflets. The internal organization of the morphological right ventricle conforms to a right-hand pattern when the atrial relationships are normal or solitus. In the presence of atrial isomerism, about half had a left-hand pattern of internal organization.[71] There are rare cases of AVSD in the presence of situs solitus, AV discordance, and therefore left-hand ventricular topology. The ostium primum atrial septal defect may be very small and in rare instances the atrial septum is intact.[55,63,70] In some patients there is gross deficiency of both the primum and secundum portions of the atrial septum, resulting in a common atrium. The usual form of ostium primum atrial septal defect is bounded below by the inferiorly displaced atrioventricular valve leaflets and above by a crescentic ridge of atrial septum that fuses with the atrioventricular valve ring at

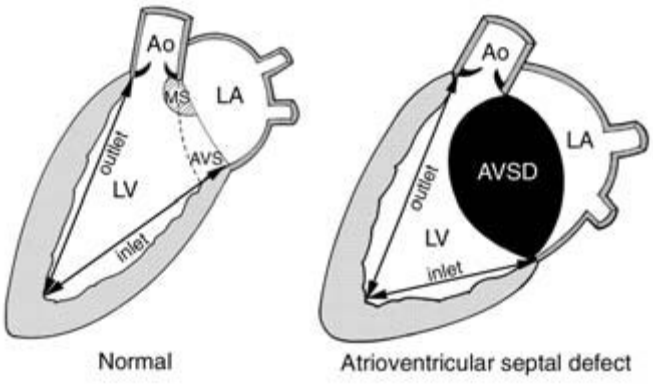


Fig. 5-1 Left side of the septum in normal heart and in atrioventricular septal defect. The unifying pathological features of the atrioventricular septal defects are: 1. Defect of the atrioventricular septum (AVSD) with variable extension to the adjacent atrial and ventricular septum. 2. Common atrioventricular annulus or junction with unwedged position of the aortic valve (see Fig. 5-2A). 3. Short inlet or diaphragmatic surface of the left ventricle. 4. Anterior displacement of the aortic valve with elongation of the left ventricular outlet. 5. 3 and 4 together resulting in left ventricular inlet/outlet disproportion. Ao = aorta; AVS = atrioventricular septum; LA = left atrium; LV = left ventricle; MS = membranous septum.

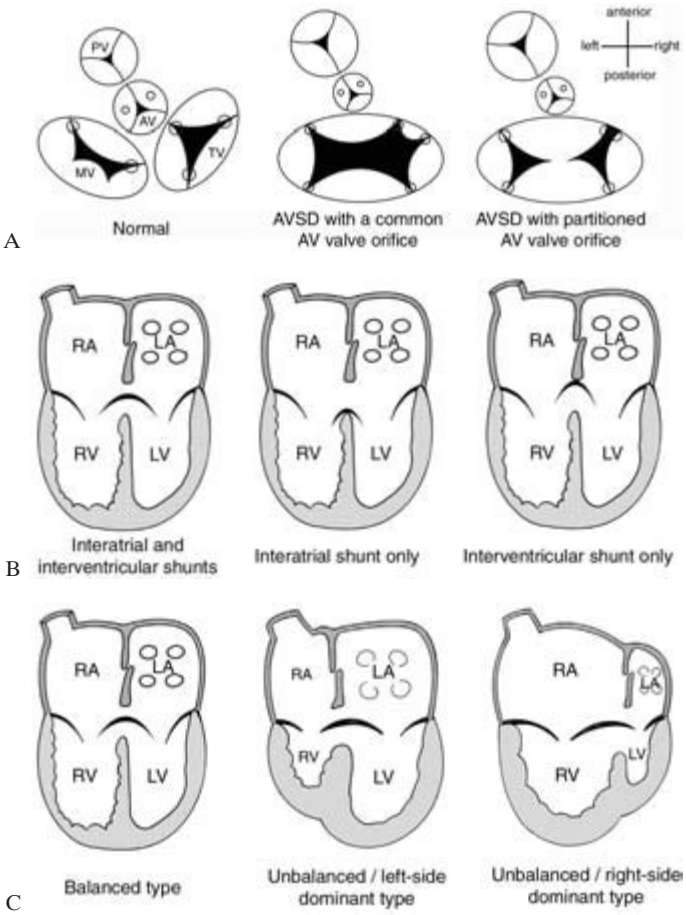


Fig. 5-2 Variations of atrioventricular septal defects. A. Common vs. partitioned atrioventricular (AV) valve orifice. Notice that atrioventricular junction in atrioventricular septal defect (AVSD) is characterized by a common annulus. Therefore, the aortic valve (AV) is not in a normal wedged position between the tricuspid (TV) and mitral (MV) valves, even if the atrioventricular orifice is partitioned as in right-hand diagram. PV = pulmonary valve. B. Attachment of the atrioventricular leaflets to the septum and the level of shunts. LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle. C. Balanced vs.. unbalanced types of atrioventricular septal defect.

its extremities.[27] A true defect of the fossa ovalis may be present or a patent foramen ovale will be evident. The septal defect extends to the adjacent inlet portion of the ventricular septum. Therefore, in the so-called partial or transitional forms of atrioventricular septal defect, a deficiency of the inlet portion of the ventricular septum immediately beneath the atrioventricular valves of variable extent should be evident.[63] The partial form is characterized by the complete attachment of the superior and inferior bridging leaflets which are connected by a tongue of valvar tissue, to the scooped out ventricular septal crest, obliterating the interventricular component, but leaving the ostium primum atrial septal defect. The transitional form, a variant of the partial form, is characterized by the chordal attachments of the bridging leaflets to the ventricular septal crest, leaving small interventricular channels between the chords as well as a large ostium primum atrial septal defect. Thus, when the superior and inferior bridging leaflets of the atrioventricular valve are firmly connected and are completely attached to the downwardly and scooped crest of the ventricular septum throughout its length, a ventricular septal defect should not be present. There may be, however, several small ventricular septal defects beneath the attachment of the bridging leaflets to the ventricular septum. The ventricular septal defect may be large and non-restrictive and in combination with a substantial primum atrial septal defect, a complete form of atrioventricular septal defect is present. A common atrioventricular orifice is usually present, and thus a tongue of connecting tissue is not present, producing a bare area on the crest of the ventricular septum. The variable attachment or bridging of the left superior leaflet formed the basis of Rastelli's classification of the atrioventricular septal defect.[53,54]

As mentioned the deficiency of the atrioventricular septum may extend to the adjacent ventricular septum. In the majority of patients, the ventricular septal defect excavates apically and includes the upper portion of the inlet septum, and this is responsible for the scooped out appearance.[36–61,63–66] The deficiency of the septum is more conspicuous at the crux of the heart rather than in the antero-superior part. Because of the deficiency at the ventricular inlet, the bridging leaflets are not at the level of the normal septal leaflet, but are rather attached more apically, thus creating a deformity of the ventricular inlets. This explains the inlet–outlet disproportion of the left ventricle, a well-known feature in hearts with anatrioventricular septal defect (Fig. 5-1). In addition, the atrioventricular septal defect is associated with true elongation of the outlet dimension. As the common atrioventricular valve orifice does not allow any space for a normal wedged position of the aortic valve, the aortic valve is placed far anteriorly, resulting in a true elongation of the left ventricular outlet. Thus in hearts with deficiency/absence of the atrioventricular septum, the outlet tract of the left ventricle is always lengthened in relation to the inlet. Almost all hearts with an atrioventricular septal defect and ventricular septal defect show some degree of scooping of the ventricular septum. This scooping is seemingly not related to the morphology of the superior bridging leaflet, nor to the severity of the valvar regurgitation.[66] Suzuki and colleagues have found the scooping to correlate with the morphology of the inferior bridging leaflet.[66] One or more additional muscular ventricular defects may also be found in association with the atrioventricular septal defect.

Pulmonary vascular disease and Down syndrome

The conclusion that patients with Down syndrome and the complete form of atrioventricular septal defect are at increased risk for the development of pulmonary vascular obstructive disease when compared to otherwise normal children with the same heart defect remains contentious.[72–86] Hemodynamic data provided by Chi and Krovetz in 1975 suggested that patients with congenital heart disease and Down syndrome have an unusually high pulmonary vascular resistance and a propensity for early development of severe damage to the pulmonary vascular bed.[72] Soudon and colleagues also in 1975 came to the same conclusion based on hemodynamic results of pulmonary vascular resistance calculations.[79] More recently and with more follow-up data, Clapp and her colleagues conclude that Down syndrome patients with complete atrioventricular septal defect have a greater degree of elevation of pulmonary vascular resistance in the first year of life and more rapid progression to fixed pulmonary vascular obstruction than patients without Down

syndrome,[30] but this was not seen in the review of Studer and his colleagues.[83] A number of investigators have addressed the morphology of the pulmonary vascular bed in patients with congenital heart disease statified (yes/no) against Down syndrome. Plett and her colleagues did not find histologic evidence that patients with Down syndrome were disadvantaged.[81] However, Frescura and colleagues correlated pulmonary vascular resistance determined from catheter-derived hemodynamic data against pulmonary vascular disease at histology (from autopsy and biopsy material) and concluded that the most severe pulmonary vascular disease was observed in patients with Down syndrome.[74] On the basis of their data they recommend that surgical correction of the complete form of atrioventricular septal defect be carried out by 6 months of age, a policy followed by most centers.

Haworth has studied extensively the pulmonary vascular bed in children with complete atrioventricular septal defect, correlating structural and hemodynamic abnormalities.[75,76] Her data were not clearly stratified against (yes/no) Down syndrome. The striking finding in her study was the inverse relation between pulmonary artery muscularity, pulmonary artery pressure and resistance, and age. Intimal damage increased with age and cases with the least amount of muscle frequently demonstrated the most severe intimal proliferation and obstruction.[170] Yamaki and colleagues analyzed pulmonary vascular disease morphometrically in 67 patients with the complete form of atrioventricular septal defect, and their data were stratified against Down syndrome.[80] These workers found the same inverse relation between pulmonary artery muscularity and intimal proliferation and obstruction, defining that the media was thinner in those patients with Down syndrome and that such thinning of the media of the small pulmonary arteries was generally observed at about 6 months of age. Yamaki and colleagues therefore recommend that intracardiac repair is desirable within 6 months of age, before maximal medial thinning for patients with the complete form of atrioventricular septal defect and Down syndrome. Whether there is an intrinsic "molecular" basis for accelerated pulmonary vascular disease in those patients with Down syndrome is uncertain. Chronic upper airway obstruction with macroglossia and an inherently small hypopharynx, hypotonia, the predisposition to chronic infection, an abnormal capillary bed morphology, and the suggestion of pulmonary hypoplasia can all adversely affect the pulmonary vascular bed.[73,84,85]

Outcome analysis

There is considerable information on the fetal recognition of atrioventricular septal defects, the association with aneuploidy, and fetal outcome.[87–92] In the study of Delisle and colleagues, prenatal diagnosis of atrioventricular septal defect was associated with a 58% risk of aneuploidy (mainly trisomy 21).[92] Furthermore, when an isolated atrioventricular septal defect was diagnosed prenatally, the odds of trisomy 21 were significantly higher than when other associated cardiac lesions were diagnosed. Allan and her colleagues diagnosed 372 cases of atrioventricular septal defect in the fetus, and of these 174 were associated with heterotaxy.[91] Of the 198 cases without heterotaxy, 107 had proven chromosomal anomalies including 92 with Down syndrome, 10 with trisomy 18, two with trisomy 13 and three with other chromosomal anomalies.[91] Left heart anomalies were recognized in 48 of the 198 cases, including coarctation of the aorta, subaortic stenosis and left heart hypoplasia. Termination of pregnancy took place in 104 of the 198 cases (53%), with spontaneous intrauterine deaths in 16. Indeed, fetal survival is poor and more than two-thirds of fetuses recognized to have an atrioventricular septal defect do not survive pregnancy.[88,90–92] Feslova and coworkers have also studied the spectrum and outcome of atrioventricular septal defect in fetal life.[92A] Of the 82 fetuses in this survey, 44 fetuses were found to have an atrioventricular septal defect without other associated cardiac malformations, while 38 fetuses had a complex form of atrioventricular septal defect. Chromosomal abnormalities were identified in 33 of the fetuses (40.2%), more frequently in cases without associated intracardiac defects (56.8%). Trisomy 21 occurred in just over one-quarter of the series, and in 43.2% without associated defects.[92A] Of the fetuses with more complex anomalies, 46.4% had some degree of hypoplasia of the left ventricle and aorta. Complete heart block was found in 10 of the fetuses (12.2%), and this was particularly common in those with left isomerism. The pregnancy was terminated in 25 instances (30.5%). Of the 57 cases continued through pregnancy, nine fetuses died before term (15.8%), 32 died postnatally, (56.1%), and only 16 fetuses (28.1%) survived. As one might expect mortality was higher in those fetuses with associated malformations, heart failure and those with complete heart block.[92A]

The outcome of live-born patients with atrioventricular septal defect depends on the specific morphology of the defect, the size of the ventricular septal defect (or interventricular component of the defect), degree of ventricular hypoplasia, degree of atrioventricular valve regurgitation, presence or absence of left ventricular outflow tract obstruction, presence or absence of coarctation of aorta, and associated syndromes (cardiac and noncardiac). Patients with the complete form of atrioventricular septal defect and large ventricular septal defect not undergoing repair die in infancy with congestive heart failure and pulmonary artery hypertension. Those who survive without surgery into childhood usually develop pulmonary vascular obstruction and eventually die with Eisenmenger's syndrome. Berger and his colleagues found that only 54% of patients born with a complete form of atrioventricular septal defect were alive at 6 months of age, 35% at 12 months, 15% at 24 months, and 4% at 5 years of age.[93] The hazard function reflecting the instantaneous rate of dying is highest in the first few months of life, gradually falling after that to nearly plateau at about 36 months of age.[93] These data alone would support surgical intervention in the first 3–6 months of age. Those with severe left ventricular underdevelopment may have a systemic circulation that is ductdependent, and their course will be similar to those babies with the hypoplastic left heart syndrome. Infants with primum atrial septal defect presenting in infancy have a poor outcome, mainly because of the associated risk factors that bring these infants to early attention.[94–98] In contrast, those with the partial form of atrioventricular septal defect (the patient with the primum form of atrial septal defect) and minimal left atrioventricular valve regurgitation seem to fare the best without surgery, although there is still likely considerable morbidity and mortality.[99] None the less, according to Somerville, 50% die before 20 years of age and only 25% survive beyond 40 years of age.[100] She noted as well that atrial fibrillation in these patients was an important cause of late morbidity and mortality.[100]

Over the past 40 years, surgery for the complete form of the defect has evolved from palliative pulmonary artery banding in infancy with later repair to primary repair, preferably in the first

3–6 months of age to prevent the development of pulmonary vascular obstructive disease. The evolution to primary repair of the patient with the complete form of atrioventricular septal defect occurred primarily in the late 1970s and early 1980s. There are numerous reports from the various eras that continue to demonstrate improving surgical results in ever younger patients, including those weighing less than 2.5 kg. Part of this improvement has been based on knowledge of specific anatomic risk factors in patients with atrioventricular septal defect. These include: (1) ventricular hypoplasia;[63,94,95,101–111] (2) left ventricular outflow tract obstruction;[112–137] (3) double-orifice left atrioventricular valve;[63,95,138–147] (4) parachute deformity of left atrioventricular valve;[63,95,148–155] (5) double-outlet atrium, right or left;[156–167] (6) association with other forms of congenital cardiac anomalies (tetralogy of Fallot; double-outlet right ventricle; hearts with right or left atrial isomerism; Ebstein's anomaly; etc.).[168–191] Fixler in his discussion of the surgical experience of the Pediatric Cardiac Care Consortium nicely summarizes the surgical history of this disorder.[101] The evolution in surgical therapy from two-stage to primary repair in early infancy is complemented by the use of cross-sectional echocardiography in the pre-, intraoperative and postoperative management of these patients.[192,193] Randolph and his colleagues from the Mayo Clinic have examined the impact of intraoperative transesophageal echocardiography during surgery for congenital heart disease.[193A] They found the major impact of these studies to be most frequent during re-operations and operations for valve (aortic and atrioventricular) repairs and for complex outflow tract reconstructions as in the Rastelli operation (see Chapter 25C). Cardiac catheterization with angiography is rarely required today unless there are specific questions that cannot be easily sorted out with echo (i.e. multiple ventricular septal defects, degree of ventricular hypoplasia, etc) or unless there are issues about pulmonary vascular resistance and reactivity, etc.

The transition from a two-stage approach to primary repair in infancy of the complete form of atrioventricular septal defect began in the late 1970s[1,83,194–196] and there are now a substantial number of reports addressing survival and risk factors for re-operation, etc.[197–201] The Pediatric Cardiac Care Consortium reported on 768 patients from 1984 to 1993 operated on with a complete form of atrioventricular septal defect.[101] The most common associated cardiac malformation was the patent arterial duct, occurring in 18.2% of the patients. The overall mortality for the 768 patients was 13.9% and for the 486 infants the mortality was somewhat higher at 16.6%. In this series of 768 patients with a complete form of atrioventricular septal defect, 577 (75%) had Down syndrome. Infants without Down syndrome operated on during the first 3 months of life had a higher operative mortality rate than those with Down syndrome. Down syndrome patients had an overall mortality of 12.6%, compared to the operative mortality of 17.8% in those without Down syndrome. Many contemporary reports report surgical mortalities of 8% or 9% or less for repair of patients with the complete form of atrioventricular septal defect.[197–201] A number of these reports address the difficult issues of the parachute left atrioventricular valve, the double-orifice valve (usually left), and the mechanisms responsible for and surgical techniques to address left ventricular outflow tract obstruction.[21,22,63,197–201] The various proponents for a one patch or two patch repair technique are well represented in the literature.

Merrill and his colleagues reported in 1991 their experience with 103 consecutive children who underwent repair of complete atrioventricular septal defect between 1971 and 1990.[202] Ninety-one patients were less than 18 months old (mean age, 6.2 months; mean weight, 5.8 kg) and were repaired using deep hypothermia and circulatory arrest. There were 15 perioperative deaths. Twelve patients were older (mean age, 40.2 months; mean weight, 18.9 kg) and were repaired using moderate hypothermia and cardiopulmonary bypass. There were two perioperative deaths. Repairs were performed with the single-patch technique. Four younger patients required repeat repair to control residual mitral regurgitation. Two of the older children required late re-operation to replace one or both atrioventricular valves. Three younger children underwent pulmonary artery banding initially; 1 died after complete repair. Three older children underwent initial pulmonary artery banding; 2 died at definitive repair, and the survivor required pulmonary artery reconstruction, which was repeated subsequently. Since 1977 their policy was to perform primary definitive repair whenever possible. Two patients died late from unrelated causes. At the most recent follow-up the majority of patients had no or minimal symptoms.

Bailey and Watson reported their modest surgical experience from September 1984 through August 1989 with 33 consecutive infants (mean age, 9 months; 13 male) who received a single-stage intracardiac repair of complete atrioventricular septal defect.[203] All infants operated on were included in the analysis. All operations used a two-patch technique for closure of the atrioventricular septal defect in association with left atrioventricular valve repair. The newly formed septal leaflet of the left atrioventricular valve was repaired using unpledgeted interrupted sutures. Preoperative and postoperative echocardiograms were used to evaluate left atrioventricular valve regurgitation and left ventricular dysfunction as mild, moderate, or severe. The 30-day mortality was 6% (2/33). Follow-up of these patients ranged from 1 month to 60 months. Postoperative left atrioventricular valve insufficiency was mild in 84% vs. 6% preoperatively, moderate in 3% vs. 52% preoperatively, and severe in 13% vs. 42% preoperatively. Left atrioventricular valve dysfunction necessitating re-operation occurred in 6% (2/31). Left atrioventricular valve function postoperatively was improved compared with preoperatively ($P < 0.001$).

Hanley and his colleagues in 1993 reviewed the surgical experience of the Boston Children's Hospital with the repair of the complete form of atrioventricular septal defect.[199] Case histories of 301 patients with complete atrioventricular septal defect presenting to their institution in infancy between January 1972 and January 1992 were reviewed with the purpose of identifying the factors responsible for the observed improvement in perioperative mortality over this time period. A retrospective analysis of hospital records examined 46 patient-related, morphologic, procedure-related, and postoperative variables for associations with perioperative death and re-operation. Operative mortality decreased significantly over the period of the study from 25% before 1976 to 3% after 1987 ($P < 0.0001$). A number of the 46 variables examined showed trends over time that were similar to that for mortality. Palliative procedures decreased over time. Re-operation for most residual lesions also decreased to the degree that they were essentially eliminated in recent years. The exception to this was re-operation for postoperative left atrioventricular valve regurgitation, which also decreased but remained at

7% in recent years. Both technical and support-related procedural variables showed no trends over time, with the exception of the performance of left atrioventricular valve annuloplasty, which increased over time. Closure of the left-sided cleft was performed in 61% of the patients, with no trend over time. Annuloplasty and cleft closure were not associated with less postoperative left atrioventricular valve regurgitation, fewer re-operations, or lower mortality. Multivariate logistic regression analysis identified only earlier year of operation, the presence of double-orifice and possibly parachute left atrioventricular valve, and postoperative residual regurgitation of the left atrioventricular valve as risk factors for death. Experience-related improvements in technical precision achieved over time best account for the reduction in the rate of re-operation for most types of residual lesions and also for the reduction in mortality. The only residual lesion that has not been essentially completely eliminated is left atrioventricular valve regurgitation, with re-operation for this condition having been reduced in recent years, but not eliminated. Intraoperative transesophageal echocardiographic evaluation of left atrioventricular valve function has been an important adjunct in the repair.

Bando and his colleagues reviewed in 1995 their 20-year experience with the surgical management of complete atrioventricular septal defects.[204] They retrospectively analyzed the hospital records of 203 patients between January 1974 and January 1995. The overall early mortality was 7.9%. But this decreased significantly over the period of the study from 19% (4/21) before 1980 to 3% (2/67) after 1990 ($P = 0.03$). Ten-year survival including operative mortality was 91.3% ± 0.004% (95% confidence limit): all survivors are in New York Heart Association class I or II. Preoperative atrioventricular valve regurgitation was assessed in 203 patients by angiography or echocardiography and was considered trivial or mild in 103 (52%), moderate in 82 (41%), and severe in 18 (8%). The left atrioventricular valve cleft was closed in 93% (189/203) but left alone when valve leaflet tissue was inadequate and when closure of the cleft might cause significant stenosis. Re-operation for severe postoperative left atrioventricular valve regurgitation was necessary in eight patients, five of whom initially did not have closure of the cleft and three of whom had cleft closure. Six patients had re-operation with annuloplasty and two patients required left atrioventricular valve replacement. Five patients survived re-operation and are currently in New York Heart Association class I or II. On most recent evaluation assessed by angiography or echocardiography (a mean of 59 months after repair), left atrioventricular valve regurgitation was trivial or mild in 137 of the 146 survivors (94%) examined; none had moderate or severe left atrioventricular valve stenosis. By multiple logistic regression analysis, strong risk factors for early death and need for re-operation included postoperative pulmonary hypertensive crisis, immediate postoperative severe left atrioventricular valve regurgitation, and double-orifice left atrioventricular valve. They suggest that routine approximation of the cleft is safe and has a low incidence of re-operation for left atrioventricular valve regurgitation, or stenosis.

Tweddell and colleagues sought to determine factors predicting mortality and morbidity after repair of complete atrioventricular septal defect.[205] They retrospectively analyzed preoperative, operative, and post-repair factors on the outcome of 115 consecutive complete atrioventricular septal defect repairs at The Children's Hospital of Wisconsin between January 1974 and December 1993. For the entire experience the operative mortality was 13.9% (16 patients). During the most recent era, January 1988 to December 1993, operative mortality was 3.6% (2 of 55 patients). This was significantly improved from the two previous eras, January 1974 to December 1980, 28% (7 of 25) and January 1981 to December 1987, 20% (7 of 35 patients) ($P = 0.02$). There were seven late deaths; 10-year actuarial survival, including operative mortality was 81%. Age at complete repair decreased; before 1982 all patients were more than 12 months of age, whereas after 1982 64% (56 of 88 patients) were 12 months of age or less. Moderate or severe preoperative left atrioventricular valve regurgitation was not a risk factor for operative mortality. For operative survivors with moderate to severe preoperative left atrioventricular valve regurgitation ($n = 17$), late postoperative left atrioventricular valve regurgitation (follow-up data available on 15 patients) was significantly reduced (severe = 1, moderate = 5, mild = 9; $P = 0.007$). In this experience early mortality was predicted by the era of surgical repair. Conversion to routine repair during infancy was achieved with a simultaneous decrease in operative mortality. For patients with moderate to severe preoperative left atrioventricular valve regurgitation, significant improvement in the degree of left atrioventricular valve regurgitation was achieved without an increase in operative or late mortality or morbidity.[205]

We have reported our surgical experience with 363 children with the complete form of atrioventricular septal defect who underwent defect repair (median age, 8.3 months; mean, 17.4 ± 1.3) from July 1982 to February 1995.[22] Tetralogy of Fallot was present in 21 patients, double-outlet right ventricle in four, subaortic stenosis in eight, ventricular hypoplasia in eight, coarctation in five, atrial isomerism in two, and other congenital anomalies in nine. Down syndrome was present in 235 (65%). One-patch technique was applied in 99, two-patch in 243. During repair, the anterior bridging leaflet was divided in 12, the posterior bridging leaflet in 31, both leaflets in 71, and neither in 249. The left atrioventricular valve (LAVV) cleft was closed partially in 181 and completely in 112. Early mortality was 10.5%; 10-year survival, 83% (95% confidence interval, 0.79 to 0.87). At 10 years, freedom from re-operation for LAVV repair was 86%; LAVV replacement, 90%; subaortic stenosis, 95%; residual ventricular septal defect, 97%; permanent pacemaker insertion, 98%; and other types of re-operation, 95%. At the time of operation, greater age, shorter ischemic time, absence of a double-orifice LAVV, and cleft closure were found to be significant independent predictors of survival (Fig. 5-3). Our data showed that repair of atrioventricular septal defects has acceptable early and late mortality and a low incidence of re-operation. In our experience, double-orifice LAVV remained a risk factor. From our data, repairs that include complete cleft closure may confer better survival. The follow-up of our patients ranged from 2 months to 14 years (mean, 5 years; median, 4 years).[22] During the follow-up, 45 patients (12%) underwent a total of 61 re-operations at a mean of 24.6 months after the initial repair. Twenty-six patients underwent re-operation for LAVV repair at a mean interval of 21 months, with seven (30%) performed within 30 days of the initial repair. Freedom from re-operation for LAVV repair at 10 years was 90% (95% CL, 0.83 to 0.89). Re-operation for LAVV replacement occurred in 8 patients at a mean interval of 53 months, and 4 of these had

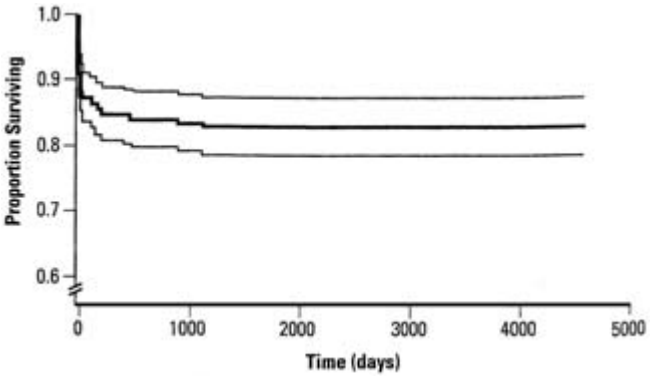


Fig. 5-3 Kaplan–Meier estimate of survival after repair of complete form of atrioventricular septal defect in 363 patients operated on between 1982 and 1995. The thin lines mark the 95% CL. (Reprinted from Najm *et al*.,[22] Copyright (1997), with permission from Lippincott Williams & Wilkins.)

undergone previous re-operation for LAVV repair. Re-operation for a residual ventricular septal defect was required in 7 patients, at a mean interval of 3 months, and five of these occurred within 30 days of initial repair, and these happened early in our clinical experience. Freedom from re-operation for ventricular septal defect at 10 years was 97% (95% CL, 0.96 to 0.98) (Fig. 5-4). Re-operation for permanent pacemaker implantation occurred in 5 patients at a mean interval of 10 months, and three had an implantation in the early postoperative period. Freedom from re-operation for permanent pacemaker implantation at 10 years was 98% (95% CL, 0.97 to 0.98). Multiple variables were examined to determine their association with re-operation. Only double-orifice LAVV was associated with higher re-operation rate. Other reports have also found that a double-orifice LAVV was associated with an increased risk of important LAVV regurgitation.[197–201]

Several papers have focused on the form and function of the LAVV both before and after initial repair of the atrioventricular septal defect (Fig. 5-5).[206–210] Some have argued that preoperative regurgitation is a risk factor both for operative mortality and postoperative regurgitation, but others have argued against this suggestion. Perhaps more consider the improvement in surgical results to reflect better understanding of the structure and variability of the atrioventricular septal defect, improved surgical technique and perioperative care, and the routine application of transesophageal cross-sectional echocardiography and color Doppler.[193] Suzuki ad colleagues studied those predisposing factors for LAVV regurgitation in the complete form of atrioventricular septal defect.[209] They found that that those with a Rastelli type C and an undivided inferior bridging leaflet had a lesser degree of progression of preoperative regurgitation. Once regurgitation had progressed, it was likely to exist and possibly worsen after complete repair. Michielon *et al.* suggest that annular dilatation and deterioration of the tissue with age plays an important role in preoperative LAVV regurgitation.[208] It is evident from the large number of surgical series that the

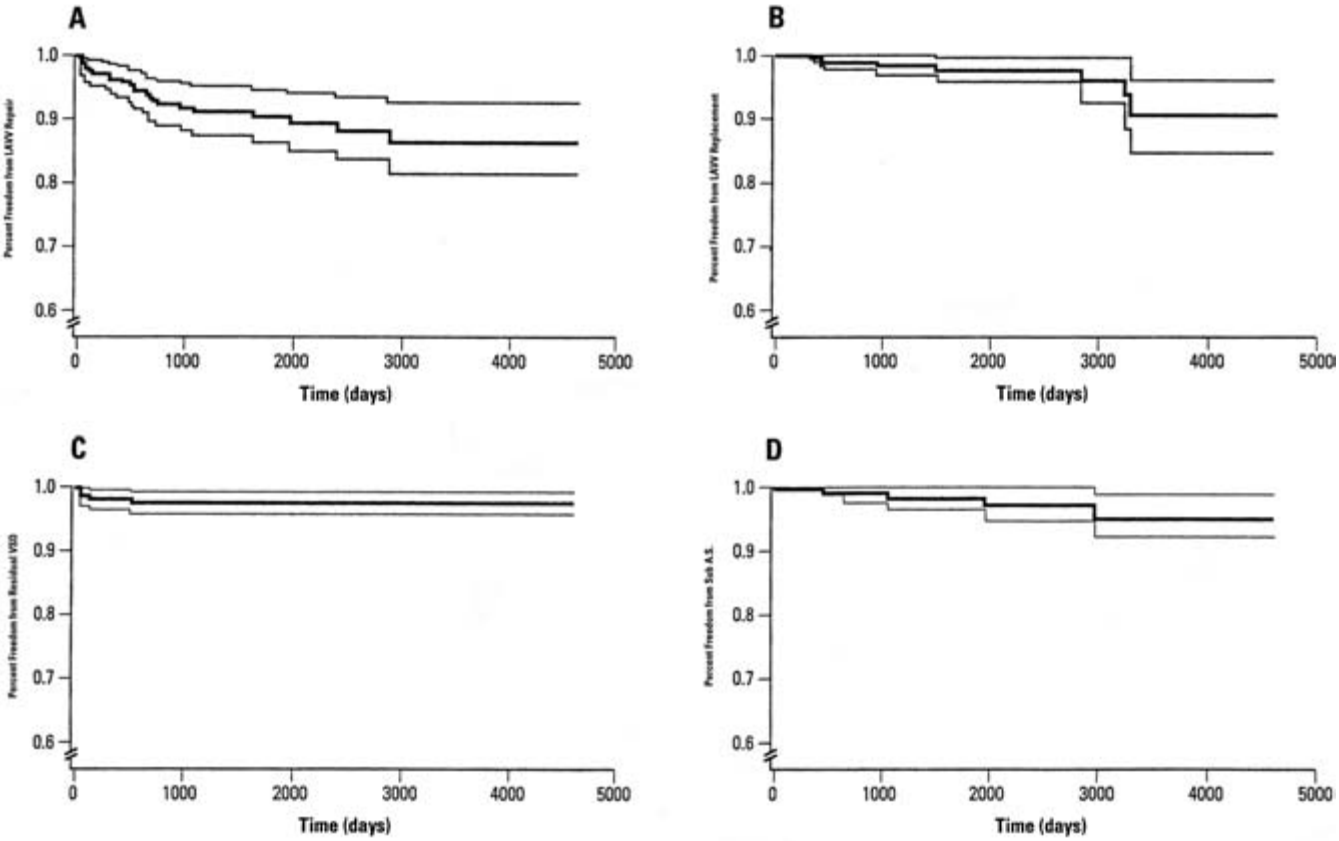


Fig. 5-4 Kaplan–Meier estimate of the percentage from re-operation. Thin lines mark the 95% CL. **A**, for left atrioventricular valve repair; **B**, for left atrioventricular valve replacement; **C**, for subaortic stenosis; **D**, for residual large ventricular septal defect. (Reprinted from Najm *et al*.,[22] Copyright (1997), with permission from Lippincott Williams & Wilkins.)

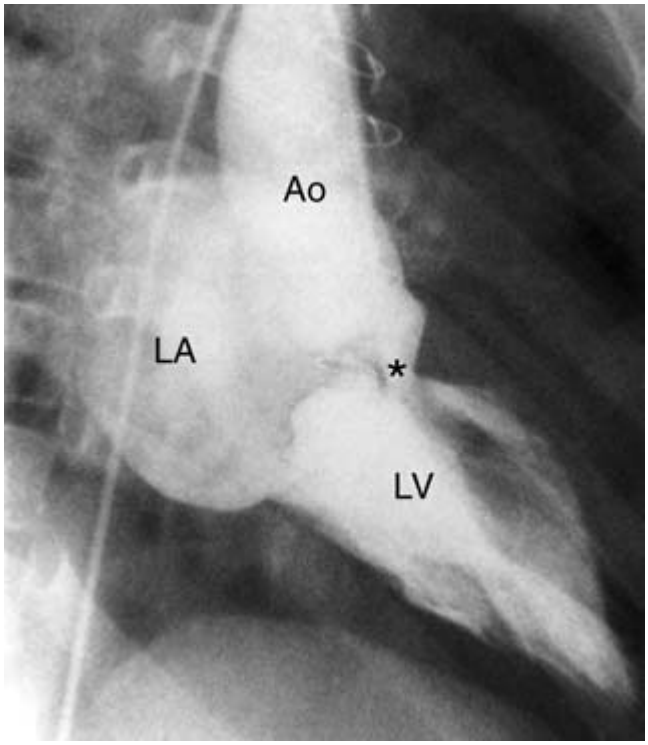


Fig. 5-5 Regurgitation of the left atrioventricular valve and residual left ventricular outflow tract obstruction after repair of atrioventricular septal defect. Left ventriculogram obtained by a retrograde arterial catheter shows opacification of the left atrium (LA) due to severe mitral regurgitation and narrowing of the left ventricular outflow tract (asterisk). Ao = aorta; LV = left ventricle.

most common reason for re-operation after repair of the complete form of the defect is LAVV regurgitation.[63,197–210] It is well known that significant LAVV regurgitation leads to a volume-loaded left ventricle, and that this can lead to eccentric hypertrophy which may eventuate in left ventricular myocardial failure. In order to preserve the functional integrity of the left ventricle, most patients with significant post-repair LAVV regurgitation will require further surgery, either LAVV repair or replacement. Moran and colleagues reported the outcome of surgical management of important LAVV regurgitation in 46 patients who had undergone earlier repair of the complete form of atrioventricular septal defect at the Boston Children's Hospital.[206] The median age at repair of the complete form of atrioventricular septal defect was 0.6 years, and the age at subsequent LAVV surgery was 2.8 years. Of the 46 patients, LAVV repair was carried out in 37 and replacement in 9. The early postoperative mortality was 2.2% and survival at 1 year and 10 years was 89.9% and 86.6% respectively. A high rate of complete heart block was found in those requiring valve replacement, 37.5%. Freedom from re-operation was similar in both groups. Rhodes and his colleagues summarized the literature in 1997 in regard to the progression of LAVV regurgitation after initial repair. They found that as many as 18% of patients require re-operation for left atrioventricular valve regurgitation.[210] The study by Rhodes and his colleagues found that mild deterioration in LAVV function was common, with progression in severity in 41% of the patients studied by serial color Doppler.[210] Much of the deterioration in LAVV function

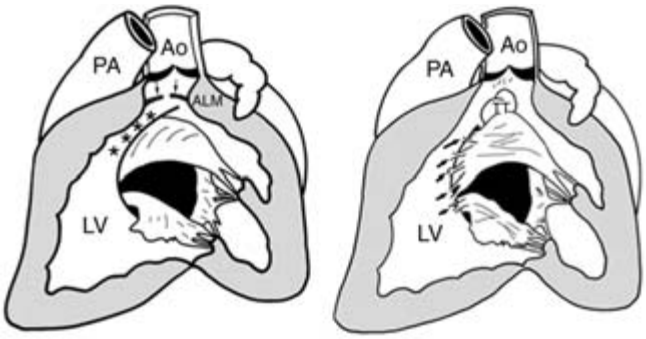


Fig. 5-6 Mechanisms of left ventricular outflow tract obstruction in atrioventricular septal defects. 1. Elongation and narrowing of the subaortic outflow tract (asterisks). 2. Prominent left ventriculo-infundibular fold (anterolateral muscle of Moulaert) (ALM). 3. Fibrous shelf (arrows in left-hand illustration). 4. Insertion of the atrioventricular tension apparatus to the outlet part of the ventricular septum (arrows in right-hand illustration). 5. Accessory tissue tag or membranous septal aneurysm (TT). Ao = aorta; LV = left ventricle; PA = pulmonary artery.

occurred primarily in the early postoperative time intervals, and after 32 months, significant progression was uncommon.

Left ventricular outflow tract obstruction remains a particularly difficult problem and has been identified both pre- and postoperatively in most forms of atrioventricular septal defect (Figs 5-5 to 5-9).[112–137] There is a substantial literature devoted to the mechanisms responsible for left ventricular outflow tract obstruction in this setting and surgical remedies for this.[112–137] Some years ago, we reported our experience in 19 children who underwent operative treatment for subaortic stenosis in the spectrum of atrioventricular septal defects.[127] Twenty-seven operations for subaortic stenosis were performed in these 19 children. Standard fibromyectomy for these patients leads to a

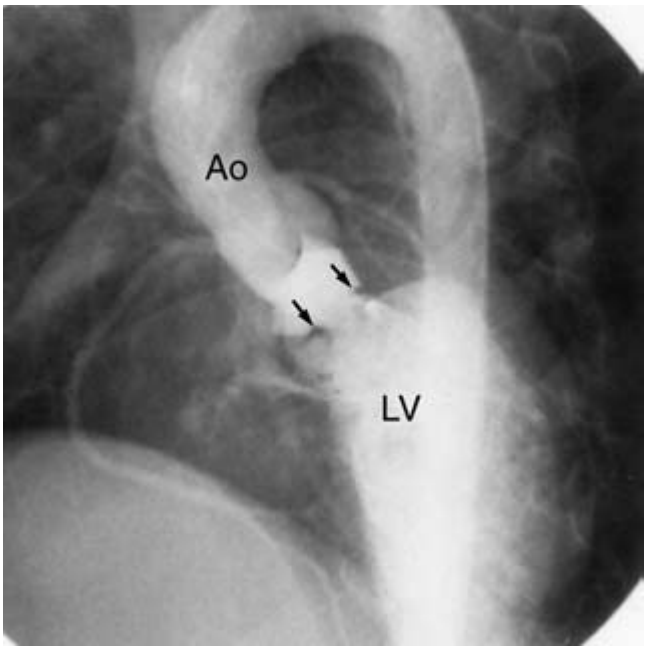


Fig. 5-7 Left ventriculogram from a patient with partial atrioventricular septal defect shows narrow subaortic outflow tract and fibrous ridge (arrows). Ao = aorta; LV = left ventricle.

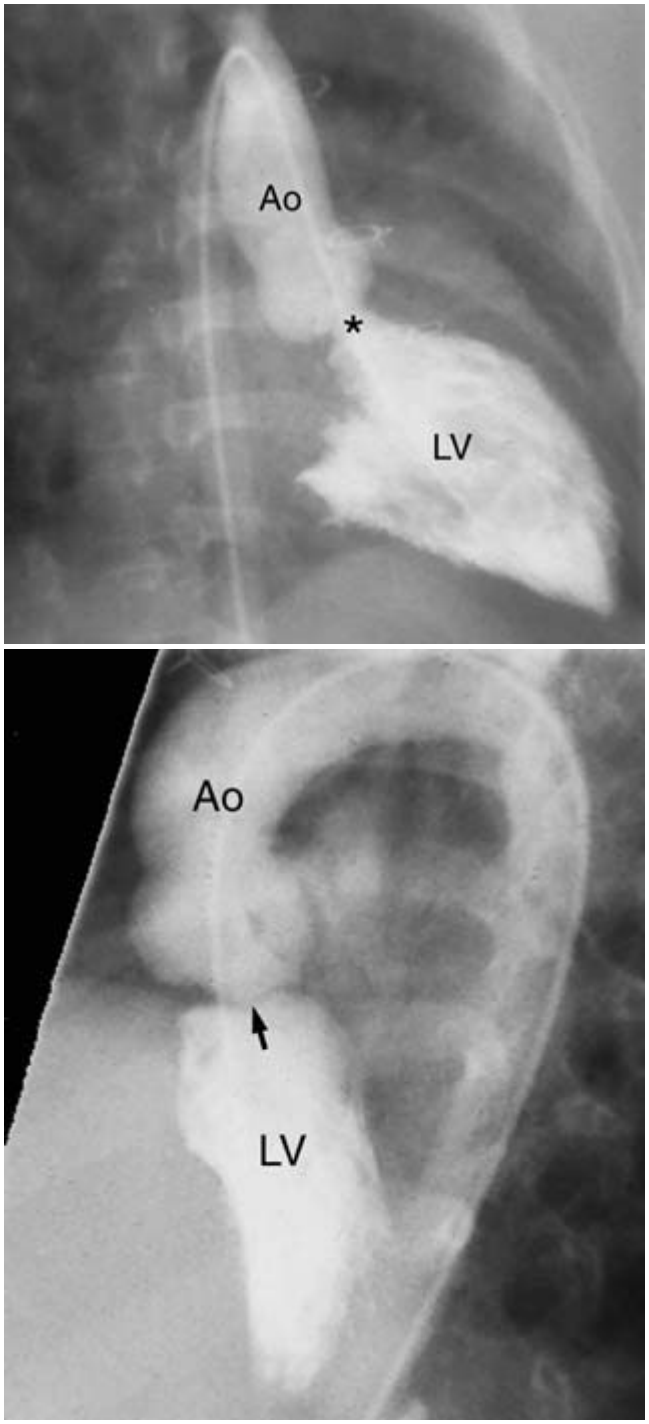


Fig. 5-8 Residual narrowing of the left ventricular outflow tract after repair of atrioventricular septal defect. **A.** Left ventriculogram in right anterior oblique view shows narrow subaortic outflow tract (asterisk). **B.** Left ventriculogram in left anterior oblique view shows a transverse ridge (arrow) in the narrow outflow tract. Ao = aorta; LV = left ventricle.

high rate of re-operation, and the six-year actuarial freedom from operation was only 66% ± 15%. Our data supported the conclusion that "solutions may be complex and palliative,"[127] a finding consistent with the experience of others as well.[112–126,128–137] Lim and colleagues have studied those echocardiographic predictors for the development of subaortic stenosis after repair of the atrioventricular septal defect.[136A] They found that the postoperative subaortic stenosis is associated with an increased displacement of the atrioventricular valve into the left ventricle with less lateral angulation of the left ventricular outflow tract.

Ventricular dominance, right or left, may complicate the surgical management of the atrioventricular septal defect (Fig. 5-2C).[94–96] In some patients where either the right or the left ventricle is grossly underdeveloped, single ventricle palliation concluding in a Fontan-type operation may be considered. In other patients where the right ventricle is only modestly underdeveloped, a "biventricular" repair can be achieved by unloading the right ventricle with a bidirectional cavopulmonary shunt.[110,111] When the left ventricle is modestly underdeveloped[94–96] it may be more difficult to assign the patient to single ventricle palliation or to consider a biventricular repair. Van Son and his colleagues suggest that when the preoperative indexed left ventricular volume is 15 mL/m^2 or greater, this allows biventricular repair.[211] As we have stated elsewhere,[94,95] left ventricular volume is but one consideration for a biventricular repair. Severe left atrioventricular valve stenosis/hypoplasia and/or severe left ventricular outflow tract obstruction in a neonate would lead some to consider single ventricle palliation.[98] In this regard, there is little information about patients with Down syndrome who have undergone the Fontan procedure. Of 533 patients who had undergone a Fontan operation between 1976 and 1997 at the Toronto Hospital for Sick Children, four had trisomy 21.[212] All four patients had unbalanced complete atrioventricular septal defect with right ventricular hypoplasia in three and left ventricularhypoplasia in one. Three patients survived, and one died of endocarditis. The three survivors have done well in the short term and medium term without complications related to the pulmonary vasculature.

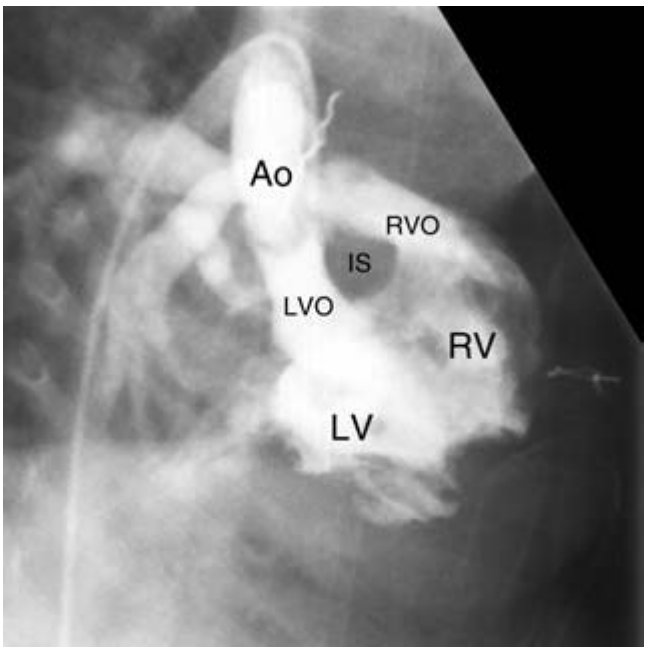


Fig. 5-9 Dynamic narrowing of the left and right ventricular outflow tract (LVO and RVO, respectively) after pulmonary artery banding. Ao = aorta; LV = left ventricle; RV = right ventricle.

The ostium primum atrial septal defect

Many of the same considerations that were discussed in reference to the complete form of atrioventricular septal defect are germane as well to the patient with the partial form of the defect, namely the ostium primum atrial septal defect. We have stated earlier that many unoperated patients with the ostium primum atrial septal defect will survive infancy and childhood, especially those with minimal left atrioventricular valve insufficiency. The prognosis is considerably worse for those patients presenting in congestive heart failure in infancy because of the associated problems precipitating their early presentation. These include severe left atrioventricular valve insufficiency, subaortic stenosis, coarctation of the aorta, or a right dominant form of the defect**.** The partial form of the defect is also associated with Down syndrome, but the association is less impressive, occurring in about 25% of patients with the ostium primum atrial septal defect. Unless there is severe left atrioventricular valve insufficiency, pulmonary hypertension with pulmonary vascular obstruction is less of a consideration than in those with the complete form of the defect. The chronic upper airway difficulties so common in children with Down syndrome may contribute to pulmonary hypertension in this group as well.[213]

The Pediatric Cardiac Care Consortium reported its surgical experience with 612 children with the partial form of atrioventricular septal defect.[101] The most commonly associated anomaly was the patent arterial duct occurring in 3.1% of the patients. The operative mortality for the entire cohort was 16 patients or 2.6%. One hundred and twelve patients were infants, and there were 10 deaths amongst these (8.9%). The surgical mortality in those over 1 year of age was 1.2%. Ten of the 16 deaths for the entire cohort occurred in the first year of life and there was no difference between the Down and non-Down groups. Also seven deaths occurred in those infants weighing less than 5.0 kg. When one assesses mortality by era, the operative mortality for patients 1 year of age or older operated on between 1984 and 1988 was 2.2%; from 1989 to 1993, the operative mortality for patients 1 year of age or older was 0.5%.[101] This decline in mortality for the partial form of atrioventricular septal defect has been experienced by other centers as well.[214–219] This is not true for the infant with the partial form of the defect presenting in the first year of life. Manning and colleagues reported on the outcome of repair of infants with primum atrial septal defect.[97] The outcome of the surgical management of these patients is poor, reflecting the complex associated left heart problems.[95,97] A similar experience has been published by Giamberti and his colleagues who documented in 35 infants seven deaths (29%) after anatomic repair, two (22%) after aortic coarctectomy, and two (100%) after Norwood operation.[98] Infants with a mitral valve diameter less than 2.5 × 10.2 m/m^2 died at repair. In a mean follow-up of 73.5 months there were five secondary mitral valve plasties and three repairs after aortic coarctectomy. They conclude from this experience that among patients with partial atrioventricular canal, there is an important subgroup with clinical signs of heart failure in the first year of life. Left-sided obstructive lesions and complex mitral valve anomalies seem to play a fundamental role in the clinical evolution and prognosis of these patients.

Agny and Cobanoglu reported their experience in 1999 with repair of partial atrioventricular septal defect in children less than 5 years of age.[220] A retrospective study was done in 38 consecutive patients from 3 to 58 months of age, who underwent correction between 1981 and 1997. Preoperatively, moderate to severe mitral regurgitation was present in 45% of the patients. Congestive cardiac failure was noted in 41% of the cases. Closure of the left atrioventricular valve cleft was performed in 92% of the cases. A need for mitral annuloplasty was felt in 28% of the cases. The majority of the ostium primum defects in their series were closed by a pericardial patch. The early, 30-day mortality was 7.9%. A significantly low incidence of late mitral regurgitation (0.9%) was noted on follow-up extending up to 14 years. There was only one re-operation during late follow-up. On their last follow-up, 87% of the patients were asymptomatic.

El-Najdawi and his colleagues from the Mayo clinic described the long-term outcome of repair of 334 patients with partial atrioventricular septal defect operated on between 1955 and 1995.[214] The median age at operation was 8 years. Only 5% had Down syndrome. There were 10 early and 31 late deaths The 30-day and 5-, 10-, 20- and 40-year survival were 98%, 94%, 93%, 87%, and 76%, respectively. Closure of the LAVV cleft and age less than 20 years at operation were associated with better survival. Re-operation was required in 38 patients (11%). The median interval between primary repair and the subsequent operation was 17.8 years. Repair of residual or recurrent LAVV regurgitation or stenosis was the most common reason for re-operation. Left ventricular outflow tract obstruction was identified in 36 patients (11%). In four of these, the diagnosis of left ventricular outflow tract obstruction was made after their first re-operation. Of the 32 patients who were diagnosed with left ventricular outflow tract obstruction subsequent to their primary operation, 10 patients underwent re-operation and seven of these received left ventricular outflow tract reconstruction at re-operation.[222] The patients operated upon at the Mayo Clinic underwent resection of the subaortic membrane and septal myotomy. One patient required a modified Konno procedure for unrelieved left ventricular outflow tract obstruction. A residual or recurrent atrial septal defect was identified in 12 patients, and seven of these had closure of the defect at re-operation. The interval from primary surgery to diagnosis of the residual or recurrent ASD was 10.6 years. Postoperative supraventricular arrhythmias, including atrial flutter, fibrillation or paroxysmal supraventricular tachycardia, were observed in 42 patients (14%). The percentage of patients who experienced supraventricular arrhythmias and who underwent operation in the first, second, third, fourth, and fifth or greater decade of life was 9%, 16%, 20%, 26% and 47%, respectively. In addition patients who underwent closure of the cleft were less likely to have postoperative arrhythmias than those in whom the cleft was not closed. Complete heart block occurred in nine patients (2.7%), five patients after operation and four late. After 1979, no patient experienced surgically related complete heart block. Finally bacterial endocarditis was documented in seven patients (2%). The median interval from primary operation to this event was 8 years.

Baufreton and his colleagues have reviewed the experience of the Hopital Laennec in Paris with 100 consecutive patients with the partial form of atrioventricular septal defect undergoing repair between January 1984 and December 1993.[221] This series included patients[220–222] with an intermediate form of the defect (31%). Congestive heart failure was present in 50% of the cases, and thus this series is different in this respect from other series dealing primarily with the ostium primum atrial septal defect.[221] The LAVV regurgitation was assessed as

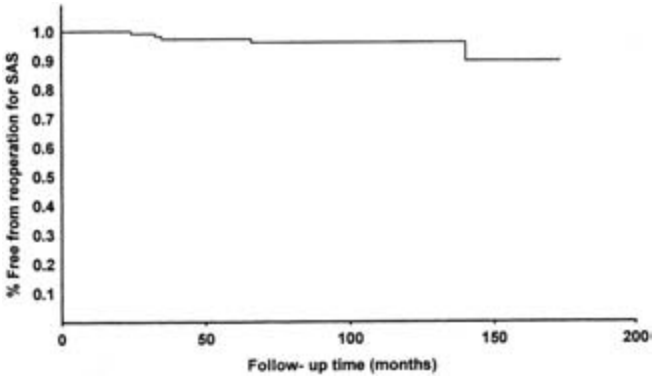


Fig. 5-10 Freedom from re-operation for subaortic stenosis (SAS). (Reprinted from Najm *et al.*,[218] Copyright (1998), with permission from The Society of Thoracic Surgeons.)

moderate to severe in 63% of the patients, and pulmonary artery hypertension was present in about half of the patients. Down syndrome was present in nine patients.[95] Abnormalities of the left subvalvular apparatus were observed in 28% of the patients. The cleft in the LAVV was closed in 76% of cases. The hospital mortality was 13% and the hospital mortality was related both to the severity of postoperative residual LAVV regurgitation and the need for early re-operation. A stepwise logistic regression with variables selected by univariate analysis identified infections and severe abnormalities of the left subvalvular apparatus as predictive factors of early death.[221]

We have also reviewed our experience with 180 children with ostium primum atrial septal defect operated between July 1982 and December 1996.[218] The median age at repair was 4.6 years and 23 of the 180 children were infants less than 1 year of age. Absent or mild symptoms were present in 145 patients (80%), but 34 had severe symptoms or congestive heart failure. Early mortality occurred in three (1.6%) and two of these were less than 1 year of age. In the last 141 operations there was one early death (0.7%). Follow-up ranged from 2 months to 14.5 years (mean, 6 ± 4.2 years). Actuarial survival is 98% at 10 years with no late deaths. In our experience, age < 1.0 year was a predictor of death. During follow-up 17 children (9%) underwent re-operation, five of whom were infants. The mean interval from primary repair to re-operation was 3.2 ± 2.9 years. Five underwent re-operation for subaortic obstruction and 12 for LAVV regurgitation, 11 of whom were repaired and one patient had the LAVV replaced. The mean interval from primary repair to re-operation for LAVV regurgitation was 2.4 ± 2.2 years. Freedom from re-operation for severe LAVV regurgitation at 10 years was 89%. Age and pre-operative moderate to severe LAVV regurgitation were predictors of re-operation. Re-operation for subaortic stenosis was necessary in five patients at a mean interval of 5.7 ± 3.6 years after the initial repair. Only one of these five had undergone subaortic resection at the primary repair. At re-operation, resection of fibromuscular tissue was carried out through the aortic valve in all children and one child required a septoplasty to enlarge the left ventricular outflow tract.[222] Re-operation for left atrioventricular valve regurgitation was required in 12 children at a mean interval of 2.4 ± 2.2 years, and only one of these children required valve replacement (Figs 5-10, 5-11).

A peculiar mechanical hemolytic anemia is a well-known complication of surgery for the atrioventricular septal defect.[223–229] This complication has been observed after repair of either the complete or ostium primum form of atrioventricular septal defect.[222–227] The usual mechanism is fragmentation of erythrocytes in the setting of LAVV regurgitation with the regurgitant jet hitting the prosthetic patch in the atrium.[222–227] This has also been called the "waring blender syndrome."[225] Much less commonly this occurs in the absence of prosthetic material.[229] When such hemolysis is very mild, spontaneous improvement may occur as the patch undergoes endothelialization. With severe hemolysis, the patient will likely require redo of the LAVV. This complication occurs in about 1–2% of our patients. Another uncommon complication of surgical repair of the of atrioventricular septal defect is aortic regurgitation.[230] This complication is iatrogenic, resulting from perforation of the non-coronary cusp of the aortic valve secondary to repair of the ostium primum atrial septal defect. Finally, there is some limited information on spontaneous resolution of the septal defects in this disorder, first reported by Chesler and colleagues in 1968.[231–234] Spontaneous closure of both the atrial and ventricular components of the atrioventricular septal defect have been observed.[231–234] As pointed out by Grech and colleagues from Malta, such events are very rare.[234]

The follow-up issues for the complete and partial form of atrioventricular septal defect reflect the heterogeneity of anatomic issues. These include:

- Form and function of the left atrioventricular valve
- LAVV regurgitation (Fig. 5-5)
- Hemolysis
- LAVV stenosis
- Left ventricular outflow tract obstruction (Figs 5-6 to 5-8)
- Late onset complete heart block[235]
- Pulmonary vascular obstruction
- Form and function of right atrioventricular valve
- Aortic regurgitation
- Late onset atrial or ventricular dysrhythmias
- Issues germane to the patient with Down syndrome
- Chronic upper airway obstruction
- Predisposition to recurrent infections.

Special problems

A small subset of patients with the complete form of atrioventricular septal defect will have right ventricular outflow tract

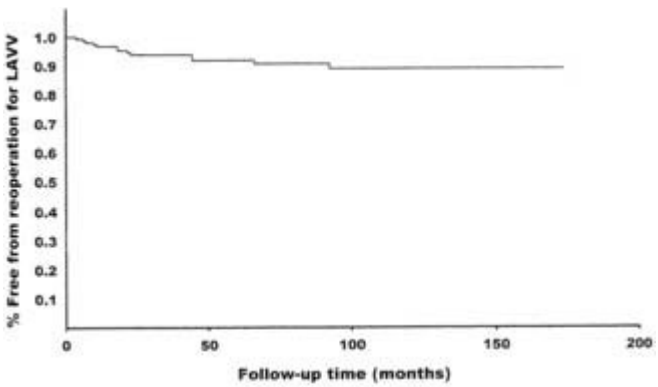


Fig. 5-11 Freedom from re-operation for left atrioventricular valve (LAVV) regurgitation. (Reprinted from Najm *et al.*,[218] Copyright (1998), with permission from The Society of Thoracic Surgeons.)

obstruction of the tetralogy type.[173–191,236–241] According to Karl, tetralogy of Fallot is encountered in 2.7% to 10% of cases of atrioventricular septal defect, and atrioventricular septal defect complicates 16.5% of cases of tetralogy. At least 75% of children with this combination have Down syndrome.[236] Most commonly the atrioventricular septal defect in this setting conforms to the Rastelli type C.[53,180,182] Rarely, other forms of the atrioventricular septal defect may be encountered.[188] There has been ongoing discussion as to the best surgical approach: staged or primary repair.[173,174,182,187,189,190,236–241] In most contemporary reports, treatment of this combination of anomalies has evolved from initial palliation followed by later repair to primary repair, and over the years mortality which had been high has also come down. In 1998. we reported 38 children referred to our institution (March 1981–August 1997) with an atrioventricular septal defect associated with tetralogy of Fallot.[191] Thirty-two of these (84%) had Down syndrome. Twenty-one had undergone initial palliation with a systemic-to-pulmonary artery shunt; of these, two (9.5%) died before complete repair. Thirty-one children underwent complete repair; 14 of these (45%) had undergone initial palliation (mean age at shunt 20 ± 24 months). Right ventricular outflow obstruction was relieved by a transannular patch in 22 (71%) and 14 (64% of 22) had a monocuspid valve inserted. Four required an infundibular patch. Two children (6.4%) died early after repair; one had undergone previous palliation. Patients with palliation underwent repair at an older age (78 vs. 36 months), required longer ventilatory support (8 vs. 4 days) and inotropic support (8 vs. 4 days), and had longer intensive care stays (11 vs. 6 days) and hospital stays (24 vs. 15 days). Eleven children (35%) underwent re-operation, seven (58%) for right ventricular outflow reconstruction and pulmonary arterioplasty. Re-operation was more frequent in the palliation group than in the primary operation group (64% vs. 12%). The single late death was related to a re-operation in the palliation group. At 10 years postoperatively, 93% of those patients treated by primary repair were alive, compared to 82% of those initially palliated and later repaired. Others have also advocated primary repair with very good results.[190,236,238] The follow-up issues are those of the atrioventricular septal defect and tetralogy of Fallot (see Chapter 16).

All references can be found at the end of the book. See pp. 620–6 for Chapter 5.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

6

Robert M. Freedom and Shi-Joon Yoo

Common Arterial Trunk

Common arterial trunk, also designated truncus arteriosus or persistent truncus arteriosus is characterized by a single arterial trunk giving origin to the coronary arteries, pulmonary arteries, and the systemic circulation.[1–4] First described by Buchanan in 1864,[5] the original classification of this disorder was proposed by Collett and Edwards (Fig. 6-1).[6] Their type 1 indicated a main pulmonary trunk; types II and III, separate origins of right and left pulmonary arteries and their type IV malformation was in retrospect more likely an example of pulmonary atresia, ventricular septal defect with multiple aortopulmonary collaterals (Fig. 6-2). The classification was revised by Van Praagh in 1966 to remedy this misconception and to include those patients with common arterial trunk and an associated obstructive anomaly of the aortic arch and as well those with non-confluent pulmonary arteries.[1] A decade later, Calder in association with Van Praagh revised the classification yet again to reflect those cases with and without an associated ventricular septal defect (Fig. 6-3).[7]

Incidence

The common arterial trunk is an uncommon cardiac anomaly and data from the New England Regional Infant Cardiac Program found a live-born prevalence of 0.030/1000 livebirths.[8] The prevalence at livebirth data from the more current Baltimore–Washington Infant Study was 0.056.[9] Data from the Hospital for Sick Children in Toronto gave an incidence for common arterial trunk of 0.7% of congenital heart disease.[10] The prospective Bohemia Survival study identified 55 children at birth with common arterial trunk, for a prevalence of 0.07 per 1000 livebirths.[11] These children accounted for 1.09% of all heart malformations encountered in this study.

This defect is not usually genetically transmitted, nor is familial aggregation common, although there are familial occurrences, and the relationship to maternal diabetes has been explored.[12–15] Pierpont and her colleagues have ascertained the incidence of cardiac malformations in relatives of children with common arterial trunk.[13] The recurrence rate of congenital heart malformations was 6.6% in uncomplicated common arterial trunk, but 13.6% in those with complex forms of truncus. This compares to 1–4% familial recurrence for more common cardiac malformations. Rarely, this malformation has been seen in both of monozygotic twins.[16]

Association with microdeletion 22q11.2

There is now extensive documentation of the association between common arterial trunk, developmental abnormalities of the neural crest and microdeletion of chromosome 22q11.2.[17–24] This deletion has been found in about 89% of DiGeorge patients and in about 40% of patients with common arterial trunk. This deletion has now been identified in a wide variety of congenitally malformed hearts, but its most frequent association is in those with conotruncal malformations including common arterial trunk, tetralogy of Fallot; pulmonary atresia and ventricular septal defect, especially those with major aortopulmonary collaterals; and interruption of the aortic arch.

Segmental analysis

Hearts with a common arterial trunk are usually left-sided and the atrial arrangement normal.[1–4,7] With rare exception, the hearts are biventricular, the atrioventricular connections are concordant, and there is often fibrous continuity between mitral valve and the truncal valve. The right-sided ventriculoinfundibular fold is often attenuated, thus permitting continuity or nearly so between truncal valve and tricuspid valve. Occasionally, the single arterial root originates entirely above the right ventricle. It has also been observed in the patient with tricuspid atresia as well as other forms of "single" ventricle.[25–30] Common arterial trunk has been observed in the patient with right atrial isomerism and presumed asplenia.[31] A common arterial trunk has also been identified in the patient with hypoplastic left ventricle and intact ventricular septum as well as in the patient with mitral atresia and a hypoplastic left ventricle.[29,32,33] Another rare variant is common arterial trunk with a discordant atrioventricular connection.[34,34A]

The truncal valve

The truncal valve can theoretically possess one to six cusps, but the unicommissural, pentacuspid, and hexacuspid valves are uncommon (Fig. 6-4).[1–4,35–49] Calder and her colleagues from Boston Children's Hospital reported that 61% had a tricuspid truncal valve; 31% a quadricuspid valve; and 8% a bicuspid valve.[7] Amongst the 54 cases reported by Butto and colleagues from the United Hospital in Minneapolis, 42% had a tricuspid truncal valve, 30% a bicuspid valve, and 24% a quadricuspid valve.[19] The truncal valve may guard the ventriculoarterial junction normally, or the valve may be stenotic or regurgitant, or both. Truncal valve leaflet thickening may be mild, moderate, or severe. In this last group the truncal valve may be nodular, polypoid, and myxomatous.[35–45,47–49]

The ventricular septum

A ventricular septal defect is present, with only a few well-documented exceptions.[7,32,33,50–53] When the ventricular septum

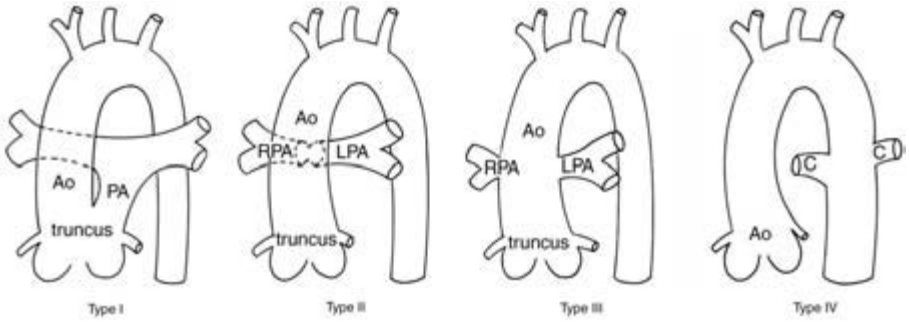


Fig. 6-1 Collett and Edwards' classification of common arterial trunk on the basis of the pulmonary arterial origin. Type I, presence of main pulmonary arterial segment (PA). Type II, no main pulmonary arterial segment with the origins of the right (RPA) and left (LPA) pulmonary arteries close together. Type III, wide apart origins of the right and left pulmonary arteries. Type IV, origin of both pulmonary arteries from the descending aorta; this form is better described as a variant of pulmonary atresia with ventricular septal defect and pulmonary arteries are supplied by collaterals (C). Ao, aorta.

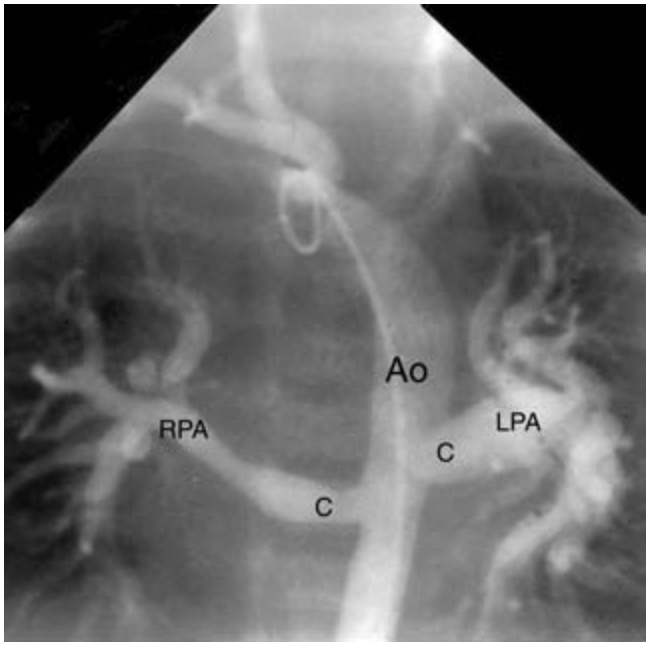


Fig. 6-2 An example of Collett and Edwards' type IV common arterial trunk. It is uncommon. This condition is now considered as a rare variation of pulmonary atresia with ventricular septal defect in which each lung is supplied by a collateral artery (C). Ao, descending aorta; LPA, left pulmonary artery; RPA, right pulmonary artery.

is intact, the common arterial trunk may originate either above the right or left ventricle. In the patient with intact ventricular septum and left ventricular origin of the arterial trunk reported by Zeevi and colleagues,[33] the right ventricle was small, hypertensive, and there were extensive ventriculocoronary connections. In those patients with exclusive origin of the truncus above the morphological right ventricle and intact ventricular septum, the left ventricle is usually underdeveloped. The ventricular septal defect results from absence of the infundibular septum and is found in the limbs of the trabecula septomarginalis.[1–4] Usually the posterior rim of the ventricular septal defect is muscular, reflecting fusion of the posterior limb of the trabecula septomarginalis with the ventriculoinfundibular fold and the defect is therefore separated from the annulus of the tricuspid valve, and thus from the conduction tissue. Less frequently the ventricular septal defect extends to the tricuspid valve and thus is both perimembranous and subarterial. Ventricular septal defects may be present remote from this area, but are uncommon. Truncus may be found with atrioventricular septal defect. The infundibular ventricular septal defect is usually large, but may be actually or potentially restrictive, especially in those patients where the truncus originates almost entirely above the right ventricle.[46,46A] This condition has the potential for resulting in postoperative subaortic stenosis.[46B] Multiple ventricular septal defects have been described in patients with truncus arteriosus.[35,48]

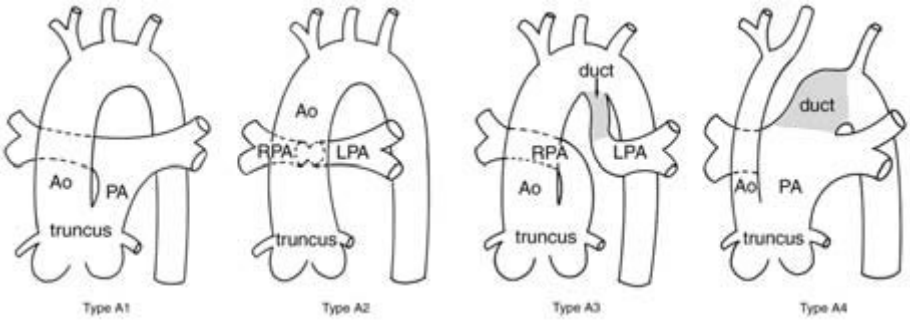
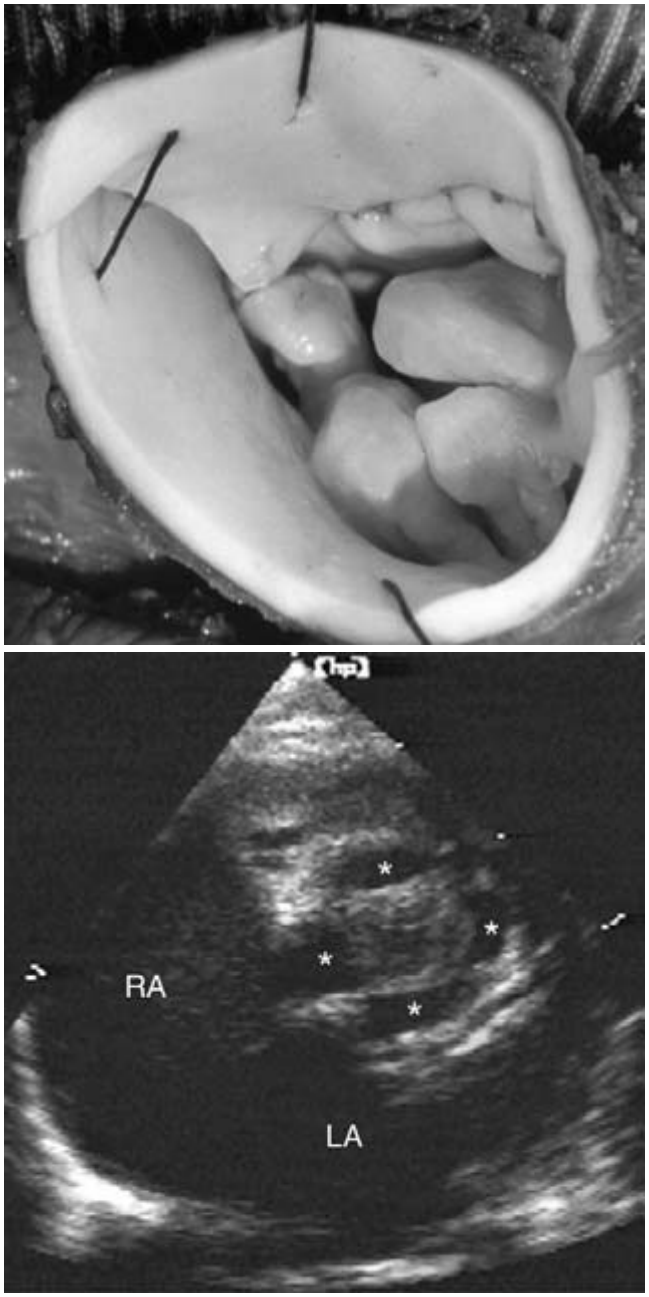


Fig. 6-3 Van Praagh and Van Praagh's classification of common arterial trunk. Type A1, partially separated main pulmonary artery (PA). Type A2, right (RPA) and left (LPA) pulmonary arteries arising directly from the truncus. Type A3, one pulmonary artery from the truncus and the other supplied by the ductus arteriosus (duct) or collateral artery. Type A4, in association with obstructive lesion of the aortic arch. Ao, aorta.



A

B

Fig. 6-4 Thickened and stenotic truncal valve. **A**. Pathologic specimen shows the truncal valve that consists of six dysplastic leaflets. **B**. Short axis echocardiogram shows four aortic sinuses (asterisks) and thickened dysplastic cusps. LA, left atrium; RA, right atrium.

Pulmonary artery anomalies or ostial stenosis

Most patients with persistent truncus arteriosus have excessive pulmonary blood flow, and if not treated, die in congestive heart failure. The pulmonary blood flow is restrictive in *c*. 10% of patients of truncus arteriosus. The mechanism responsible for limiting the pulmonary blood flow in most of these patients is ostial stenosis resulting from an obstructive truncal leaflet.[1–4,48,49,53] Less commonly the pulmonary arteries will be truly underdeveloped. Significant pulmonary artery anomalies include: distal ductal origin of one pulmonary artery; origin of a pulmonary artery from an aortopulmonary collateral; unilateral absence of one pulmonary artery; or hypoplasia of one pulmonary artery; pulmonary arterial stenosis.[53–59] Pulmonary atresia has also been described, albeit rarely.[60] Crossed or malpositioned pulmonary arteries have been identified in a few patients with common arterial trunk.[61–63]

The coronary arterial circulation

The coronary arteries exhibit a variable pattern of origin independent of the number of truncal valve leaflets.[1–4,48,49,64–72] Abnormally high origin of a coronary artery, usually the right, has been observed in this disorder. Frank myocardial ischemia reflects the disordered hemodynamics with a torrential pulmonary blood flow, a volume loaded left ventricle, and a low aortic diastolic or coronary artery driving pressure. Rarely a coronary ostium will be congenitally stenotic, and this will promote an ischemic myocardium. Uncommonly, the coronary ostium will be just superior to the truncal valve commissure, and a bulky, fleshy truncal valve leaflet will obstruct the coronary ostium, resulting in coronary insufficiency[64–72] Anderson, McGoon and Lie described large infundibular branches of the right coronary artery which crossed the upper anterior surface of the right ventricle to supply the anterobasal surface of both ventricles and the upper portion of the ventricular septum, indicating the vulnerability of these arteries to surgical right ventriculotomy.[64] Lenox, Debich, and Zuberbuhler and others have examined the role of coronary artery abnormalities in the prognosis of truncus arteriosus.[66,70] A substantial instance of coronary ostial and arterial abnormalities was found in the study of Lenox and her colleagues of 30 pathologic specimens of truncus arteriosus including the left coronary ostium in a posterior and high position; proximity of the left coronary ostium to the pulmonary artery segment in tri-leaflet truncal valves; stenosis of the coronary ostium; acute angle takeoff of the coronary artery; single coronary artery, etc.[70] It is of historical interest (because banding is rarely used today) that Daskaloupoulos and colleagues described a patient who died of acute myocardial ischemia at the time of pulmonary banding.[67] The pulmonary artery band compromised flow into a circumflex coronary artery originating from the right pulmonary artery. Ventriculocoronary connections have been identified in the patient with truncus arteriosus and an intact ventricular septum.[33] A congenital ostial membrane restricting coronary blood flow has been treated in a patient with common arterial trunk.[71A]

Aortic arch

Aortic arch interruption or coarctation of the aorta is found in from 15% to 20% of patients with common arterial trunk.[1–4] The aortic arch is right-sided in about one-third of patients.[1–4] The arterial duct is usually but not invariably absent in those with a normal, unobstructed aortic arch. Rarely, a double aortic arch is present.[73,73A]

Outcome

There is considerable experience with the prenatal diagnosis of common arterial trunk in the fetus.[74–79] In the combined series reported by Sharland of 25 fetuses recognized to have a common arterial trunk, 9 pregnancies were terminated; 5 babies died in the neonatal period; 4 in later infancy and there are 7 survivors.[80] Duke and his colleagues reported in 2001 the

outcome of 17 prenatally diagnosed patients with common arterial truck.[75] Pregnancy was terminated in 4 patients (24%) and there were 13 livebirths. One child was not intensively treated and died. Another 4 patients (31%) died preoperatively, and 8 (61%) underwent surgery, with a 30-day mortality of 2 of the 8 (25%). There was 1 late death after cardiac catheterization. Thus from an intention-to-treat perspective, overall survival was 5 of 12 patients (42%). Five of 6 patients with a prenatal truncal valve velocity above the normal range were found to have postnatal truncal valve stenosis. Two fetuses recognized to have truncal valve stenosis died suddenly preoperatively.[75]

Untreated, patients with a common arterial trunk have a very high mortality, with many babies dying in the neonatal period or early infancy in congestive heart failure, often with an ischemic myocardium.[1,19,48,49,81–84] Those reasons promoting myocardial ischemia are complex, reflecting both an unusual physiology as well as an often abnormal coronary arterial anatomy. A common arterial trunk causes a large pulmonary blood flow dilating the left ventricle, and the runoff from the aorta to the pulmonary arteries results in a low aortic diastolic pressure, thus compromising coronary blood flow. Important truncal valve regurgitation, stenosis, or a combination occurs in *c.* 15–20% of patients and also compromises myocardial perfusion. About 65% of patients treated medically fail to survive beyond 6 months of life, and > 90% die before 1 year of age.[3,9,16–18] Data from Butto *et al.*,[47] Collett and Edwards[6] and Van Praagh and Van Praagh[1] summarized by Stanger [84] suggest that of 100 babies born with truncus and surgically untreated, 20 will die in the first week and at least 86 have died by 1 year of age. A rare patient will survive with pulmonary vascular obstructive disease into the fourth decade of life or beyond.[81] Clinical experience also indicates that some patients with common arterial trunk will survive past infancy without developing fixed and irreversible pulmonary vascular obstructive disease, but such patients are not common.[48,83] Survival data published from the Bohemia Survival study on the 55 children born with common arterial trunk were very unfavorable.[11] In the first week of life, the survival curve had decreased to 63.63%, and an additional decline to 1-year of age to 12.72%. By 15 years, survival was only 7.27%.

Surgical management

Before the advent of complete correction with the use of some form of tube connecting the right ventricle to the disconnected pulmonary arteries or main pulmonary trunk, palliation took one of two forms: (1) banding of the usually short main pulmonary trunk or bilateral banding of each pulmonary artery; (2) the creation of ostial stenosis.[85–87] Either of these two maneuvers carried a high mortality and because of the usually short main pulmonary trunk, banding was not particularly attractive either. Often the band severely compromised flow to one pulmonary artery, usually the right, leaving the other pulmonary artery relatively unprotected.

Complete repair was first carried out in the late 1960s[88] and today the treatment of choice is primary repair. Those rare patients with some form of associated single ventricle pathology will be considered for single ventricle palliation concluding in the Fontan, but this has not been achieved in our patients.[89] Today a complete biventricular repair is usually, but not invariably, carried out with the use of some form of conduit between the right ventricle and pulmonary arteries.[90] In some patients "complete" repair will require reconstitution of an obstructed or interrupted aortic arch. In others surgical attention will be directed to truncal valvuloplasty or truncal valve replacement. Surgical results usually reflect the "tip of the iceberg," and it is often difficult to sort out how many patients in any given center were not offered surgery, or died in hospital before surgery could be undertaken. Furthermore, one assumes that most centers would exclude those patients with a common arterial trunk complicated by tricuspid atresia or some other form of univentricular atrioventricular connection. But none the less, surgical results for early repair of common arterial trunk continue to improve. Surgeons have introduced a variety of truncal valve reparative techniques to obviate the necessity of valve replacement.[90–102] In some large clinical experiences severe truncal insufficiency preoperatively continues to be associated with increased operative mortality, despite improving results.[103] As we will show, some centers have neutralized severe truncal valve stenosis or regurgitation and interruption of the aortic arch as risk factors for mortality. In the evolution of surgical therapy for common arterial trunk, the imaging modality has evolved from one of angiography to cross-sectional echocardiography.[103A] Cardiac catheterization may still be required to evaluate the operability of the pulmonary vascular bed, especially when there is only a solitary pulmonary artery[56,57] and to assess the ventricular septum when there are multiple ventricular septal defects.[48,49]

The Pediatric Cardiac Care Consortium has analyzed its experience with 185 newly diagnosed infants with common arterial trunk between 1985 and 1993.[104] The median age at diagnosis was 45 days and the mean weight at operation was 3.6 ± 1.0 kg. Forty-five per cent were neonates at the time of operation. Interrupted aortic arch was encountered in 27 patients, severe truncal valve insufficiency in 20, truncal valve stenosis in 11, pulmonary arterial hypoplasia or stenosis in 3, coronary artery anomalies in 2. Multiple ventricular septal defects were diagnosed in 1 patient. A complete repair was attempted in 163 infants, with 62 of these procedures requiring enlargement of the ventricular septal defect, and 7 required repair or replacement of the truncal valve. There were 82 operative deaths (44%) among the infants undergoing repair. Mortality was highest in 1986 (60%) and lowest in 1992 (25%). Twenty deaths occurred in the 27 patients with interrupted aortic arch. Nine of 20 patients with truncal valve insufficiency and 5 of 11 with truncal valve stenosis died. Reoperation was common in this experience for conduit replacement, rehabilitation of pulmonary arterial stenoses, and truncal valve surgery. In this experience, interruption of the aortic arch and/or important truncal valve dysfunction were risk factors for a poor outcome. Jahangiri and his colleagues from the Childen's Hospital in Boston have reviewed their experience with repair of the truncal valve and interrupted aortic arch in patients with common arterial trunk.[93] Of 50 patients undergoing repair of common arterial trunk between January 1992 and August 1998, 5 underwent truncal valve repair and 1 replacement and 9 had interrupted aortic arch. Only 2 operative deaths occurred, both in patients with unrepaired truncal valve regurgitation. None of the patients with associated interruption of the aortic arch died. The actuarial survival was 96% at 30 days, 1 year and 3 years. None of the patients has required reoperation because of truncal valve problems or recurrent aortic arch obstruction at a median age of 23 months. Brizard and his colleagues have also had an excellent outcome for patients with common arterial

trunk and interrupted aortic arch, with no deaths in the 10 patients with this combination of defects.[105]

Brown and his colleagues have recently reported their experience with repair of common arterial trunk of 60 patients from November 1978 to January 2000.[95] The average age at repair was 76 days (range, 3 days to 20 months). Associated cardiac anomalies were frequently encountered, the most common being severe truncal valve regurgitation ($n = 7$), interrupted aortic arch ($n = 6$), coronary artery anomalies ($n = 6$), nonconfluent pulmonary arteries ($n = 4$), and total anomalous pulmonary venous return ($n = 1$). Truncal valve replacement was performed initially or subsequently in seven patients with severe regurgitation (mechanical prostheses in six patients and a cryopreserved aortic homograft in one patient). Right ventricle–pulmonary artery continuity was established with an aortic ($n = 16$) or pulmonary homograft ($n = 32$) in 48 patients, a Dacron polyester porcine valved conduit in 5, a non-valved polytetrafluoroethylene (PTFE) tube in 3, direct anastomosis to the right ventricle with anterior patch arterioplasty in 3, and a bovine jugular venous valve conduit in 1 patient There were 10 hospital deaths (17%; 70% CL, 7–25%). Multivariate and univariate analyses demonstrated a relationship between hospital mortality and associated cardiac anomalies. In the 43 patients without these associated cardiac anomalies, the early survival was 91% (group I). In the 17 patients with one or more of these risk factors, the survival was 71% (group II, $P = 0.002$). There was 1 late death. Twenty-three patients (46%) required reoperation for right ventricular outflow tract (RVOT) obstruction at a mean follow-up time of 59.1 months. In 23 patients, the RVOT reconstruction was performed with a PTFE monocusp, and 6 patients had a variety of replacement conduits inserted. Postoperatively, there were 34 (68%) patients in New York Heart Association functional class I and 16 (32%) in class II. Twenty-eight surviving patients are reported as doing well without any medication. The freedom of reoperation in the 39 hospital survivors (group I) without risk factors was 64% at 7 years; and 36% at 10 years in the 11 patients (group II) surviving with risk factors. In this experience associated cardiac anomalies were risk factors for death after the repair of common arterial trunk. In the absence of these associated lesions, this anomaly can be repaired with an excellent surgical outcome in the neonatal and early infancy period.

Danton and his colleagues from the Birmingham UK Children's Hospital have taken a considered approach to right ventricular outflow tract obstruction.[106] In repair of truncus arteriosus the accepted methods of establishing right ventricle (RV) to pulmonary artery (PA) continuity utilize an allograft or xenograft valved conduit. Alternatively, the PA confluence may be directly anastomosed to the RV with anterior patch augmentation, which may allow growth and delay or avoid subsequent RVOT obstruction. These methods of RVOT reconstruction were evaluated in infants undergoing truncus arteriosus repair. A retrospective analysis of 61 infants undergoing repair of truncus arteriosus between November 1988 and June 2000 was performed. The median age was 34 days (range 1 day to 6.4 months). The patient cohort was subdivided into two groups: (1) valved conduit group, RV to PA continuity performed with a conduit in 38 patients using allograft[28] or xenograft;[10] (2) direct anastomosis group, direct RV–PA anastomosis performed in 23 patients, augmented anteriorly with monocusp[15] or simple pericardial patch.[8] There were 8 hospital deaths (13%; 95% CL, 5–21%). Hospital mortality did not differ significantly between group 1 and 2 (3 patients (8%) vs. 5 patients (22%), respectively, $P = 0.23$). By multivariate analysis, low operative weight ($P = 0.023$), severe truncal regurgitation ($P = 0.022$) and major coronary abnormalities ($P = 0.018$), were independent risk factors for hospital death. The hospital survivors were followed up from 1.3 months to 11.8 years (mean 4.2 ± 3.4 years). Eight late deaths occurred with survival of 73 ± 6% at 2 years and beyond. Survival was not influenced by the method of RVOT reconstruction (conduit vs. direct RV–PA anastomosis, 2.76 ± 7%, 63 ± 10%, respectively, $P = 0.23$). Freedom from surgical RVOT reintervention was 56 ± 10% in group 1 and 89 ± 10% in group 2 at 10 years ($P = 0.023$). The use of a xenograft conduit was an independent risk factor for reintervention ($P < 0.001$). They found that RV to PA continuity established by a direct anastomosis was associated with a low incidence of surgical RVOT reintervention. These authors concluded that this technique has the potential for RVOT growth and may be a useful alternative when an appropriate allograft is unavailable, particularly in the neonate where the risk of pulmonary hypertension and pulmonary vascular disease is lower.

Thompson and his colleagues have recently reviewed their experience with repair of truncus arteriosus in neonates, with a focus on early and intermediate outcomes.[94] From July 1992 to December 1999, 65 patients 1 month of age or less underwent primary complete repair of truncus arteriosus. The median age of repair was 10 days, and the median weight was 3.2 kg. Major associated anomalies included moderate or severe truncal valve regurgitation in 15 patients (23%), interrupted aortic arch in 8 (12%), coronary artery abnormalities in 12 (18%), and nonconfluence of the pulmonary arteries in 3 (5%). Median durations of cardiopulmonary bypass and cardioplegic arrest were 172 min and 90 min, respectively. Circulatory arrest was used only in 7 patients undergoing concomitant repair of interrupted arch. Reconstruction of the right ventricular outflow tract was achieved with an aortic ($n = 39$) or pulmonary ($n = 26$) allograft valved conduit (median diameter, 12 mm). Replacement ($n = 6$) or repair ($n = 5$) of a regurgitant truncal valve was performed in 11 patients, and interrupted arch was repaired in 8. There were 3 early deaths (5%). Early reoperations included reexploration for bleeding in 3 patients, emergent replacement of a pulmonary outflow conduit that failed acutely in 1 patient, and placement of a permanent pacemaker in 1. Mechanical circulatory support was required in 1 patient. During the median follow-up of 32 months, there were 2 deaths. The Kaplan–Meier estimate of survival was 92% at 1 year and beyond. The only demographic, diagnostic, or operative factors significantly associated with poorer survival over time were operative weight of 2.5 kg or less ($P = 0.01$) and truncal valve replacement ($P = 0.009$). Actuarial freedom from conduit replacement among early survivors was 57% at 3 years. These superb results indicate that in some centers, repair of truncus arteriosus in the neonatal period can be performed routinely with excellent survival, even in those patients with major associated abnormalities. Chiu and colleagues have found that in patients with a regurgitant quadricuspid truncal valve, one could restore competency by excising one of the leaflets with its truncal wall.[91A]

The results from the Toronto Hospital for Sick Children have been less satisfactory, although in recent years, surgical mortality for neonatal repair of common arterial trunk is < 5%[103] (Fig. 6-5). Williams and her colleagues reported in 1999 the outcome of all 205 consecutive patients presenting with common arterial

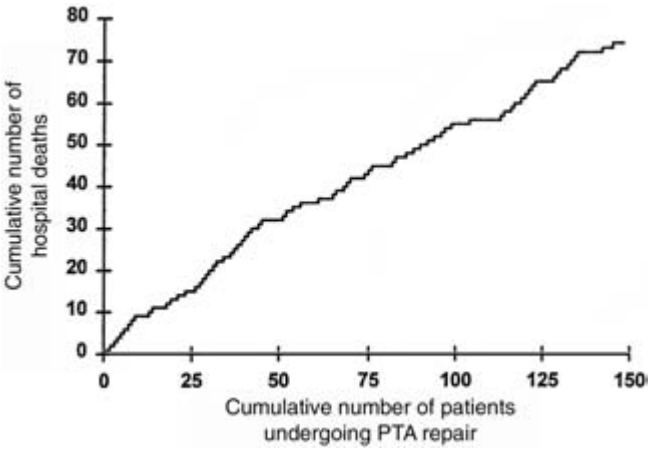


Fig. 6-5 Cumulative hospital mortality with consecutive surgical repairs of common arterial trunk (PTA). (Reprinted from Williams *et al.*,[103] Copyright (1999), with permission from The American College of Cardiology Foundation.)

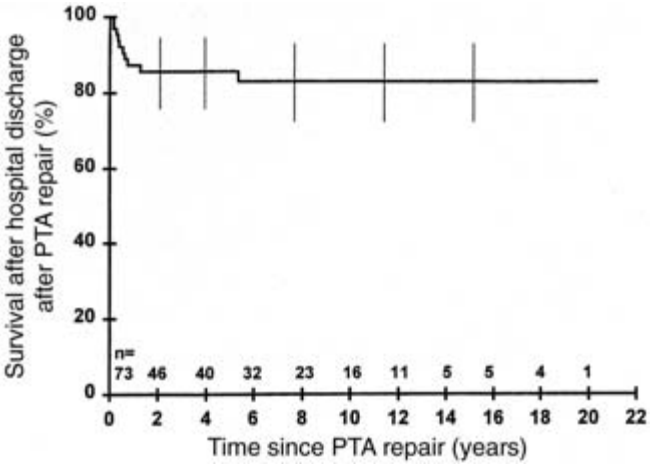


Fig. 6-6 Kaplan–Meier estimates of late death after hospital discharge in survivors of repair of common arterial trunk (PTA). Vertical lines, 95% confidence limits. (Reprinted from Williams *et al.*,[103] Copyright (1999), with permission from The American College of Cardiology Foundation.)

trunk from 1953 to 1997.[103] We addressed trends in outcome by year of birth: 1953–67, 13 cases; 1968–77, 42 cases; 1978–87, 69 cases; and 1988–97, 81 cases. The median age at first assessment was 8 months, 42 days, 7 days, and 2 days, respectively. The proportion having no surgery was 58%, 27%, 22%, and 11%, respectively. Some form of initial palliation was carried out in 25%, 37%, 6%, and 2%, respectively. The proportion undergoing repair of the common arterial trunk was 31%, 59%, 72%, and 88% and the age at repair was 11.2 years, 1.1 years, 1.6 months, and 12 days, respectively. The proportion dying before hospital discharge was 50%, 63%, 56%, and 41%, respectively. From 1995 to 1998, the surgical mortality was 18%, and even lower in the last few years. This experience included 28 patients with interrupted aortic arch (14%). Moderate-to-severe truncal valve regurgitation was present in 24% of the patients, and severe truncal valve stenosis in 17%. Thirty-four patients underwent 42 conduit replacements, with 1 hospital death (Figs 6-6 to 6-8). Several patients required truncal valve replacement and rehabilitation of stenotic pulmonary arteries with balloon angioplasty ± endovascular stenting was common.

Rajasinghe and his colleagues have published their observations in 1997 on the long-term follow-up of patients with common arterial trunk repaired in infancy at the University of California, San Francisco.[107] This 20-year experience included 165 patients who survived repair at a median age of 3.5 months beginning in 1975. Eighty-one percent of patients were < 1 year of age at repair. Patients were followed up to 20.4 years with a median of 10.5 years. Twenty-three late deaths occurred, 8 of which occurred within 6 months of repair and 8 within 1 year of repair. Ten late deaths were related to reoperation. Actuarial survival among all the hospital survivors was 90% at 5 years, 85% at 10 years, and 83% at 15 years. During the follow-up, 107 patients underwent 133 conduit replacements, with a median time to conduit replacement of 5.5 years. Twenty-six patients underwent 30 truncal valve replacements. Actuarial freedom from truncal valve replacement among patients with no preoperative truncal valve regurgitation was 95% at 10 years. It was significantly lower at 10 years (63%) for those with truncal valve insufficiency before initial repair. At last follow-up all but 3 patients were in New York Heart Association functional class I. These observations have been extended by McElhinney and his colleagues who addressed the issue of reintervention after repair of common arterial trunk in neonate and young infants.[108] He reviewed their institutional experience from 1975 to 1998 with reintervention in 128 survivors of 159 patients younger than 4 months of age at the time of repair. The median follow-up was 98 months. One hundred and twenty-one reinterventions were performed in 81 patients. Actuarial freedom from reintervention was 50% at 4 years and actuarial freedom from a second reintervention was 75% at 11 years. Freedom from the first conduit reintervention was 45% at 5 years. Reintervention on the truncal valve was performed on 22 occasions in 19 patients, including 21 valve replacements in 18 patients, and repair in 1. Freedom from truncal valve intervention was 83% at 10 years. Surgical or balloon intervention for pulmonary artery stenosis was required 41 times in 32 patients, and 13

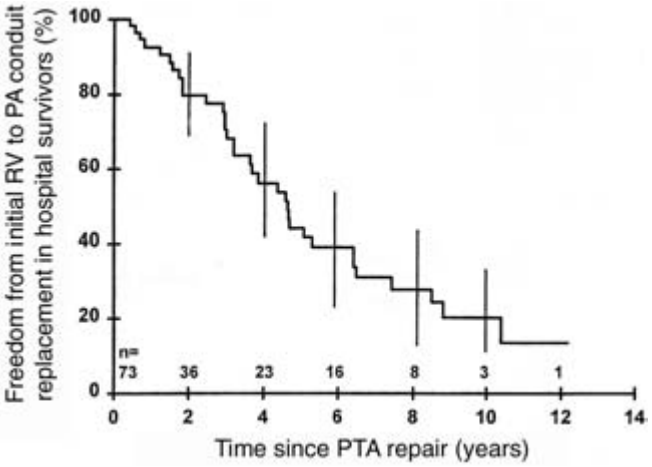
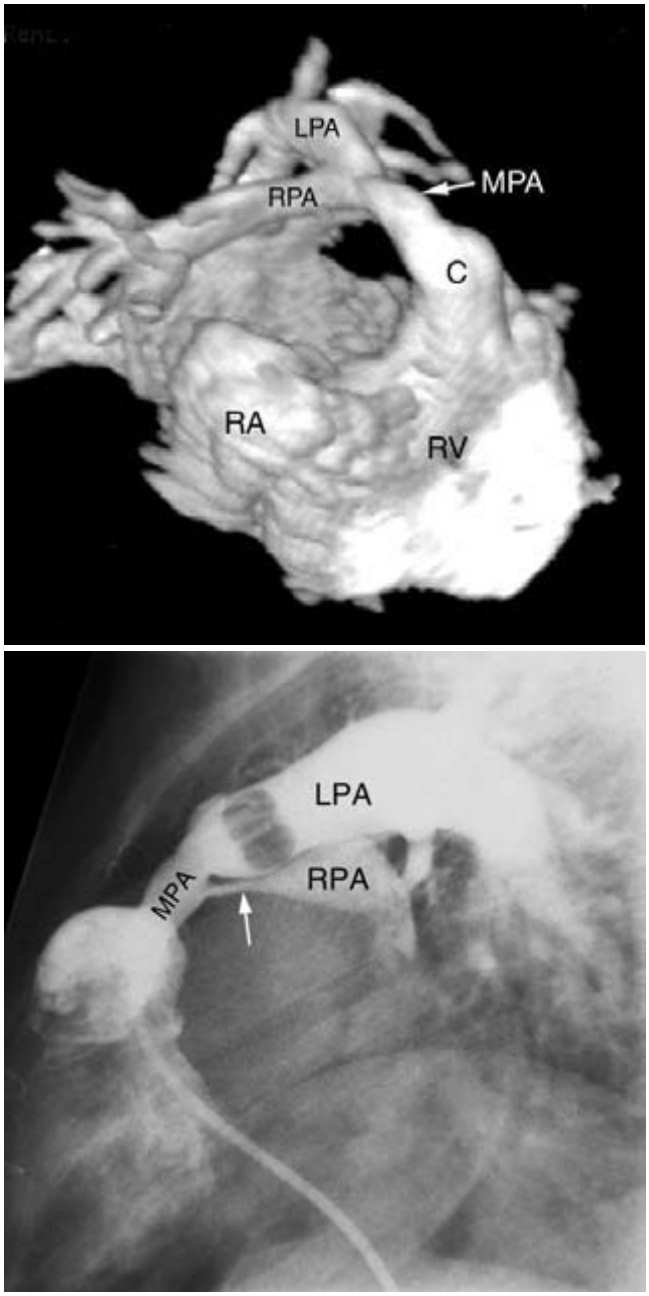


Fig. 6-7 Kaplan–Meier estimates of freedom from first right ventricle (RV) to pulmonary artery (PA) conduit replacement in hospital survivors of repair of common arterial trunk. Vertical lines, 95% confidence limits. (Reprinted from Williams *et al.*,[103] Copyright (1999), with permission from The American College of Cardiology Foundation.)



A

A

Fig. 6-8 Postoperative stenosis of the right ventricle-to-pulmonary artery conduit and pulmonary arteries. **A.** Contrast-enhanced MR angiogram shows narrowing of the conduit (C) and main pulmonary artery (MPA). Right (RPA) and left (LPA) pulmonary arteries also show mild stenosis. **B.** X-ray angiogram from a different patient shows severe narrowing (arrow) of the proximal part of the right pulmonary artery. The main pulmonary artery is also narrow.

patients required closure of a residual ventricular septal defect, all of whom had been repaired with continuous suture technique. Eight of the 16 late deaths were related to reintervention.[108] Rodefeld and Hanley have provided a thoughtful overview of surgical techniques and clinical management for patients with common arterial trunk.[108A] As with some other forms of congenital heart disease, bronchial compression had occurred following repair of complex forms of common arterial trunk, usually those who required repair as well of an interrupted aortic arch.[109] It is interesting that in the experience of Wells and his colleagues, homograft conduit failure was not usually owing to somatic outgrowth, but rather was the result of shrinkage, homograft valvular stenosis, distal anastomotic stenosis, or sternal compression[109A] (see also Chapters 16, 18, and 25C).

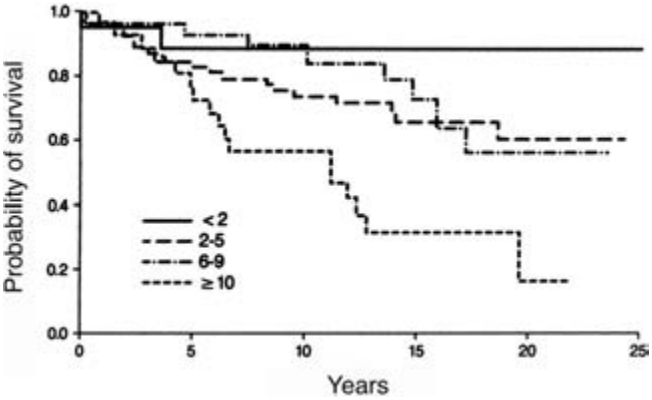


Fig. 6-9 Probability of patient late-survival according to age group at operation. Survival is best under 2 years of age and decreases with each older age group. (Reprinted from Mair *et al*.,[110] Copyright (2002), with permission from Elsevier.)

Mair and his colleagues have provided follow-up on 137 patients with common arterial trunk repaired at the Mayo Clinic,[110] extending the observations of DiDonato and his colleagues.[111] Actuarial survival was 46.4% at 24 years, and late survival was significantly improved for those having surgery during the first 2 years of life when compared to those operated on after this age[110] (Fig. 6-9). A single pulmonary artery was also a risk factor for poorer late survival (Fig. 6-10). In this series, late mortality was secondary to reoperation, most commonly for truncal valve replacement, progressive pulmonary vascular obstructive disease and right ventricular failure, or progressive left ventricular deterioration and failure. Of the 86 patients in the Mayo Clinic experience, many of whom are now adults, 78 (91%) were in NYHA class I or II, and participating in full-time education or employment.[110]

Niwa and colleagues in 1999 reported the outcome of Eisenmenger syndrome in adults with common arterial trunk.[112] The

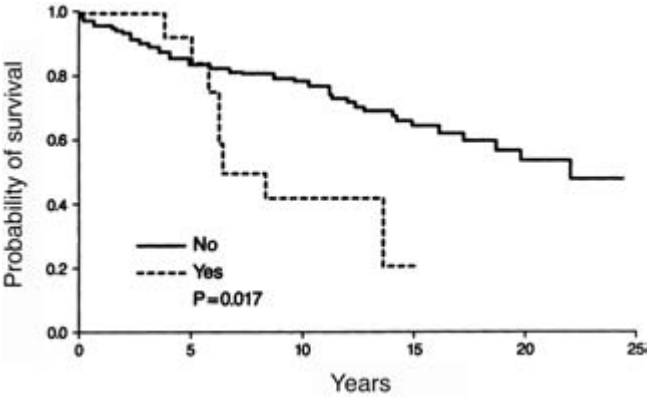


Fig. 6-10 The effect of a single pulmonary artery on late survival after repair of common arterial trunk. (Reprinted from Mair *et al*.,[110] Copyright (2002), with permission from Elsevier.)

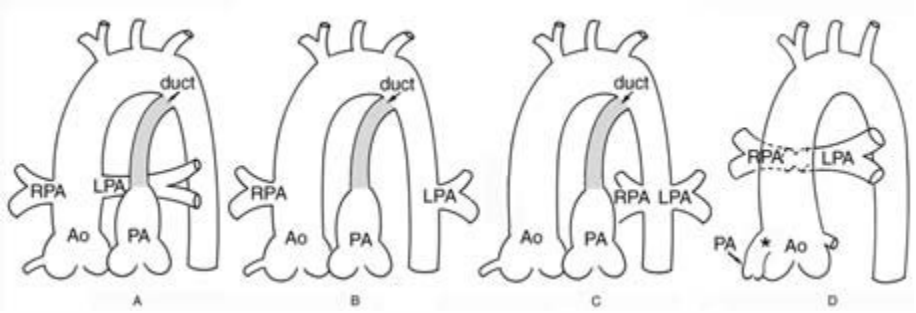


Fig. 6-11 Rare conditions simulating common arterial trunk. **A.** Normal truncal septation with anomalous origins of the branch pulmonary arteries from the ascending aorta (Ao). **B.** Normal truncal septation with origin of the right pulmonary artery (RPA) from the ascending aorta and the left pulmonary artery (LPA) from the descending aorta through a collateral channel. **C.** Normal septation with both pulmonary arteries arising from the descending aorta through collaterals. **D.** Cross or transitional form between common arterial trunk and aortopulmonary septal defect. There is a tiny window (asterisk) between the aorta and miniature main pulmonary artery (PA).

14 patients with common arterial trunk were reviewed, aged 27–50 years, mean 33.7 ± 7.3 years. There were 5 male and 9 females and the follow-up was 6–18 years (mean 7.7 ± 5.1 years). Interestingly, none of these 14 had been hospitalized for congestive heart failure in early childhood, and neonatal cyanosis had been reported in 5 patients (36%). Eleven of these adults were moderately to severely cyanosed when first seen, with a mean oxygen saturation of 80%. Of the 4 deaths in this series, 3 were sudden. Others have also reported survival without surgery to the fifth decade of life.[112A]

In the follow-up of those patients with repaired common arterial trunk, surveillance must be focused on:

- function of the conduit (Fig. 6-8)
- function of the truncal valve
- pulmonary arterial stenoses at the distal anastomosis of the conduit (Fig. 6-8)
- residual ventricular septal defect
- progressive pulmonary vascular obstruction in those repaired after infancy
- right and left ventricular function
- cognitive, speech pathology, etc., in those with chromosome 22q11 deletion

Finally there are some unusual forms of congenital heart disease bearing some similarities to those hearts with a common arterial trunk. These include hearts with so-called normal truncal septation, but separate origins of the right and left pulmonary arteries from the aorta (Fig. 6-11A).[49,113–116] Vizcaino and his colleagues recently reported a neonate in whom the main pulmonary trunk was nonbranching and opened into the descending aorta via a patent arterial duct.[116] The right and left pulmonary artery branches both originated from the posterior wall of the ascending aorta via a single ostium that led into a short common pulmonary artery that bifurcated into right and left pulmonary artery branches.[116] On the basis of this unusual specimen, they speculate that truncus arteriosus A1 is tetralogy of Fallot with infundibular atresia and an aortopulmonary septal defect, and that truncus arteriosus A2 is tetralogy of Fallot with infundibular atresia, absence of the main pulmonary artery and origin of both branch pulmonary arteries from the ascending aorta.[116] In addition, Pauliks and colleagues have reported a most peculiar patient whose heart malformation appeared to be a "cross" between truncus arteriosus and aortopulmonary septal defect (Fig. 6-11D).[117] Individualized surgical strategies have been and will be used to salvage these and other patients whose ventricular morphology conforms to a "single ventricle."[118–122] Finally, another condition to be differentiated from the common arterial trunk is the solitary arterial trunk with absence of the ascending ascending aorta.[123]

The situation for common arterial trunk can be summarized as follows.

- Results for surgical repair of common arterial trunk continue to improve.
- The most serious confounding anatomical factors including aortic arch interruption and/or truncal valve incompetence have been neutralized in some of the more recent surgical experiences.
- Patients with common arterial trunk have a particular relationship with 22q11 microdeletion.
- Long-term outcomes will be characterized by reoperation or reintervention because of conduit problems, conduit replacement, pulmonary arterial stenoses or truncal valve insufficiency.

All references can be found at the end of the book. See pp. 626–9 for Chapter 6.

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Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

7

Robert M. Freedom and Shi-Joon Yoo

Anomalous Origin of One Pulmonary Artery from the Ascending Aorta

Anomalous origin of one pulmonary artery, much more frequently the right pulmonary artery from the ascending aorta, is an uncommon congenital cardiovascular malformation that historically has carried a poor prognosis (Fig. 7-1).[1–23] This condition is distinct from common arterial trunk [24] and from those rare cases where in the presence of so-called normal truncal septation separate origins of the right and left pulmonary arteries from the ascending aorta occurs.[25–27] Anomalous origin of one pulmonary artery from the ascending aorta was first reported by Fraentzel in 1868, the patient being a 25-year-old woman who died in congestive heart failure.[28] Interestingly, in addition to origin of the right pulmonary artery from the ascending aorta an aortopulmonary septal defect was also noted at autopsy.

Nearly 20 years ago, Penkoske and her colleagues from the Children's Hospital in Boston reviewed their surgical experience in three cases and with Richard Van Praagh provided a review of the variable morphologies of this condition.[29] These authors described six forms of so-called aortic origin of one pulmonary artery:

- right pulmonary artery from ascending aorta
- left pulmonary artery from ascending aorta
- distal ductal origin of right pulmonary artery
- distal ductal origin of left pulmonary artery
- collateral arterial origin of right pulmonary artery
- collateral arterial origin of left pulmonary artery.

We think that the origin of a pulmonary artery via a fifth aortic arch should also be considered in this continuum of anomalies.[30,31] For the purpose of this outcome review we will consider only those cases with unequivocal origin of the right or left pulmonary artery from the ascending aorta (and thus proximal to the origin of brachiocephalic arteries). Aru and his colleagues reported a 3-week-old baby with anomalous left pulmonary artery from the ascending aorta.[31A] Interestingly, the media of the abnormal vessel and main pulmonary artery were fused but without any communication.

Incidence

We reviewed several years ago a 36-year institutional experience with anomalous origin of one pulmonary artery from the ascending aorta.[32] We identified from 1960 to 1996, only 16 patients with this condition from the Toronto Hospital for Sick Children.[32] In 12, the anomalously connected pulmonary artery from the ascending aorta was the right and in 4, the left. There was 1 patient with Down syndrome. We did not identify familial cases. Furthermore, in 1 patient there was an association with the partial DiGeorge syndrome, and this relationship has also been established elsewhere in a patient with anomalous origin of the left main pulmonary artery from the ascending aorta.[33,33A,34]

Pathology and associated conditions

The pathologic anatomic features and associated cardiovascular anomalies of patients with anomalous origin of one pulmonary artery from the ascending aorta have been thoroughly reviewed by Kutsche and Van Mierop and others.[1,2,4,5,10–15,18,19,23,29 32,35–37] From the 99 cases in the literature and 9 from their own institution, Kutsche and Van Mierop[35] conclude that anomalous origin of the right pulmonary artery from the ascending aorta was far more common (89) than origin of the left (19).[35] The anomalous right pulmonary artery usually originated from the posterior aspect of the ascending aorta close to the aortic valve (Fig. 7-2). Occasionally, it arose from the lateral ascending aorta just proximal to the innominate artery. Aortopulmonary septal defect and patent arterial duct are commonly associated with anomalous origin of the right pulmonary artery, while other cardiovascular anomalies are rare (Fig. 7-3).[1,2,4,5,10–15,18,19,23,29 32,35–37] Amongst patients with anomalous origin of the left pulmonary artery from the ascending aorta, right aortic arch and tetralogy of Fallot are common (Fig. 7-4).[1,2,4,5,10–15,18,19,23,29 32,35–37] A right aortic arch is found in 75% of patients with anomalous origin of the left pulmonary artery from the ascending aorta, and in 100% of those where this is the only malformation.[31A] Aru and his colleagues state that through 1999, there have been 42 reported cases of anomalous origin of the left pulmonary artery from the ascending aorta.[31A] Table 7-1 summarizes the associated cardiovascular anomalies in our 16 patients.

The paradox of pulmonary artery hypertension in the normally connected pulmonary artery

When one pulmonary artery originates from the ascending aorta in isolation, that pulmonary artery is usually hypertensive, with a driving pressure equal to that in the aorta, unless there is a proximal obstruction or stenosis in the abnormally connected pulmonary artery.[1,2,5,10–12,15,17–19,29,32,37–39] The contralateral pulmonary artery is also usually hypertensive.[1,2,5,10–12,15,17–19,29,32,37–39] The reasons for the hypertension in the lung not connected to the aorta is unclear. Reflex vasoconstriction or some circulating vasoconstrictor agents have been

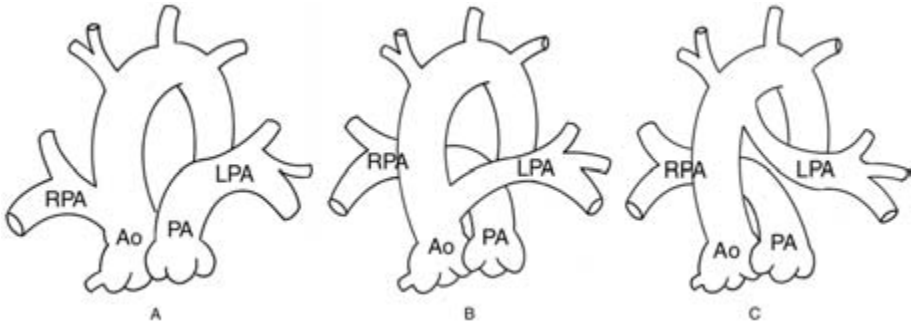

Fig. 7-1 Various types of anomalous origin of one pulmonary artery from the ascending aorta (Ao) in the presence of a left aortic arch. **A**. Origin of the right pulmonary artery (RPA) from the proximal ascending aorta. **B**. Origin of the left pulmonary artery (LPA) from the proximal ascending aorta. **C**. Origin of the left pulmonary artery from the distal ascending aorta. The connecting channel is considered to be a fifth aortic arch. PA, main pulmonary artery.

suggested as causal, but these have not been substantiated. Somewhat surprisingly, lung biopsies have not invariably demonstrated significant differences between the two lungs in the very young baby or infant, but in the older child, both lungs may exhibit severe pulmonary vascular damage.[39] Occasionally the protected lung (i.e. that with right ventricular origin) will demonstrate the more advanced histopathological changes. Finally, while most unoperated patients die in infancy or early childhood, an occasional patient will survive to adulthood without surgery.[40]

Diagnosis

As with most aspects of congenital heart disease, there has been an ongoing evolution in the diagnosis of this uncommon condition.[41–51] Today, the role of cardiac catheterization with angiocardiography[1,2,12,52] has largely been replaced by cross-sectional echocardiography. Magnetic resonance imaging has also been used in the diagnosis of anomalous origin of one pulmonary artery from the ascending aorta (Fig. 7-3).[44A,44B] Cardiac catheterization with angiography may be required for those patients with associated complex lesions, and for the evaluation of pulmonary vascular reactivity in those patients presenting beyond a few months of age.

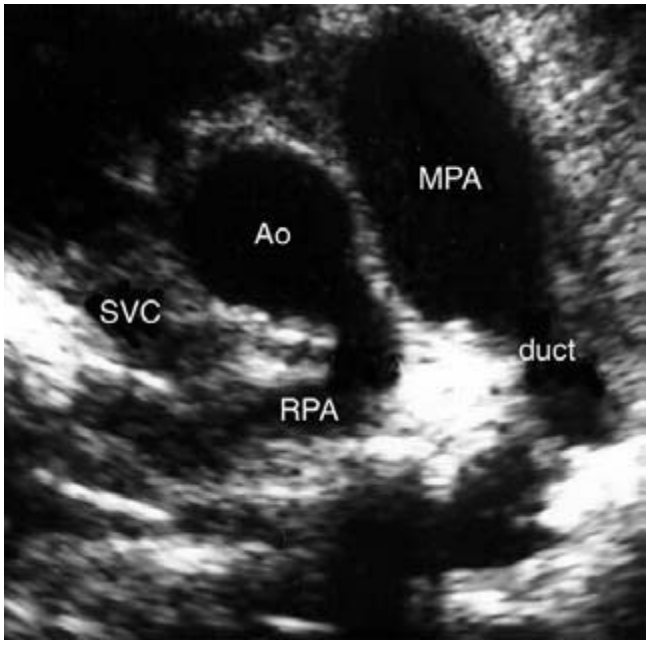

Fig. 7-2 Origin of the right pulmonary artery (RPA) from the ascending aorta (Ao) in an otherwise normal heart. MPA, main pulmonary artery; SVC, superior vena cava. (From Jung and Yoo[52A] with permission.)

Outcome analysis

This condition is only rarely diagnosed in the fetus.[52A] Fontana and his colleagues reviewed from their experience (2 patients) and the literature 65 patients with origin of the right pulmonary artery from the ascending aorta.[37] Their data with all the intrinsic errors of a retrospective review from different centers and over different eras showed a 1-year survival without surgery of 30%, and with surgery of 84%.[25A] Fontana and his colleagues provided an excellent review of this disorder through 1986. The pulmonary vascular disease in the normally connected lung poses considerable threat to the patient with this condition. Single case report has showed immediate resolution of severe pulmonary hypertension following surgical repair. Data from our center and those other centers concerning this rare condition has accumulated over several decades. Today we and others are better able to manage pulmonary hypertensive crisis with the use of pharmacological vasodilators including prostacyclin and nitric oxide.

We have reviewed the outcome of 16 consecutive children presenting with anomalous origin of one pulmonary artery from the aorta.[32] The median age at presentation was 2 days (range, birth to 3.2 years) and associated cardiac anomalies were noted in 9 patients. No intervention was attempted in 2 patients: one was considered inoperable because of complex associated lesions with severe pulmonary vascular obstruction; the second patient died before repair. Fourteen patients underwent surgical intervention, with 3 operative deaths (21%). Of 11 operative survivals, 8 developed pulmonary arterial stenosis, considered severe in 2, moderate in 1, and mild in 5. Thus far there have been no late deaths, giving a total mortality of 25%.

There are at least two important issues that must be considered carefully in the follow-up of these patients who have undergone the surgical repair. One must exclude important surgical stenosis of the reconnected anomalous pulmonary artery, whether or not surgical repair takes the form of a direct anastomosis or the use of interposition graft. Secondly, one must

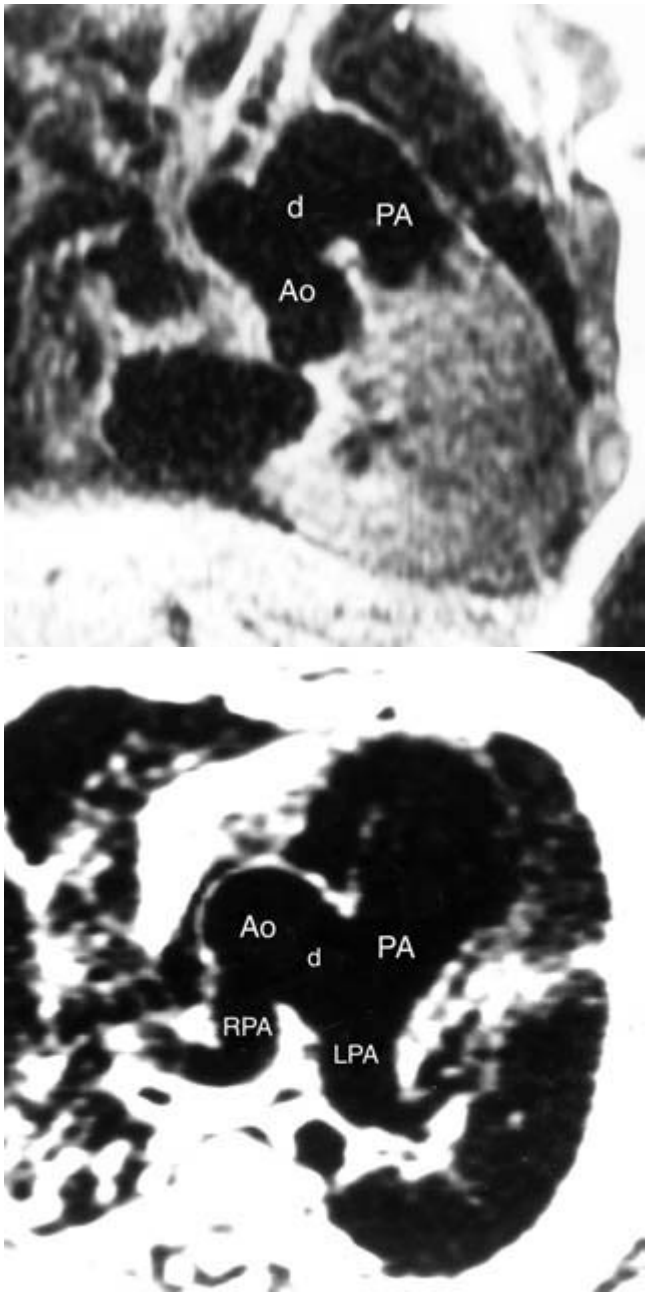

Fig. 7-3 Origin of the right pulmonary artery (RPA) from the ascending aorta (Ao) in association with aortopulmonary septal defect (d). **A**. MR in right anterior oblique view shows the aortopulmonary septal defect. **B**. MR in transverse view shows the aortopulmonary septal defect and anomalous origin of the right pulmonary artery (RPA) from the ascending aorta. This patient also had interruption of the aortic arch. (Reprinted from Yoo *et al.*[44A] with permission from the *American Journal of Roentgenology*.)

define whether the pulmonary vascular changes in both lungs have remodeled from damaged to a healthy state. In this regard the observations of Yamaki and his colleagues are germane.[39] They reported the histopathological findings in a 1-year-old with isolated aortic origin of the right pulmonary artery. They showed that medial hypertrophy of small pulmonary arteries in the right lung was much less remarkable than in the left lung. In contrast, intimal lesions in the right lung were much more advanced than those in the left lung. The judicious use of noninvasive imaging modalities including cross-sectional echocardiography and magnetic resonance imaging combined with phase-contrast flow measurement or radioisotope pulmonary perfusion scan may provide findings that obviate the need for cardiac catheterization with angiography. If the postoperative pulmonary perfusion scan demonstrates a significant imbalance of flow to the surgi-

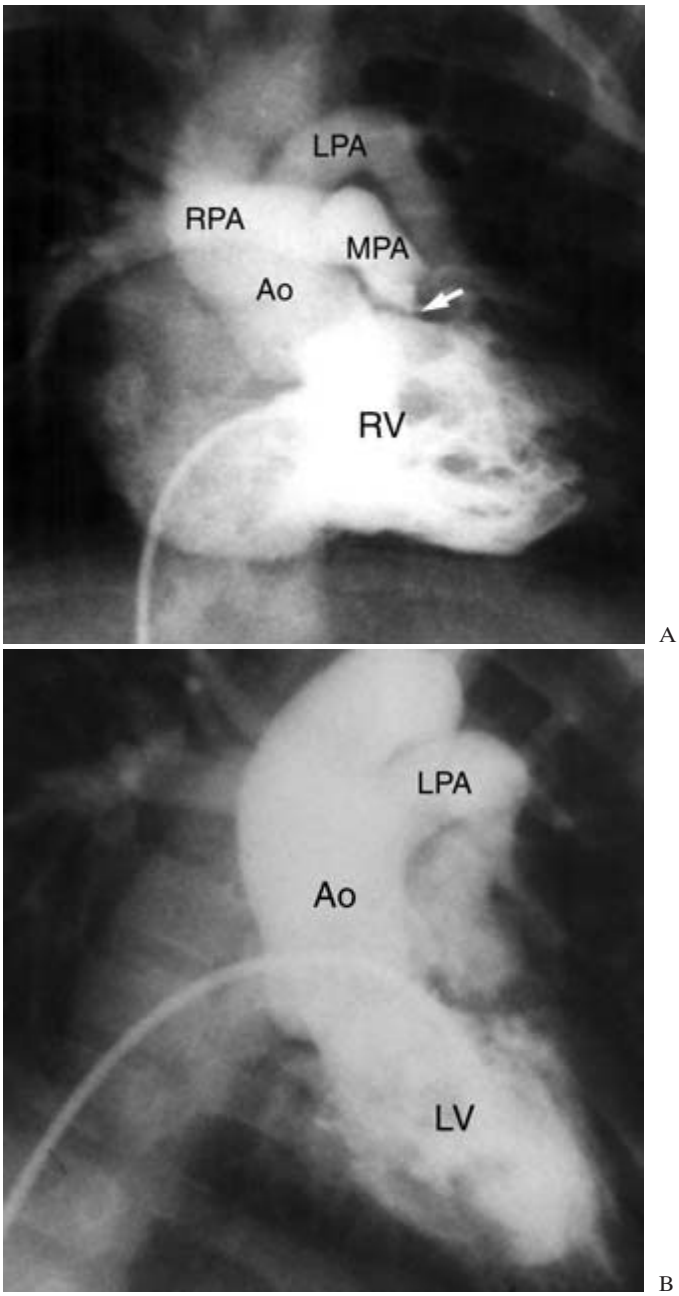

Fig. 7-4 Origin of the left pulmonary artery (LPA) from the ascending aorta (Ao) in association with tetralogy of Fallot. **A**. Right ventriculogram shows subpulmonary obstruction (arrow). The main pulmonary artery (MPA) continues as the right pulmonary artery (RPA). **B**. Left ventriculogram shows origin of the left pulmonary artery from the ascending aorta. LV, left ventricle.

Table 7-1 Associated cardiac anomalies

Associated cardiac anomaly	Anomalous right	Pulmonary left	Artery total
Total	12	4	16
Patent arterial duct	6	0	6
Atrial septal defect	3	0	3
Ventricular septal defect	3	0	3
Tetralogy of Fallot with pulmonary stenosis	0	1	1
Tetralogy of Fallot with pulmonary stenosis and absent pulmonary valve	0	1	1
Tetralogy of Fallot with pulmonary atresia	0	2	2
Aortic coarctation	1	0	1
Aortic arch hypoplasia	1	0	1
Right aortic arch	0	1	1
Anomalous right subclavian artery	0	1	1

cally connected lung, this might suggest important pulmonary vascular obstruction in the contralateral, normally-connected lung. Conversely the postoperative pulmonary perfusion scan may demonstrate a significant imbalance of flow away from the surgically connected lung and into the normally connected pulmonary "artery" and lung. This might suggest important stenosis at the site, surgical anastomosis, or pulmonary vascular disease in the re-connected lung.[53,54] Rarely, this unusual condition may be recognized late in the adult. Severe pulmonary artery hypertension is inevitably present and such patients may be candidates for single or bilateral lung transplantation.[55,56] Finally the Pediatric Cardiac Care Consortium identified 25 patients between 1984 and 1993 with anomalous origin of a pulmonary artery from the ascending aorta.[57] In only three patients was the left pulmonary artery arising from the ascending aorta. Tetralogy of Fallot and aortopulmonary window were each identified in three patients, but the most frequent anomaly was the arterial duct in 14 patients. As in other reports, they indicate that > 80% of patients will die in the first year of life without surgical intervention.[57]

In summary:

- Ascending aortic origin of the pulmonary artery is an uncommon condition usually not associated with 22q11 microdeletion.
- This can occur in isolation and then it is usually the right pulmonary artery that originates from the ascending aorta.
- Ascending aortic origin of the pulmonary artery occurs with a wide spectrum of congenitally malformed hearts, notably tetralogy of Fallot or pulmonary atresia with ventricular septal defect. With tetralogy or its variants, it is usually the left pulmonary artery that has the anomalous origin. It can also occur with interruption of the aortic arch and associated aortopulmonary window, and then the right pulmonary artery has the anomalous origin.
- Pulmonary hypertension may be particularly severe in the normally-connected lung.
- Surgical results of reconnection have continued to improve especially with the use of prostacyclin and NO, etc., to modulate the pulmonary vascular bed.

All references can be found at the end of the book. See pp. 629–31 for Chapter 7.

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Kalyani R. Trivedi, Robert M. Freedom, and Shi-Joon Yoo

Distal Ductal or Ligamental Origin of the Pulmonary Artery

Distal ductal or ligamental origin of one or both pulmonary arteries is an uncommon congenital cardiovascular anomaly (Figs 8-1 to 8-4)[1–24] Ductal origin of one pulmonary artery can be seen in relative isolation but this condition has been recognized in association with many forms of congenital heart disease. Perhaps its more frequent associations are in the patient with tetralogy of Fallot; tetralogy with absent pulmonary valve syndrome; the patient with pulmonary atresia and ventricular septal defect, or in patients with visceroatrial heterotaxia.[2–7,20,22,23] Bilateral distal ductal origin of the pulmonary arteries is most frequently identified in the patient with complex pulmonary atresia, usually of the Fallot type (Fig. 8-4). Very rarely nonconfluent pulmonary arteries have been identified in the patient without associated intracardiac malformations.[25] Congenital distal ductal origin of a pulmonary artery is different from acquired pulmonary artery non-confluence reflecting ductal-mediated stenosis and then atresia.[26–30] So-called pulmonary artery agenesis is but one cause of the unilateral hyperlucent lung.[21]

Distal ductal origin of the right or left pulmonary artery reflects absence of the proximal right or left sixth aortic arch respectively.[1–4,6,15–19,31] With functional and anatomic closure of the arterial duct, the ipsilateral pulmonary artery and lung become isolated. Progressive diminution in the size of the isolated pulmonary artery, lung, and hemithorax is an inevitable consequence of this condition.[4,32–34] Some of these patients will develop small direct and indirect aortopulmonary collateral arteries. Chest wall collaterals and collateral arteries originating from the subclavian arteries may provide a limited amount of so-called nutritive pulmonary blood flow. These patients will demonstrate a profound mismatch between ventilation and perfusion. Furthermore, with continued hypoplasia of the affected lung, the ipsilateral hemithorax will become smaller and some patients may develop important scoliosis.[4]

How does one clinically recognize so-called absence of a unilateral pulmonary artery?[4,32–40] Once familiar with the diagnosis, it might be suspected from a chest radiograph (Fig. 8-2). The right lung volume is diminished and oligemic. The heart is mildly displaced to the right side but the cardiac apex is still pointing to the left side. The left heart border is clear. It is in contrast to scimitar syndrome in which the right border is indistinct in most cases. Not uncommonly it is misdiagnosed as chronic lung disease. It can also be suspected when either the central or mediastinal right or left pulmonary artery is not identifiable. Injection of contrast material into a tenuously patent arterial duct would likely demonstrate the pathology. Because chest wall collaterals and collateral arteries originating from the subclavian artery(s) may connect through serpiginous channels to the distal ligamental pulmonary artery, selective injections of contrast into the subclavian artery or into the descending thoracic aorta should also demonstrate the involved pulmonary artery. In most patients, however, the technique of pulmonary vein wedge angiography will demonstrate to advantage the calibre of the involved pulmonary artery. The whole pathology can easily be defined by contrast-enhanced CT or MR angiography (Figs 8-2, 8–3). In the setting of distal ductal (or ligamental) origin of one pulmonary artery, it is more frequent to have the involved duct and "absent" pulmonary artery on the side opposite the laterality of the aortic arch; thus with a left aortic arch, distal ductal origin of the right pulmonary artery and with a right aortic arch, distal ductal origin of the left pulmonary artery. Many but not all of the patients with distal ductal or ligamental origin of one pulmonary artery will have bilateral arterial ducts. In those patients with complete isolation of the pulmonary artery, the presence of a ductal diverticulum ipsilateral to the isolated pulmonary artery is evidence of this condition's pathogenesis (Figs 8-1, 8-3). Rarely, the collateral circulation to the affected lung will be mediated by an anomalous collateral artery from the coronary artery.[41,41A,41B]

The diagnosis of congenitally absent pulmonary artery may be heralded by intractable pulmonary infection which may necessitate pneumonectomy as in the patient reported by Canver and colleagues and by others.[42,42A,43] Indeed the clinical presentation may be subtle when this condition occurs in isolation. Hemoptysis, resulting from rupture of abundant bronchial submucosal vessels perfused by enlarged systemic collaterals supplying the affected lung, has been reported in the adult.[42–44] Pneumonectomy has been recommended as definitive treatment in the adult patient presenting with hemoptysis.[43]

Reconstitution of the nonconfluent pulmonary arteries may require initially some form of systemic-to-pulmonary artery anastomosis.[4,6,7,11,20,45,45A,46] We have used a modified Blalock–Taussig shunt to promote growth of a hilar pulmonary artery, while others have occasionally used an internal thoracic artery graft. Others have interposed a graft between the main pulmonary trunk and the isolated pulmonary artery at its hilum to reconstitute the pulmonary arteries. Considerable difference in size of the isolated hilar pulmonary artery has been observed, and this may influence the type of surgical repair. When the obliterated ductus can be probed, the ductal patency can be restored by placing a stent (Fig. 8-3).

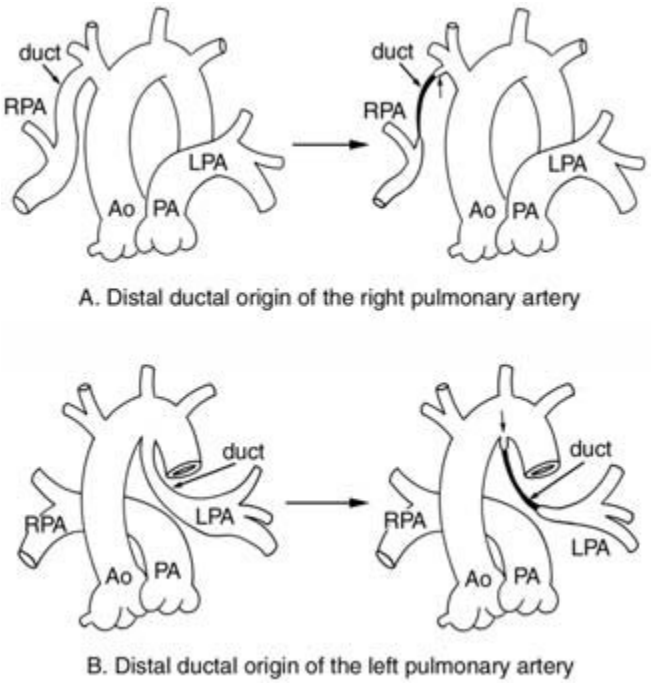
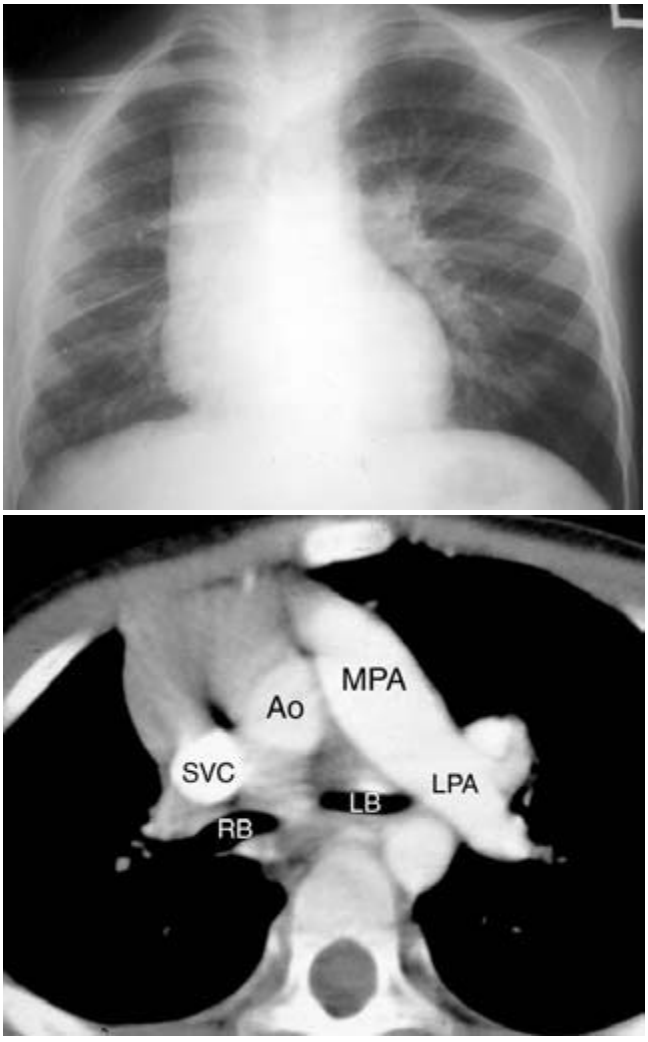


Fig. 8-1 Distal ductal or ligamental origin of the pulmonary artery in the presence of a left aortic arch. Origin of the right pulmonary artery (RPA) from the right ductus arteriosus that arises from the innominate artery. With time, the ductus closes and the right pulmonary artery can be isolated, which is commonly described as unilateral absence of the right pulmonary artery. A diverticular outpouching (arrow) from the innominate artery is common in this condition. A similar pathology can be seen in distal ductal origin of the left pulmonary artery when there is a right aortic arch. Origin of the left pulmonary artery (LPA) from the left ductus that arises from the aorta. With time, the ductus closes and the left pulmonary artery is isolated. This form is not common. A similar condition can be seen in distal ductal origin of the right pulmonary artery when the aortic arch is left-sided. Ao, aorta; PA, pulmonary artery.

Outcome analysis

This is an uncommon condition in isolation and as stated earlier, distal ductal or ligamental origin of a pulmonary artery may complicate a large number of congenital cardiovascular anomalies, particularly tetralogy of Fallot; tetralogy with absent pulmonary valve; pulmonary atresia and ventricular septal defect, and pulmonary atresia in the setting of heterotaxia. Ductal origin of one or both pulmonary arteries has also been identified in the patient with right or left atrial isomerism and in the patient with pulmonary atresia and intact ventricular septum. Clearly then, in some patients the prognosis reflects the associated intracardiac pathology, i.e. the patient with right atrial isomerism, pulmonary atresia, and obstructed pulmonary venous connections.

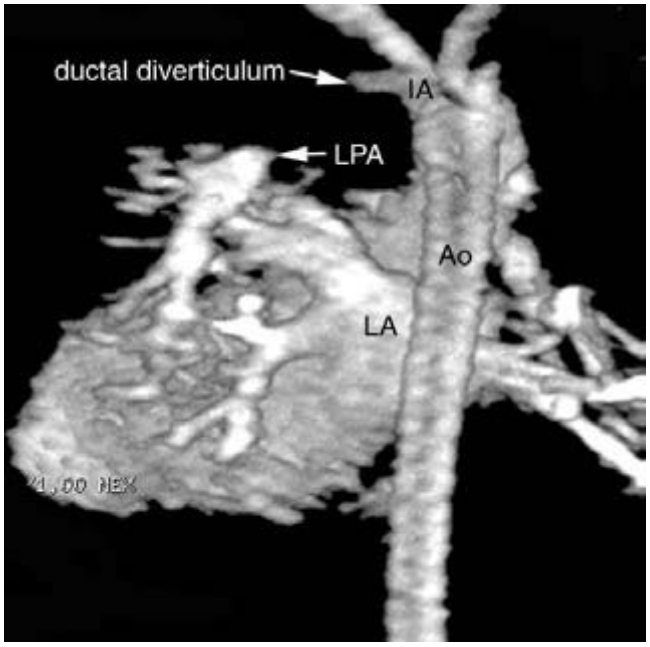
We identified 43 (49% male) consecutive patients presenting to the Toronto Hospital for Sick Children between 1964 and 2001 with distal ductal origin of the pulmonary artery.[47] The median age at presentation was 14 days (range, birth to 8 years). Distal ductal origin of the pulmonary artery occurred as an isolated condition ($n = 16$, 37%), in conjunction with tetralogy of Fallot ($n = 10$, 23%), pulmonary atresia–ventricular septal defect ($n = 13$, 30%) or heterotaxy syndromes ($n = 4$, 9%). Right-sided distal ductal pulmonary artery occurred in 44%, left in 42% patients, and 14% had bilateral distal ductal pulmonary artery. The aortic arch was right sided in 23%. The (arterial duct) to the pulmonary artery was patent in 24 (58%) at presentation. Pulmonary venous wedge angiography was required to demonstrate the isolated pulmonary artery in 19 (44%). Surgical connection to the main pulmonary artery was achieved in 20 (46%). Of these 20 patients, 15 (75%) survived. Surgical reconnection was required in 3 and transcatheter interventions in 12. There were 16 (70%) survivors of 23 (54%) patients in whom the pulmonary artery was not connected to the main pulmonary artery. In this group, 3 of 7 deaths occurred before intervention. Kaplan–Meier estimate of survival after presentation for the entire group was 81% at 6 months, 75% at 2 years and 69% at 5–20 years (Fig. 8-5). No improvement in survival was demonstrable over time (Fig. 8-6). Survival was similar with or without connection of pulmonary artery to the main pulmonary artery,



A

B

Fig. 8-2 Unilateral absence of the right pulmonary artery. **A**. Frontal chest radiogram shows small right lung volume with displacement of the heart to the right and decreased vascularity. In contrast to scimitar syndrome (see Fig. 24B-1C), the heart border is preserved. **B**. Contrast-enhanced CT shows that the mediastinal segment of the right pulmonary artery is missing. Right lung volume is diminished. Ao, ascending aorta; LB, left main bronchus; LPA, left pulmonary artery; MPA, main pulmonary artery; RB, right main bronchus; SVC, superior vena cava.



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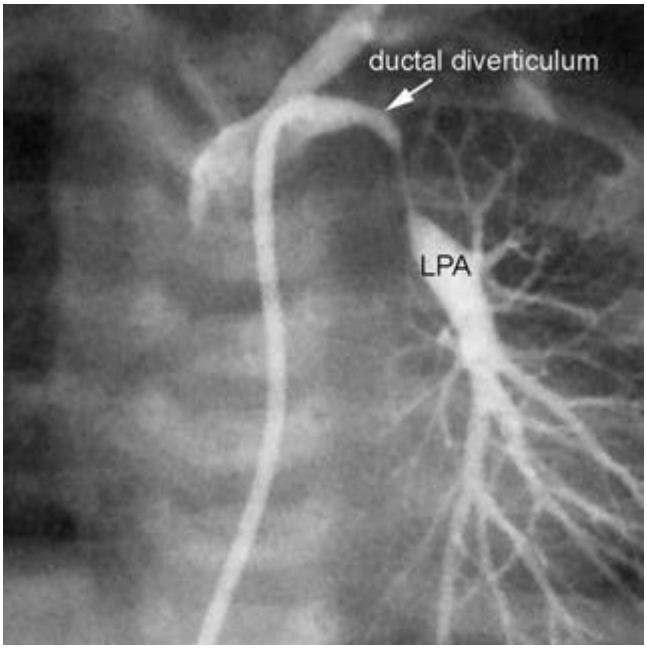

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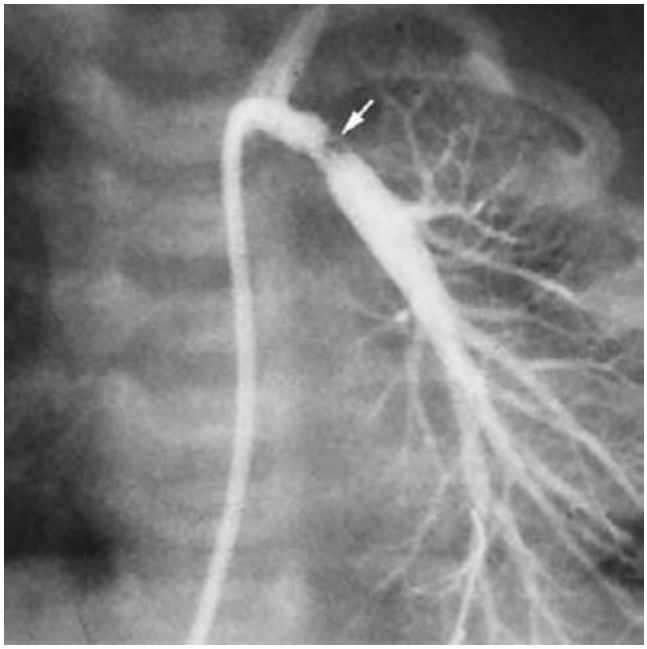

C

Fig. 8-3 Ligamentous origin of the left pulmonary artery in a patient with tetralogy of Fallot and right aortic arch. **A**. Three-dimensional contrast-enhanced MR angiogram of the thorax as seen from behind demonstrates the small intraparenchimal left pulmonary artery (LPA). Notice the ductal diverticulum in the base of the innominate artery (IA). **B**. The ligamentous ductus was probed. **C**. Angiogram shows that the ligamentous ductus was dilated with stent placement (arrow). Ao, descending aorta; LA, left atrium.

and did not relate to the presence of associated cardiac lesions or pulmonary artery dimensions. At latest follow-up, right ventricular hypertension was present in 75%, congestive heart failure in 13%, ipsilateral lung hypoplasia in 73% and scoliosis in 42%. Exercise tolerance was NYHA class I in 19, II in 4, III in 1 and IV in 1 patient.

Conclusion

While collaborative interventional and surgical strategies may succeed in rehabilitating the isolated PA, survival remains suboptimal and long-term complications are common. In the patient with ductal or ligamental origin of a pulmonary artery in isolation, the long-term effects of this condition impact on the growth of the hemithorax, the potential for scoliosis and for pulmonary hemorrhage. Pneumonectomy has been required because of intractable pulmonary hemorrhage. In those patients in whom continuity has been surgically achieved, continued surveillance is necessary to ensure that obstruction of the graft/conduit from the main pulmonary trunk to the hilar pulmonary artery does not occur. It is likely that there will always be some maldistribution of flow favoring the normally connected pulmonary artery. Thus serial pulmonary perfusion studies and echo-Doppler examinations will be necessary. As our data have shown, a considerable number of these patients will develop pulmonary artery hypertension and congestive heart failure. When ductal tissue is used to repair this anomaly, as in the premature infant reported by Salaymeh and colleagues, post-anastomotic pulmonary arterial stenosis is inevitable.[48]

In summary:

- Distal ductal or ligamental origin of one or both pulmonary arteries is an uncommon condition.

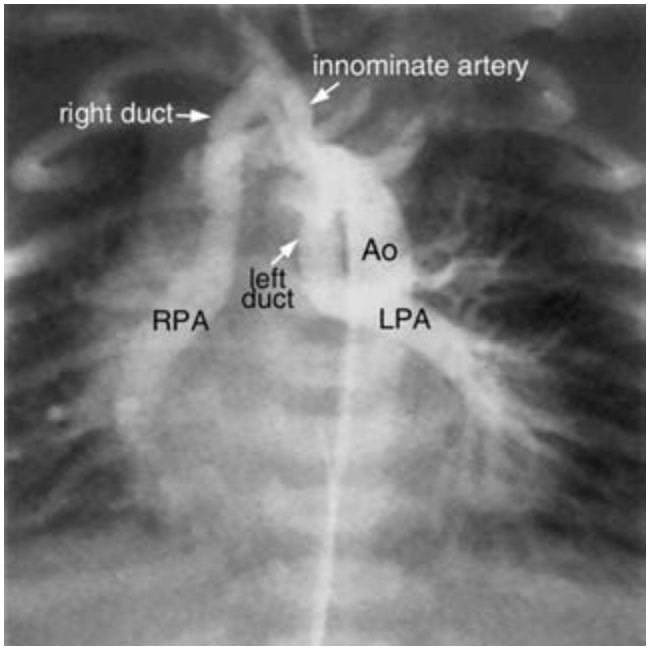

Fig. 8-4 Bilateral ductal origin of the pulmonary arteries. The left duct arises from the undersurface of the aortic arch (Ao). The right duct arises from the proximal innominate artery. LPA, left pulmonary artery; RPA, right pulmonary artery.

- The inference of this condition is that of bilateral arterial ducts.[4,5,24,49]
- It is most commonly associated with tetralogy of Fallot, pulmonary atresia and ventricular septal defect and hearts with right isomerism/pulmonary atresia.
- The outcome is more likely related to the associated cardiac malformation than to the non-connected lung.
- The consequences of longstanding distal ligamental origin of the pulmonary artery include hypoplasia of the ipsilateral lung and thorax; kyphoscoliosis; ventilation/perfusion mismatch; hemoptysis from rupture of thin-walled pleural collaterals; and severe infection.
- Whether or not the affected lung is connected to the rest of the pulmonary circulation does not seem to influence survival, at least not in childhood.
- MR imaging often provides excellent visualization of the distal pulmonary artery and its extension beyond the hilum and thus its accessibility for reconnection.

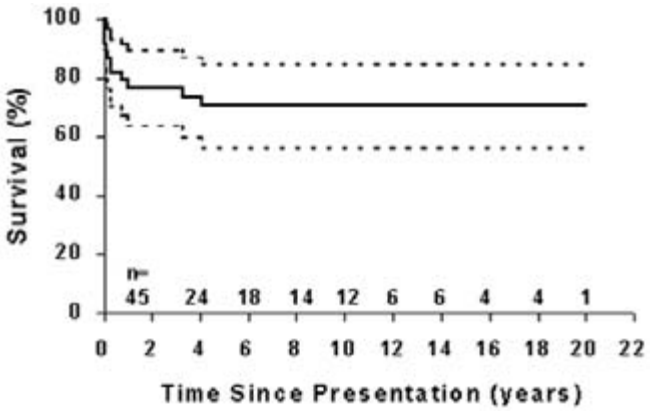

Fig. 8-5 Kaplan–Meier curve depicting survival of entire cohort of patients with distal ductal origin of one pulmonary artery.

- A number of procedures have been used to rehabilitate the affected lung.
- If a tube graft is used to establish continuity, there is the potential for graft obstruction and for replacement with growth of the patient. Pulmonary perfusion scans may be particularly helpful in the longitudinal follow-up of these patients.

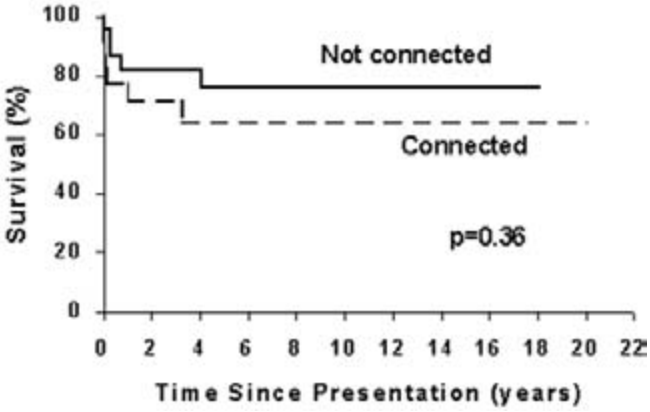

Fig. 8-6 Kaplan–Meier curves depicting survival depending on whether pulmonary artery connected or not.

All references can be found at the end of the book. See pp. 631–3 for Chapter 8.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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The Patent Arterial Duct

History

Since Galen's original Greek descriptions of the fetal circulation (AD 129–200), it was clear that he was aware of the presence of the arterial duct. These descriptions were revised and re-published by Kuehn (1821–33), who pointed out that, although Galen did not realize that blood circulated, he was familiar with many aspects of the fetal circulation. He understood that fetal blood was aerated in the placenta, and that blood was diverted away from the liver by a short vessel connecting the portal to the inferior caval vein. Galen also knew that blood crossed the oval foramen to bypass the right ventricle and reach the left heart directly. He realized, none the less, that some blood still entered the right ventricle and pulmonary trunk, from whence it was shunted into the aorta through a "special fetal channel," thereby bypassing the lungs. This clearly indicates Galen's understanding of the fetal circulation and the dramatic readjustment of the circulation at birth. Botallo described postnatal patency of the oval foramen. By a series of misinterpretations, and careless translations, his name became, quite unjustifiably, attached to the arterial duct.[1] William Harvey, who was a pupil of Fabrizi d'Acquapendente in Padova for 2 years, synthesized previous anatomical descriptions in his own writings, but his genius resided in proposing the concept of active circulation of the blood. He stressed the large size of the arterial duct and the fact that, during fetal life, blood flowed from right to left through it.[2]

Highmore,[3] a friend of Harvey, described closure of the oval foramen and arterial duct as occurring with the onset of respiration. He believed that, as a consequence of blood being diverted to the lungs, the arterial duct collapsed. It was Virchow[4] who first suggested that closure of the arterial duct results from contraction of its mural smooth muscle, while Gerard[5] introduced the concept of two-stage closure, in which functional constriction is followed by anatomic obliteration. Several ingenious theories to explain closure of the duct have been reviewed by Dawes,[6] all being based on postmortem appearances, and all invoking mechanical factors. When Huggett[7] exteriorized a fetal goat, and maintained it in stable condition with the placental circulation intact, he brought further studies of the duct into the realm of the physiologist rather than the anatomist. His experimental technique led to the first systematic investigation of how the duct constricts at birth. This eventually led to our understanding of the role of oxygen in effecting functional closure by muscular contraction. In 1907, in an address to the Philadelphia Academy of Surgery, John Munro first suggested surgical ligation of a patent arterial duct.[8] Thirty-one years later, Graybiel *et al.*[9] reported the first attempt to perform this operation in a 22-year-old woman with bacterial endocarditis. Unfortunately, although the patient survived the surgery, she died a few days later from complications of the infection. Thus, it was Robert Edward Gross from Boston who performed the first successful ligation of a patent duct in a 7-year-old child with intractable heart failure.[10] He thereby introduced an amazing era of progress in the surgery of congenital malformations of the heart.

Nomenclature and definition

From time to time, authors have argued that the terms "patent" or "persistent" are redundancies, which should be avoided when describing the arterial duct. In our view, this oversimplifies the situation, and both terms remain useful. "Persistence" implies that the duct is present after the time of its expected closure, and therefore distinguishes a pathologic from a physiologic state. The term "patent" remains useful in the perinatal period, especially in the premature infant in whom patency can be used to signify a duct, which is functionally open, as opposed to one which is functionally closed, but which retains the potential to reopen.

Functional closure in full-term infants occurs within 10–15 h of birth. Anatomical closure may not be complete for up to 3 months. On this basis, true persistence of the duct has been defined as continued patency in infants older than 3 months.[11] This definition should be applied only to infants born at term.

Embryology, histology and anatomy

During early fetal development, six arterial arches link the aortic sac with the paired dorsal aortas, although all six arches are never present simultaneously. This symmetrical arrangement is transformed to the configuration seen in postnatal life as some arterial segments disappear and others realign.[12] The normal duct develops from the dorsal portion of the left sixth arch. From their inception, the sixth arches, which are first identifiable at the 5-mm crown-rump stage and become canalized by the 7-mm stage, are associated with the developing lung buds. These buds are initially supplied by a plexus of capillaries, which develops from the aortic sac and later connects to the dorsal aorta. The sixth arches develop from the resulting vascular connections between the aortic sac and the dorsal aorta. When the developing arterial segment is divided to form the aorta and the

pulmonary trunk, the sixth arches remain continuous with the latter. On the right side, the ventral portion of the sixth arch ultimately becomes the proximal portion of the right pulmonary artery, while the dorsal portion regresses. On the left side, the ventral portion is absorbed into the pulmonary trunk and the dorsal segment becomes the arterial duct. The fetal arterial duct is a short and wide vessel of variable length. It connects the pulmonary arteries to the lesser curve of the arch of the aorta at the point of transition from arch to descending aorta, joining just distal and opposite to the origin of the left subclavian artery. In the fetus, the duct appears very much as the direct continuation of the pulmonary trunk, while the left and right pulmonary arteries are seen as considerably smaller branches from the trunk. The duct is related posteriorly to the left main bronchus while anteriorly, it is crossed by the vagus nerve. This gives off the left recurrent laryngeal nerve, which encircles the duct before ascending behind the aortic arch into the neck. The pulmonary arterial end of the vessel is covered by a reflection of the pericardium.

Developmental anomalies of the aortic arch may be associated with an abnormally situated arterial duct, either patent or represented by a ligament. In such cases, the duct may form part of a vascular ring.[13] A right aortic arch, in the greater majority of cases, tends to be associated with intracardiac anomalies.[13] These cause blood to be ejected towards the right rather than the left of the primitive arterial arches. One-quarter to one-third of patients with tetralogy of Fallot have such right-sided aortic arches, usually with mirror-imaged branching, along with a left-sided arterial duct or ligament arising from the brachiocephalic trunk. The duct may then connect the left pulmonary artery either to the subclavian portion of the brachiocephalic (innominate) artery or to the upper descending aorta by a remnant of the left dorsal aorta. In the latter case, there is a complete vascular ring.[14] A right-sided duct can also be found with a right-sided ascending and descending arch.[15] Such a right-sided duct, or ligament, occurs much less frequently with a right arch and mirror imaged branching, and it is also associated with the presence of intracardiac anomalies, especially tetralogy of Fallot.

A right aortic arch with an aberrant left subclavian artery and a left duct is the most common form of a complete vascular ring and probably arises as an independent developmental error. It is less frequently associated with intracardiac anomalies.[13] Numerous reports exist of this anomaly both in children and adults.[13] A very rare ductal anomaly, also associated with a vascular ring, is the so-called ductal sling,[16] where the duct connects a left descending aorta to the right pulmonary artery, passing between the trachea and esophagus. A right aortic arch with an aberrant left subclavian and a right-sided duct is exceedingly rare, but does occur.[17,18]

In the most common form of double aortic arch, both arches are patent, usually with the right being larger than the left, while the upper part of the descending aorta is also to the left. In these cases, the duct is also on the left and connects the left pulmonary artery to the aorta. Double aortic arch, in which both limbs are patent with either a right duct, or bilateral ducts, has not been reported, although the arrangement with bilateral ducts has been induced experimentally in rats deficient for vitamin A.[19] Atresia may also occur between the left duct and descending aorta, the left subclavian artery and the duct, or between the left common carotid and subclavian arteries.[20] If the atresia is between the left subclavian artery and the duct, or between the left common carotid and subclavian arteries, the duct passes between the left pulmonary artery and the caudal end of the left dorsal aortic root (descending aortic diverticulum). An atretic right arch is exceedingly rare. In at least two reported cases, the atresia involved segments of the subclavian artery and a right duct.[21,22] A right duct associated with a normally branching left aortic arch has also been observed. Similarly, the combination of a left aortic arch, right descending aorta and left duct has been described.[23,24] There is no ring when the duct connects the right pulmonary artery to the base of the brachiocephalic artery. But, if the connection is to the descending aorta by means of a partially persistent right aortic arch, then it produces a complete vascular ring. The persistence of bilateral arterial ducts, although rare, has been widely documented. In the majority of the cases, they are associated with the presence of complex intracardiac anomalies.[25–27] Kelsey *et al.*[28] reported a patient who also had a right-sided heart, ventricular septal defect and pulmonary atresia with a patent right duct and a left ligament. The aortic arch was left-sided and branched normally. Bilateral ducts with a right aortic arch and a right-sided descending aorta, or isolation of the left subclavian artery, have also been described,[29,30] as has the same combination with the additional anomaly of absence of the proximal left pulmonary artery.[31] Persistent right, left or bilateral duct may replace the proximal pulmonary artery. The origin of one pulmonary artery from a duct on the same side is not uncommon,[32] particularly in the setting of tetralogy with pulmonary atresia.[33,34] Bilateral ductal origins for the pulmonary arteries are rare.[25,27,35–37] Absence of the arterial duct was first described as an autopsy finding in 1671, being seen in a grossly malformed infant with an extrathoracic heart and tetralogy of Fallot.[38]

Emmanouilides *et al.*[39] and several others[40,41] reported the association of tetralogy of Fallot, absent pulmonary valve and absent duct. They postulated that absence of the duct early in fetal life might contribute to the massive dilation of the pulmonary arteries, which typifies this syndrome. In the presence of high fetal pulmonary vascular resistance, and increased right ventricular stroke volume secondary to pulmonary regurgitation, the pulmonary arteries become progressively distended because the normal outlet through the duct for most of the right ventricular output is lacking.[39,40,41] Lack of such marked aneurysmal dilation in those patients with absence of the leaflets of the pulmonary valve and intact ventricular septum in whom the duct is patent, tends to support their hypothesis.[42,43] Isolated examples of absent pulmonary valve with a patent duct and dilated pulmonary arteries, none the less, have been reported.[44] The duct is also absent in approximately three-quarters of patients with a common arterial trunk. Absence of significant flow through the duct in the presence of a larger aortopulmonary connection permits the duct to disappear early in fetal life. In more complex varieties of common arterial trunk, however, such as those with so-called "absence" of one pulmonary artery, the pulmonary artery itself may originate from a duct. Similarly, in those patients with an associated interruption or atresia of the aortic arch, patency of the duct is essential to maintain systemic perfusion.[32,45]

A number of teratogens, which may influence the development of the duct, have been identified, including rubella, alcohol, amphetamines and the anticonvulsant hydantoin.[46] The most sensitive period during which the arterial duct is susceptible to teratogens is from 18 to 60 days of gestation. Absence of the duct has been induced experimentally in chick embryos by the administration of β receptor agonists. Associated malfor-

mations, including anomalies of the aortic arch, ventricular septal defect, overriding aorta or double outlet right ventricle, aortopulmonary window or common arterial trunk, were also induced. Frequencies of malformations were related to the beta-stimulating potency of the drug used, and this frequency was reduced by pretreatment with blocking agents, especially beta-1 blockers. Caffeine and theophylline both potentiated the frequency of malformations, as did cocaine. These findings led Gilbert *et al.*[47] to propose a mechanism of cardiovascular teratogenesis mediated by cyclic adenosine 3′, 5′ monophosphate.

Langer[48] is credited with being the first to recognize that the histological features of the duct differ from those of the adjacent pulmonary artery and aorta. Normal structure of the unconstricted vessel is difficult to study. Most reports relate to tissues that have either undergone partial or complete constriction, or else to those which have been subjected to mechanical handling and fixation. Many studies fail, however, to distinguish between structural changes resulting from functional constriction and those leading to anatomic obliteration. There is general agreement that the duct is a muscular artery endowed with an intima, media and adventitia. Microscopically, it differs from the adjacent pulmonary trunk and aorta. While the media of the aorta is composed mainly of circumferentially arranged elastic fibers, the media of the duct consists largely of spirally arranged smooth muscle cells directed clockwise and counterclockwise, and has an increased content of hyaluronic acid. The intimal layers are thicker than the adjoining vessels, and contain increased amounts of mucoid substance.[49,50] Its tissues in the newborn are rather loosely arranged, with a well-defined internal elastic lamina that may be single or focally duplicated, with small interruptions encountered regularly. The outer two-thirds of the lamellae of the aorta and pulmonary arteries merge into the adventitia of the duct without forming an external elastic layer, whereas the inner third passes into the internal elastic lamella. The internal elastic laminae of the great vessels disappear during gestation by splitting into the elastic lamellae. Scattered throughout the media are concentrically arranged layers of elastic tissue, with sparse elastic fibrils running irregularly between them. In longitudinal sections, the elastic fibers of the aorta and pulmonary artery are seen to condense into a coarse elastic band at the orifice of the duct.[51] Electron microscopic studies confirmed the presence of fine branching strands of microfibril-coated elastin between the layers of smooth muscle cells.[52] At birth, the arterial duct constricts, and it cannot close by isolated contraction of circularly arranged muscle alone.[53] Coincident shortening of the less abundant longitudinally arranged muscle fibers is, therefore, critical to effective closure. This shortening probably depends on active attachment of the muscle to the collagen framework of the great vessels in the junctional zones. The duct possesses vessels in its walls, which may have a role in fueling contraction at birth.[52,54] Some degree of hyperemia of these vessels is common in newborn infants. The intimal thickenings, or cushions, become irregular ridges protruding into the lumen, running mainly lengthwise. By their extrusion, they exert traction on the media causing disorganization and formation of mucoid lakes located mainly on the border between cushions and media. Anatomic obliteration follows functional closure. The process begins with necrosis of the inner wall due to anoxia followed by the formation of dense fibrous tissue. Loss of nuclei, absence of cellular infiltration, and persistence of an unaltered elastic skeleton within the wall characterize this cytolytic necrosis. Nutrition to the intima and inner media is maintained by diffusion from the lumen and by the still functioning vessels in the wall. A process of luminal fibrosis, probably representing organization of mural or occlusive thrombus, progressively obliterates the lumen. The initial constriction occurs at the pulmonary arterial end, and extends towards the aorta, giving a typical conical shape. This conical aortic end, the ampulla, may persist for many weeks, or in some cases years, after closure. Occasionally, there may be a diverticulum originating from the proximal left pulmonary artery. Eventually, the duct becomes converted into a fibrous strand, the arterial ligament, which may become calcified. Anatomic obliteration may take several weeks to complete. About two-thirds of ducts are obliterated by 2 weeks,[55] and almost all by 1 year.

Incidence and epidemiology

Several attempts have been made to estimate the incidence of the persistent duct seen in isolation, but all studies published thus far contain potential sources of error. This is especially so concerning the inclusion of cases owing to prematurity or to maternal rubella. Anderson[56] estimated that the incidence was between 1 in 2500 and 1 in 5000 births. In this study, isolated patency of the duct accounted for 12% of all congenital cardiac malformations. The most extensive study of a relatively homogeneous population is that by Carlgren.[57] He charted the incidence of congenital heart disease in children born in the Swedish city of Gothenburg. This study reported an overall incidence for all cardiac malformations of 6.4 per 1000. Persistent patency of the duct was the third most common lesion identified, representing about 0.04% of livebirths. Mitchell *et al.* reported data from 12 North American centers including 55 044 livebirths. It was estimated an incidence of 0.06%.[58] As with Carlgren's study, some of these arterial ducts were probably associated with prematurity or maternal rubella. A significant higher incidence of ductal patency is observed in infants born with low weight.[58–60] Almost half of infants weighing < 1750 g at birth, and up to four-fifths of those weighing < 1200 g, have clinical evidence of patency of the duct.[61–70] With the advent of surfactant for the treatment of the respiratory distress syndrome in neonates, many more preterm infants are now encountered with ductal patency.[71–76]

Zetterquist[77] made a thorough study of the families of 435 patients undergoing surgical closure of persistent ducts in Sweden. Females predominated in a ratio of 3:1. He found an incidence of 2.5 ± 0.7% among 484 children of these patients. This figure is almost identical to that found for the siblings of the original patients (2.3 ± 0.6%). Nora[78] reported a somewhat higher risk to the offspring of 4.3%, given one affected parent. This incidence is some 45 times greater than the risk for the general population. The risk to further children in sibships where two children have already been affected is probably about 10%. It undoubtedly increases for each affected sibling.[79,80] Sibships of up to five with persistently patent duct have been observed.[81]

Maternal rubella was first linked to persistent ductal patency by Gregg.[82] Histological examination of ducts from patients with rubella syndrome showed them to have a thinner wall, with absence of both an internal elastic lamina and intimal proliferation. They thus resemble a very immature duct.[83] The amount of smooth muscle was also reduced.[84] Persistence of the duct also occurred as part of the thalidomide syndrome,[85] while defi-

ciency of copper in rats has resulted in high rates of ductal patency.[86] A patent arterial duct is more likely to be found in infants born at high altitude.[87] These findings, however, were not confirmed in further studies.[88] Persistence is more common in females, except in cases due to rubella where the ratio of genders is almost equal.[89] The incidence of re-patency of the arterial duct after initial closure has been estimated in 0.9%.[90]

Natural history

Like many congenital cardiac malformations, completely reliable information concerning the natural history of untreated patients with a patent arterial duct is non-existent. The data available originate from the short period of time, which elapsed between the condition being diagnosed and to its being relieved by surgical or interventional procedures, or spontaneous closure. Campbell[91] attempted an overview of the natural history, based on both his own extensive clinical experience and the literature. Inevitably, such calculations tend to overemphasize the number of patients who experience events, be they favorable or adverse. They perhaps underestimate the number of patients with an asymptomatic and undetected arterial duct. By combining four series, consisting mainly of "unselected" school children with persistent duct, Campbell deduced a mortality rate of 0.42% per annum during the first two decades. Thereafter, the calculated mortality rates per year are 1–1.5% in the third decade, 2–2.5% in the fourth, and 4% for each subsequent year. These calculations indicate that one-third of patients with a persistent arterial duct die by the age of 40, in contrast to < 1/20 of the normal population. Many of the figures are based on data obtained in the era before antibiotics became available. As infective endocarditis is a major cause of death, the impact of antibiotics must also be taken into consideration. These figures agree fairly well with age at death as reported in necropsy series. Abbott,[92] for example, found the mean age at death, having excluded those who died in infancy, to be 30 years. In another series, the mean age at death was 36.5 years.[93] Despite this agreement, the fact remains that calculations from autopsy series and from clinical series are extrapolations from rather small numbers. They undoubtedly exaggerate the adverse aspects of the natural history.

The importance of the arterial duct in the fetal circulation and its role in the pathophysiology of congenital cardiac malformations

The arrangement of the fetal circulation, with the ventricles working in parallel, permits fetal needs to be met most efficiently. Early in the first trimester, the fetal duct is sufficiently developed to carry most of the right ventricular output, which accounts for about two-thirds of the total combined ventricular outputs. The relative sizes of the great vessels and duct are dependent on the magnitude of this flow, and significantly influence the form of many cardiovascular malformations.[94,95] In the normally developing heart, the duct meets the aorta proximally at an acute angle of < 45º, while the distal angle is obtuse, at around 130º.[11] Most of the output from the right ventricle traverses the duct, accounting for about three-fifths of the combined flow,[96] and provides *c*. 85% of the flow to the descending aorta, and therefore the majority of placental flow. Only about one-tenth of the output of the right ventricle in the fetal limb is directed to the lungs.[96] Thus, the arterial duct diverts blood from the high resistance pulmonary circulation to the descending aorta and the low resistance placenta. Unlike the adult circulation, in which blood always traverses the heart twice in any one total circulation, the fetal circulation minimizes "double pumping" to the small volume of pulmonary venous return. The demands on the fetal myocardium for work are thereby reduced to a minimum. Whether the duct regulates the distribution of right ventricular output in the fetus is unknown. It is conceivable that the fetal lungs have significant metabolic functions. In this case, the ability to alter the amount of blood directed to the lungs would be advantageous. The behavior of the duct in the immediate postnatal period may be crucial when the heart is congenitally malformed. When either the pulmonary or systemic circulation is entirely supplied through the duct, survival itself depends on the patency of the duct. Flow of blood to the lungs may be entirely duct dependent. This situation is epitomized by pulmonary atresia with an intact ventricular septum, and by tetralogy of Fallot with pulmonary atresia but no systemic-to-pulmonary collateral arteries. In these settings, the duct tends to be long and narrow, appearing as a downwardly directed branch of the distal aortic arch so that the proximal angle is much less acute and often obtuse.[97] The distal angle, in contrast, is often acute.[95] When this is not the case, it can be inferred that the development of pulmonary atresia occurred in late gestation.[98] In other situations, such as severe pulmonary stenosis, tricuspid atresia with pulmonary stenosis, double outlet right ventricle with pulmonary stenosis, and tetralogy of Fallot where major obstruction to normal pulmonary blood flow is present, a patent duct is required. Arterial oxygen saturation in all these settings depends on the volume of pulmonary blood flow. Although these patients never experience a normal postnatal rise in arterial tension of oxygen, closure of the duct usually occurs but frequently is delayed for 24–48 h, or longer.[99] The stimulus for closure under these circumstances is unexplained, despite the presence of coexisting hypoxemia. Systemic blood flow may also be partially or entirely dependent on the duct. In patients with aortic atresia as part of the hypoplastic left heart syndrome, the systemic circulation is entirely duct dependent. In this instance, the distal angle of ductal insertion to the descending aorta is closer to normal, although the proximal angle is less acute and the duct is shorter and broader.[97] Partial dependence of the systemic circulation exists when there is interruption of the aortic arch.

The duct also plays an important role in patients with coarctation of aorta.[100,101] While the duct remains open, its aortic end can act as a bypass for flow from the aortic isthmus to the descending aorta. When it closes, the full significance of the coarctation becomes apparent.

Patients with complete transposition, especially when the ventricular septum is intact, depend on adequate mixing between the two parallel systemic and pulmonary circulations. Much of this mixing takes place at the atrial level, especially after balloon septostomy or atrial septectomy. Its amount is then determined by the relative compliances of the two ventricles. Patency of the duct can contribute favorably to mixing in complete transposition. Left-to-right flow of desaturated blood from the aorta to the pulmonary trunk via the duct is balanced by increased left-to-right flow of fully saturated blood from left atrium to right atrium. The net effect is to increase arterial oxygen saturation, and can acutely stabilize the infant until medical or surgical intervention can safely be accomplished.[102] The duct may also act as a "safety valve" for patients with pul-

monary vascular disease. By facilitating run-off from the pulmonary circulation, it may prevent right ventricular failure, but at the cost of differential cyanosis.

Intrauterine ductal closure

The duct can close in early gestation. Intimal cushions, the substrate for functional and anatomic closure, have been noted as early as the fourth month of gestation. Several drugs are known to influence intrauterine ductal constriction and closure, particularly the inhibitors of prostaglandin.[103–107] These can result in fetal heart failure and intrauterine death.[108–112] Transient neonatal tricuspid regurgitation and persistent fetal circulation have also been postulated to be the result of premature ductal closure.[113,114]

Complications of the patent arterial duct

Among the complications of the persistence of the arterial duct are congestive heart failure, infective endarteritis, pulmonary vascular disease, aneurysmal formation, thromboembolism, and calcification.

Congestive heart failure

Congestive heart failure resulting from an isolated persistent duct either develops in infancy or during adult life. Heart failure in infancy usually has its onset before the age of 3 months. Occasionally, its presence may not be recognized until after that time. A delayed normal fall in pulmonary vascular resistance may cause the left-to-right flow to increase progressively. The clinical picture is initially that of left heart failure, with tachypnea and pulmonary edema. Ultimately, signs of right heart failure appear with hepatomegaly. Although initially there may be a good response to medical treatment, this is seldom maintained. Closure is advisable. Amongst adults, there used to be a group with cardiomegaly and features of left ventricular overload and strain. Such patients must now be rare in countries with well-developed systems of health care, as it is unlikely that their lesion will have escaped detection. Congestive heart failure may also occur in patients in whom an elevated pulmonary vascular resistance is present and if so, transcatheter closure appears to be the treatment of choice.[115]

Infective endarteritis

Infective endarteritis in a patient with an uncomplicated persistent duct is uncommon in childhood. In the era preceding antibiotics and surgical treatment, it was a major cause of death. It accounted for almost half of all deaths in several pooled autopsy series.[92,93,116] Campbell[91] calculated an infection rate of between 0.45% and 1.0% per annum based on the figures of Cosh[117] for patients after the first decade. Infection occasionally follows surgery, when it is probably secondary to infected sutures. Vegetations are usually found at the pulmonary arterial end of the duct and they may cause recurrent pulmonary embolization episodes. Infection may also cause a ductal aneurysm, especially those occurring postoperatively.[118] A single case of endarteritis on a clinically silent and nonhypertensive duct has been reported. This has implications for treatment in such situations.[119]

Pulmonary hypertension

Pulmonary hypertension develops either because of a torrential left-to-right shunt or as the consequence of raised pulmonary vascular resistance. It has not been possible to calculate accurately the risk of progressive pulmonary vascular disease in patients with a large persistent duct mainly because surgical treatment has been available almost as long as clinical recognition. The information in terms of natural history necessary to answer the question is not available, nor would such a study now be feasible. Campbell[91] does not address this problem in his calculations. There are several reports in the literature, none the less, concerning this complication.[120–122] These are based on selected groups of patients and overemphasize the frequency of the problem. Nor do they all distinguish adequately between pulmonary hypertension with high flow and true pulmonary vascular disease. The presence of pulmonary hypertension secondary to structural changes within the pulmonary vasculature increases the surgical risk, with mortality in more than half of a small group of such patients.[120]

Aneurysm of the duct

Aneurysm of the arterial duct has been described either pre- or postnatally.[123,124] It likely develops in the third trimester due to abnormal intimal cushion formation or elastin expression. Different series report an incidence that varies from 1.5% to 8.8%.[123,124] Although a rare lesion, it can be associated with several complications including thromboembolism, dissection, rupture, inspiratory stridor, left recurrent laryngeal nerve palsy, pulmonary artery obstruction and death.[123–128] True aneurysm of the duct is rare and presents either at or shortly after birth[129,130] or during childhood or later life.[131,132] Sepsis may be involved in the pathogenesis of some cases in infancy. The type found in infancy is much more common and may not be uncovered until autopsy for death from other causes.[133] Regression can occur, presumably due to thrombosis and organization.

Thromboembolism

Thrombosis of the duct was first described as a source of neonatal embolus by Rauchfuss.[134] Several cases, mostly fatal, have been described.[135,136] Early diagnosis may provide an opportunity for successful intervention, which may include thrombectomy, anticoagulation, and resection of infarcted tissue.

Outcomes

Once the diagnosis of uncomplicated persistent patency of the arterial duct is established, elimination of the shunt should be recommended by surgical ligation or catheter occlusion, even when the shunt is small. The justification for closure of small communications resides in the prevention of infective endocarditis, coupled with an extremely low procedural morbidity and mortality. In the occasional patient who develops congestive heart failure, excluding those patients to be discussed below in the context of prematurity, drugs should be administered to combat the failure, but only until intervention can conveniently be arranged.

Surgical intervention

Robert Gross achieved the first successful ligation of a persistent arterial duct in a 7-year-old girl in 1939.[10] Usually, the duct is approached through a left posterolateral incision, using the third interspace in infants, and the fourth space in children over 1 year. Uncommonly, the duct is on the right side, especially in the presence of a right aortic arch. It must then be approached from the right. The duct may be ligated or divided. The relative merits of each procedure continue to be hotly debated by surgeons. Excellent results have been reported using both procedures. Ligation using two heavy silk ligatures, plus an umbilical tape ligature, is simple and safe.[137] Transfixation as proposed by Blalock does not seem to be necessary. Using this technique, the incidence of recanalization is about 1%.[137–139] However, Jones[140] reported 12 instances of recurrent or residual ductal flow amongst 61 patients in whom the duct had been ligated using heavy tape. Clinically detectable shunts after surgical intervention have ranged from 0.4% to 3.1%.[141] Recent echo-Doppler studies, however, have detected flow in clinically silent ducts, suggesting the incidence of residual flow to be higher.[142,143] Large ducts exceeding 7–10 mm diameter, or those associated with pulmonary hypertension, should be divided. Recurrent ducts, short wide vessels, or those with spontaneous or infected aneurysms should also be divided using an approach through the left chest. Controlled hypotension may help control bleeding in patients with pulmonary hypertension or friable ducts.[144]

By 1939, Gross was able to publish details of ductal ligation in 14 patients varying in age from 3 to 24 years, with 2 having endarteritis owing to *Streptococcus viridans*. There were neither deaths nor significant complications in his early series, but division rather than ligation was advocated.[145] Further reports of more extensive experience followed.[138,140,146] Jones, reporting on a large experience extending over 25 years, had only 1 of 431 patients dying with an uncomplicated duct, giving a rate of mortality of 0.2%.[140] A figure of 0.5% was reported by Panagopoulos *et al.*[141] Once the safety of the operation was established in older children and adults, it was natural for surgeons to attempt closure in infancy.[147] Mustard[148] reported successful ligation in four infants. Many surgeons then demonstrated the ease with which the duct can be ligated even in premature infants.[149] In most units, surgical ligation is reserved for those premature infants who have failed an adequate course of indomethacin, or when there are contraindications to its administration. Some have advocated prophylactic ductal ligation, although the only demonstrated advantage of such a strategy has been a reduction in the incidence of necrotizing enterocolitis in babies weighing < 1000 g.[150] The need for accurate anatomical definition before intervention in the premature infant was underscored by Fleming *et al.*[151] Ligation or division of the duct is usually associated with an immediate rise in systemic arterial pressure. This may be sustained for several days before subsiding to normal level.[152] Pulmonary arterial pressure, if elevated and in the absence of pulmonary vascular disease, falls to normal. The continuous murmur disappears and the size of the heart is reduced. Left atrial and left ventricular enlargement, as judged by echocardiography,[153] also diminish. Complications are uncommon. Injury to the recurrent laryngeal nerve injury can occur occasionally, but is usually temporary.[140,154] Rarely, a false aneurysm may develop prompting urgent surgical reoperation after ligation[155–157] or division.[158–160] Damage to the phrenic nerve has also been reported, occurring most frequently in the premature infant.[154] Chylothorax can also occur. Inadvertent ligation of the distal left pulmonary artery occurs infrequently. This is a hazard when the duct is large and the recurrent laryngeal nerve has an unusual course.[161] Ligation of the descending aorta can occur, especially when the duct is approached from a median sternotomy. Signs of aortic coarctation may also be unmasked after ductal ligation.[162] This is a constant hazard in the premature infant. Abnormal findings after ductal ligation, such as decreased femoral pulses or declining urinary output, should prompt rapid reevaluation.

Thoracoscopic closure without thoracotomy is a recent innovation. Laborde *et al.*[163] first reported use of the video-assisted endoscopic technique in 38 patients with a mean age of 23.3 months, and mean weight of 9.5 kg. Clinical evidence of successful closure was found in all, although two attempts were necessary in 2 patients. Damage to the recurrent laryngeal nerve occurred in 1, while 4 suffered pneumothorax. Increasing experience with the procedure has reduced the incidence of complications.[164] Continued experience has shown this approach to shorten hospital stay, and to provide a cost-effective, safe and rapid technique compared to open thoracotomy. Damage to the recurrent laryngeal nerve, and residual shunts, can occur.[165–171] Recently, a transaxillary muscle-sparing thoracotomy has been developed for the neonate and infant. This provides excellent exposure for ductal division, produces less postoperative pain, and achieves an acceptable cosmetic result.[172–175]

Closure in the cardiac catheterization laboratory (Fig. 9-1)

Porstmann and collegues[176–179] first described a percutaneous approach for closure of the arterial duct through the femoral artery. Using this technique, closure was accomplished using an Ivalon™ plug and a prerequisite for this approach was that the lumen of the duct must be conical in shape and smaller than the lumen of the femoral artery. It was technically a complicated procedure, requiring placement of a large sheath in the femoral artery. A loop was then constructed from the femoral artery, through the duct, and to the femoral vein. Because of this, the technique has not been found suitable for infants and small children. Other devices, such as polyvinyl alcohol umbrellas with steel wires, umbrella-sponge plugs, or polymers with a memory for their shape, have been used to close artificial ducts created in dogs from either the arterial or venous circulations.[180–182] A detachable silicone double balloon has been described by Warnecke *et al.*,[183] although it did not undergo extensive clinical trials. Magal and colleagues[184] described a device consisting of a small nylon sack, which could be filled with segments of guidewire, and fixed with a distal flexible crossbar. Rao *et al*.[185] described a successful modification of a single disk device originally designed for closure of atrial communications. Rashkind & Cuaso, as long ago as 1979, proposed using a device consisting of a stainless steel grappling hook, filled with a cone of foam.[186] The prosthesis was introduced in a collapsed state and then expanded when released from the tip of the catheter. Since that initial clinical application, and with improvements in the design of the equipment, experience from a multicenter clinical trial[187] has defined the setting for successful occlusion in the catheterization laboratory, and has led to its use as an effective

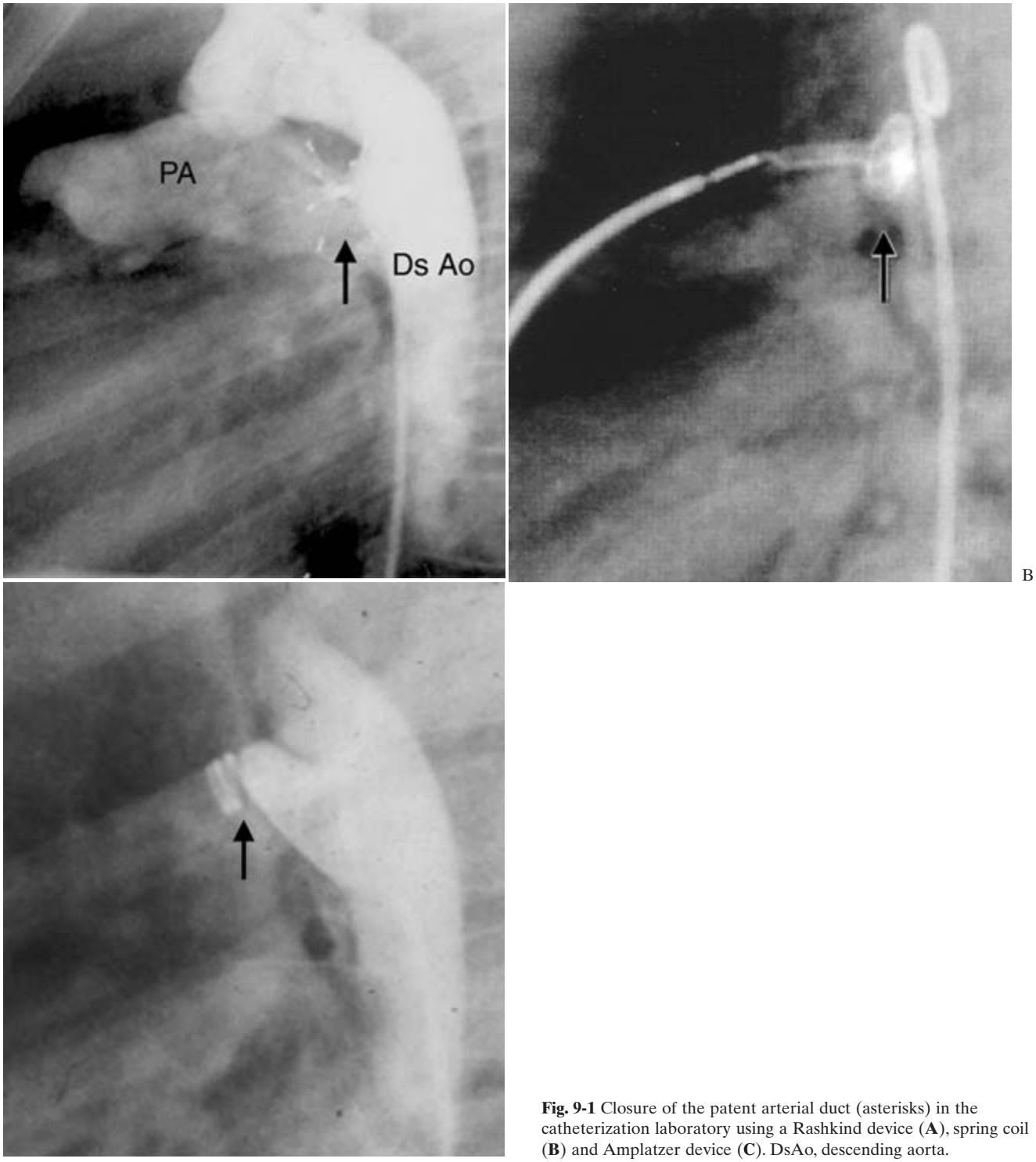

Fig. 9-1 Closure of the patent arterial duct (asterisks) in the catheterization laboratory using a Rashkind device (**A**), spring coil (**B**) and Amplatzer device (**C**). DsAo, descending aorta.

alternative to surgery. In the early 1990s, spring coils, originally designed for peripheral vascular embolization, were introduced to achieve closure of the arterial duct.[188,189]

More recently, antegrade catheter closure of moderate- to large-sized arterial ducts using a self-expandable, repositionable device (Amplatzer Duct Occluder™ AGA Medical, MN) has been reported.[190–192] Alternatively, in patients with a very small arterial duct, balloon dilation in preparation for transcatheter occlusion was described.[193]

The Rashkind ductal occluder

Using this device, closure can be accomplished from either venous or arterial entry.[187] The use of a long sheath placed across the duct from the venous circulation, as described by Bash and Mullins,[194] became the technique of choice. Closure in this fashion was achievable in infants and young children. Modifications in this technique have been developed.[195,196] It is not, however, possible to close ducts > 8–9 mm in diameter, nor

to achieve closure in premature infants. The occluder consisted of two open-pore disks made of medical grade polyurethane foam mounted on opposing spring assemblies with three arms resembling opposing umbrellas. When released, the arms spring perpendicular to the shaft of the catheter and self-seal. The device was available with diameters of 12 and 17 mm, the larger device being made with four arms per disk, but with the same spring and mechanism for attachment to the catheter. As with surgical management, the clinical diagnosis should be confirmed noninvasively before catheterization by color Doppler echocardiography, with particular emphasis placed on the presence of associated lesions which could complicate the procedure, such as azygous continuation of the inferior caval vein, presence of an additional lesion which requires surgical intervention, or the presence of pulmonary vascular disease. Special attention should also be directed to the transverse arch and isthmic region to exclude unsuspected coarctation. The procedure was ideally suited for patients weighing 10 kg or more. It was not routinely performed in smaller infants because of the risk of compromise to the left pulmonary artery.[142,197] There is considerable variation in procedural details as practiced amongst centers, such as the use of coincident arterial cannulation, the number and type of angiograms, and so on. The majority of procedures, however, can be performed in an outpatient setting, with discharge the afternoon of study.[195,198] A number of clinical series have been published involving hundreds of patients.[187,195,198–210] Successful implantation could be accomplished in almost all (> 96.5%), with elimination of clinical signs of left-to-right shunting. Within the first 48 h, ductal murmurs could still be heard in a few patients despite correct placement, although a number may have residual shunts without murmurs. Evidence of shunting is often provided by Doppler interrogation over the superior aspect of the device.[142,199] The average immediate occlusion rate was 68% and increased to 97% at 2-year follow-up for small- to moderate-sized arterial ducts.[187,195,198–213]

Reported complications are few: acute bacterial endarteritis has occurred after implantation when appropriate prophylactic medication was not applied,[199,200] embolization to both systemic and pulmonary circulations, thrombosis which resolved with heparin infusion[214] and hemolysis after placement of the device with coexistent residual shunting.[215–219] Standard surgical ligation of the duct with either leaving the occlusion device *in situ* or with device removal[215,216] as well as closure of the residual leak using detachable coils[217] or a second device[218] were reported as efficacious treatment for this infrequent complication. Device retrieval was also accomplished using snares, baskets, or grasping forceps.[187,200] Reocclusion with a second device for persistent shunting has been performed.[220]

Pulsed and color flow Doppler techniques have been used to evaluate the rates of occlusion.[142,205,206,220,221] Hosking *et al.*[220] reported that just over one-third of their patients had Doppler evidence of shunting detected 1 year after the procedure, falling to one-fifth at 2 years, and less than one-tenth at 40 months. Others[206,221] have reported similar observations. A number of patients have undergone repeat procedures, with successful placement of a second device.[220,221] In a few patients, there was evidence of increased flow at the origin of the left pulmonary artery subsequent to implantation, presumably due to turbulence or encroachment of the device into the mouth of the left pulmonary artery without hemodynamic consequences. There was an increased incidence of this finding when the Rashkind device was placed in children < 10 kg in weight.[222] This device is no longer commercially available.

Closure using the Ivalon transfemoral plug

The Porstmann plug is inserted using a catheter placed from the femoral artery and threaded across the duct into the right heart. Either the catheter itself or an exchange guide wire is snared from the vein on the opposite side and exteriorized, forming an arteriovenous loop through the duct. The Ivalon plug is introduced through a tubular applicator and threaded over the track wire. The lower age for closure using this device is between 3 and 4 years.[178,223] The success of the technique depends on the ratio of the lumen of the femoral artery to that of the duct, allowing an appropriately sized plug to be placed retrogradely.[224] Many patients with a persistent arterial duct have undergone occlusion in this fashion. In 109 cases reported by Porstmann, no mortality and only minor morbidity were noted.[179] The method was unsuccessful in 8 patients, in 5 of these because the duct was too large and the plug slipped into the pulmonary artery. Since the plug was still attached to the guide wire, it could be maneuvered into the femoral vein and removed by venectomy. In the remaining 3 cases, because of the rigidity or small size of the duct, the plug could not be fixed. It was permitted to embolize to the aortic bifurcation and removed by arteriotomy. Disadvantages of the Porstmann technique include arterial entry, with need for arterial exposure under certain circumstances, and possible arterial damage, the requirement for a transductal arteriovenous loop necessitating venectomy should the device have to be retrieved, and the limitation on age for closure. Advantages, however, include a secured delivery system that avoids free embolization with placement, and little or no residual or recurrent shunting.[225] Despite the early clinical trials and success of this approach, it remains technically complex. Except for a few centers, it has not achieved large clinical application.[226–228] A similar conical polyurethane plug, the Botallooccluder, requires only transvenous delivery, but suffers from the requirement of a large bore catheter.[209,228]

Closure using the Amplatzer duct occluder

Using a Nitinol™ wire framework, Kurt Amplatz has designed a cone-shaped ductal plug delivered through a long transvenous sheath technique using small catheters (5–7 Fr), with unique characteristics including self-centering, easy delivery and retrievability. This system is also suited for the small child with the larger duct (e.g. > 2.5 mm) where coil implantation may be unstable. Large series have shown a median closure rate of 68% (range, 44–92%) immediately, 85% (range, 66% to 100%) at 24 h, 97% at 1 month, 99% at 6 months and 100% at 1 year follow-up. The minimum diameter of the arterial duct ranged from 1 to 12.5 mm (mean 3.4 mm).[190–192,229–232] A few complications were reported including device embolization,[192,233] aortic and left pulmonary artery obstruction,[192,234] and severe hemolysis.[192,235] Hemolysis following closure of the arterial duct using an Amplatzer duct occluder has been successfully reversed with percutaneous deployment of fibered platinum coils within the nitinol wire cage.[236] Modifications of the original arterial duct occluder device using different angulations to adapt the device to the arterial duct morphology have been developed.[237,238]

Other devices have also been designed for closing the arterial duct, although few have undergone large clinical trials.[238–240A]

Closure using spring coils

Using spring coils designed for embolization of peripheral vessels, Cambier[189] first reported successful occlusion of ducts < 2.5 mm diameter. Lloyd,[188] and Moore,[241] then applied the procedure to a large number of patients, commenting that the approach was simple and not technically demanding, and could safely be performed in an outpatient setting. In particular, the requirement for only small catheters for delivery made this approach attractive even in the small infant and child. The duct may be cannulated from either a venous or arterial approach, or both for simultaneous implantations**.** This technique has now been used worldwide due to the availability of the implant, its low cost,[231] and its high rate of complete occlusion. The average immediate occlusion rate has been estimated at 59%, increasing to 79% at 6 months and 97% at 1-year follow-up in several large series.[241–253]

Occlusion, using spring coils compares well to results achieved using the double umbrella implant in terms of rates of occlusion,[244,247,254] and has been used successfully for closure of residual surgical shunts[255] or after attempted occlusion using the double umbrella device.[256–258] While comparatively fewer procedures have been performed in the adult,[259] similar rates of occlusion are possible. As with other techniques for transcatheter ductal occlusion, recannulation has been noted, albeit rarely.[249,252]

Coils have also been used to close larger ducts (> 2.5 mm diameter), although heavier gauge wire (0.052 inch in contrast to 0.038 inch)[260,261] or multiple implants,[262] are often required. Improvements in the technique of delivery, using detachable control mechanisms,[263–269] a snare,[270–272] modified delivery catheters,[273] forceps[261,274,275] or balloon occlusion,[246,276] have further simplified the procedure. Simultaneous multiple coil implantation technique has been described for closure of large arterial ducts.[261,275,277] Several complications have been reported following coil occlusion of the arterial duct such as hemolysis,[278–285] early and late embolization,[243,286] giant aneurysm development,[287] iatrogenic development of coarctation of aorta,[288,289] thrombus formation,[290] and left pulmonary arterial stenosis.[246,291] Early reopening and recanalization after successful occlusion has been encountered.[292,293] Complete endothelialization of the coils appears to occur by 6 months after occlusion.[294]

Management

Because many ducts will eventually close in premature infants, there has been an understandable reluctance to apply aggressive interventional techniques as soon as a significant left-to-right shunt is recognized. The presence of a ductal shunt, however, has been implicated in the pathogenesis of bronchopulmonary dysplasia, and as a significant factor in the duration of ventilator support. This increased risk of chronic lung disease has led many to advocate an early, effective treatment strategy. Early experience with surgical ligation demonstrated that congestive heart failure could be controlled, although mortality and morbidity from the respiratory distress syndrome remained high. With further surgical experience, mortality directly due to the operation has been reduced to < 1%. Some centers have advocated, and successfully performed, surgery in the nursery, thereby avoiding the hazards of transport to and from the operating room. Once the role of E-type prostaglandins in maintaining ductal patency during fetal life was established, pharmacologically induced closure was soon reported in the premature infant.[295–297] Rates of success varying between 18% and 89% were reported in a number of subsequent uncontrolled clinical trials in which various doses of oral indomethacin were used. Vert and colleagues[298] showed that the plasma half-life of indomethacin correlates inversely with postnatal age. This, and the fact that the bioavailability of oral indomethacin varies quite considerably, accounted for many of the reported differences. Transient renal insufficiency and mild gastrointestinal bleeding are the major side effects. Despite its widespread usage, questions remain concerning regarding the proper dosage, duration of treatment, and optimal timing of administration. Several studies involving large numbers of infants were performed[299,300] to address some of these issues, and have been summarized by Clyman.[301] Although the effectiveness of indomethacin in prompting ductal closure depends on both dosage and the timing of administration,[302–304] the major determinants of success were gestational and postnatal age. There is, as yet, no consensus regarding the optimal approach to a hemodynamically important duct in the premature infant. The trend is to earlier closure, by medical or surgical means. In infants weighing < 1000 g, without evidence of cardiac compromise, the administration of indomethacin has been associated with improved outcomes.[305–307] This was in contrast to those infants weighing > 1000 g, where outcomes where unaltered. As only one-third of such infants with low birth weight become symptomatic, this approach would result in the needless administration of indomethacin to some babies. Once the problem is recognized, however, intake of fluid should be restricted, and furosemide given in a dose of 1 mg/kg. If the shunt remains large after 24 h, indomethacin should be given, preferably intravenously although nasogastric administration can be successful. Extreme prematurity, very low birth weight, and advanced conceptional or postnatal age are all factors that reduce the chances of successful closure using indomethacin. Renal and/or hepatic insufficiency, serious hyperbilirubinemia, or coagulopathies are contraindications to its use. Dosages are largely selected on an empiric basis. The initial dose is 0.2 mg/kg, while subsequent dosages depend on age at time of initial treatment. If < 48 h of age, the subsequent two doses are 0.1 mg/kg; if 2–7 days of age, 0.2 mg/kg; and if ≥ 7 days, 0.25 mg/kg. Prolonged treatment with indomethacin has also been attempted to prevent recurrence with good effect.[308,309] The rate of re-opening is highest in the extreme premature, occurring in one-third of patients at weights < 1000 g, and in less than one-tenth of those weighing 1500 g.[310,311] If there is no response to indomethacin, surgical ligation should be considered. Indomethacin induced closure of the duct is followed by immediate and progressive clinical improvement, with a decrease in requirements for oxygen and in mean airway inflation pressure during mechanical ventilation.[312] Lung compliance has been shown to improve both after surgical ligation and closure with indomethacin.[303,313] Duration of ventilation, length of hospitalization, and the costs of medical care were also reduced by early treatment.[299,300,314] Such studies have not been able to demonstrate any substantial difference in the outcome of infants treated either surgically or medically. They did observe a generally favorable neurologic, developmental, visual, audiologic and renal outcome of infants given indomethacin. Reversal of indomethacin induced ductal closure by administration of prostaglandin, in the presence of ductal dependent cardiac malformations, has been possible.[315] Ibuprofen has also

been used for ductal closure.[316,317] When compared with indomethacin, ibuprofen had fewer effects on renal function in terms of urine output and fluid retention, with much the same efficacy and safety in closing patent ductus arteriosus in preterm infants with respiratory distress syndrome.[317,318]

Powell and De Cancq first reported surgical ligation of the persistent duct in premature infants in 1963. Overall mortality remains high, but is more often related to continuing repiratory distress, intracranial hemorrhage, or coagulopathy,[319–321] rather than the surgery itself. As with indomethacin, surgery has been associated with a decreased need for ventilatory support, and reduced hospital stay,[322] particularly in infants weighing < 1500 g.[323,324] Surgery can be safely carried out in the neonatal intensive care unit to avoid the stress of transportation to the operating theatre.[325,326] Many questions remain unanswered concerning the true impact of a large left-to-right ductal shunt on the course and outcome of prematurity and respiratory distress syndrome. In a large multicentered trial, one-third of patients with a significant duct had spontaneous closure, while indomethacin induced closure in seven-tenths of patients treated. There was no difference in the rate of closure if indomethacin was given immediately on diagnosis, or after 48 h of intensive medical therapy. Mortality rates were identical in patients treated with indomethacin early, with indomethacin given late, or with surgery, being about 13% overall in each group.[327]

Use of prostaglandins to maintain patency of the duct

The critical role of the duct during the newborn period in the pathophysiology of many congenital heart malformations has been discussed earlier in the chapter. The demonstration that E-type prostaglandins maintain ductal patency during fetal life suggested the clinical use of prostaglandin E_1 or E_2 in newborns with heart disease. Successful maintenance of the duct was first reported in patients with duct dependent pulmonary blood flow such as occurs in pulmonary atresia with or without a ventricular septal defect.[295,328,329] Prostaglandin E_1 is infused intravenously in a starting dose range of 0.05–0.1 mg/kg/min. This can often be further reduced to 0.01–0.02 mg/kg/min after an initial effect, thus reducing side effects. Intra-arterial administration does not appear to have any therapeutic advantages, and may cause potent systemic vasodilatation associated with local edema. Furthermore, potential complications from the arterial line are likely to be more serious. Arterial tension of oxygen usually rises within minutes of starting treatment in patients with duct-dependent pulmonary blood flow. The response is remarkably uniform. Infants < 4 days of age, and those with the lowest tensions of oxygen before infusion, tend to show the most dramatic increases. Those with birth weights exceeding 4 kg tend to respond less well.[100] The improved oxygenation provides "a period of grace," during which metabolic acidosis can be reversed and palliative surgery organized semi-electively. Treatment with prostaglandin E_1 generally needs to be maintained for only a few days. Under special circumstances, such as low birth weight, prolonged administration appears to be safe and tolerance does not develop.[330]

Prostaglandin E_1 is also valuable in the emergency care of infants with duct-dependent systemic blood flow, such as coarctation of the aorta, interruption of the aortic arch, and hypoplastic left heart syndrome. In patients with interruption of the aortic arch, the pressure in the descending aorta increases markedly, and differences in pressure across the duct are reduced or abolished. Patients with coarctation of the aorta show a trend to equalize the blood pressures in the upper and lower limbs. In both lesions, previously decreased urinary output usually increases. The partially constricted duct relaxes more slowly than in those patients with cyanotic malformations. The infusion should be continued for 2–3 h before concluding that a response is unlikely. Clinical improvement can be anticipated in about four-fifths of acyanotic patients. Failure to respond may be due to previous complete closure of the duct, to congenital absence or intrauterine closure of the vessel, or to extreme hypoplasia of the pulmonary arteries, which intrinsically limit pulmonary blood flow despite adequate dilation of the duct.

Reported side effects of prostaglandin administration include fever, bradycardia, hypotension, apneic spells, cutaneous flushing, and seizure-like activity. Apneic spells occur in about one-tenth of treated infants. They are more common in those < 2 kg, and are probably dose dependent. Assisted ventilation should be available when prostaglandin E_1 therapy is initiated. Pulmonary arterial smooth muscle may also be reduced by infusion of prostaglandin E_1. This effect may be associated with the formation of localized aneurysmal dilations.[331] Long-term treatment with prostaglandins may induce cortical hyperostosis in the long bones and anthral hyperplasia.[332] This effect seems to be completely reversible when therapy is discontinued. Oral prostaglandin E_2 has been used to maintain ductal patency over several weeks or months.[333] While successful in raising the tension of oxygen, oral therapy carries the disadvantage of frequent administration, uncertain absorption, and potential vascular damage.[334] Even after prolonged systemic or oral therapy, in the majority but not all cases the duct retains its ability to constrict when administration is discontinued. The impact of prostaglandin E_1 on the mortality and morbidity of serious congenital heart malformations in the newborn period is difficult to measure because of the many concurrent improvements in surgical technique and postoperative management. It has been a significant factor in the improved outlook for these children. The only group of patients in which its effect may be adverse are those with pulmonary venous obstruction. In these, administration of prostaglandin may precipitate pulmonary edema and cause a marked deterioration in condition.[335]

Infiltration of formalin, balloon dilation, and implantation of stents

Rudolph *et al.*[336] described a technique of subadventitial formalin infiltration of the wall of the duct designed to maintain long-term patency of the vessel in patients with duct-dependent cardiac malformations in whom surgery was either inadequate or not feasible. Satisfactory results were reported when formalin infiltration was combined with valvotomy or infundibuloplasty.[337] When used alone, the technique seemed less successful.[338] However, Deanfield and colleagues,[339] found that infiltration of formalin did not ensure ductal patency even for a short time. They abandoned the technique in favor of infusion of prostaglandin E_1. Furthermore, Seibert *et al.*[340] reported two patients who developed delayed damage to the left recurrent laryngeal nerve function after infiltration of formalin. In view of the alternatives, therefore, there is little now to recommend this procedure. Percutaneous balloon dilation has also been proposed as a method to maintain ductal patency.[341–344] Temporary

patency can be achieved, but abrupt closure, thrombosis, or rupture can occur, making this a less reliable means of assuring patency. Except for special instances, this technique has not been pursued clinically.

To provide a mechanical scaffold for the ductal wall, resistant to the constrictive forces of ductal closure, Coe and Olley [345] proposed the implantation of endovascular stents. This approach, using either self- or balloon expandable stents, has had limited clinical application. First reported in animal models in 1991,[345,346] the worldwide experience in stent implantation to the arterial duct is quite limited. Small series in children with controversial results have been described. Between the two major groups of patients who require stent implantation to maintain ductal patency, the hypoplastic left heart syndrome group has shown high mortality and only short-term palliation. In the pulmonary atresia group better palliation was achieved, although repeated angioplasty is necessary to counteract intimal hypoplasia.[347–352]

Bioengineering of the arterial duct for therapeutic gain

Novel methodology for maintaining ductal patency into the postnatal period to sustain life and allow surgical intervention of duct-dependent cardiac malformations is emerging. Recently, Mason *et al.*[353] described the maintenance of ductal patency through surgical transfection of fetal lambs. By targeting the ductal smooth muscle cells with an expression vector encoding a "decoy" mRNA of the fibronectin message, it proved possible to sequester the protein which binds, thereby preventing up-regulation of fibronectin and arresting intimal cushions. This approach emphasizes both the importance of fibronectin to the process of ductal closure and identifies a new therapeutic modality and target. While fetal surgery is not feasible in the clinical setting so far, an alternative approach, such as that employed by Arap and Ruoslahti,[354–356] targeting chemotherapeutic agents given by systemic infusion to different vascular beds by unique peptide "zipcodes," may offer bright therapeutic avenues. Studies identifying and characterizing the cellular and molecular mechanisms involved in ductal patency and closure have tremendously advanced our understanding of this developmentally programmed fetal vessel. The impact of these advances extends beyond the scope of ductal remodeling, as they have provided insight into the pathogenesis of occlusive vascular diseases, processes that seems to utilize similar pathways. Humpl and colleagues[357] have recently shown that transcatheter transfection of the arterial duct with PGE_2 synthase to increase PGE_2 production *in situ* is possible using a newborn lamb model, and observed no adverse effects. Patency of the arterial duct was achieved for 1 week.

This work has also positioned the field towards further leaps associated with the development of safe therapeutic measures by which to maintain ductal patency for patients with cyanotic congenital heart disease, ultimately translating into improved care and clinical outcome.

All references can be found at the end of the book. See pp. 633–41 for Chapter 9.

The Natural and Modified History of Congenital Heart Disease
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10

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Anomalous Left Coronary Artery from the Pulmonary Artery

The anomalous left coronary artery from the pulmonary artery is a rare condition and yet is one of the primary congenital abnormalities in the pediatric population promoting myocardial ischemia and infarction (Fig. 10-1). First described by Brook in 1886[1] and then by Abbott in 1908,[2] there was little interest in this condition until the report in 1933 by Bland, Garland, and White who described an infant with this condition and recorded the electrocardiogram showing an anterolateral myocardial infarction.[3] There is now an extensive literature on this condition describing the clinical presentation, evolving methodologies of diagnosis, differential diagnoses, surgical therapies, and early and late outcomes.[4–13] An interesting narrative of the history of the anomalous left coronary artery including its pathophysiology and surgery has been provided by Shumacker[6] and recently Dodge-Khatami and coworkers have provided a collective review of surgical therapy.[7]

Incidence and associated conditions

The anomalous left coronary artery from the pulmonary artery makes up *c.* 0.25–0.50% of congenital heart disease.[7,9,11,12] Keith suggested that this condition occurred once per 300 000 live births, thus accounting for 0.5% of all congenital heart disease.[14] The prospective Bohemia Survival Study identified 11 children with this condition, giving a prevalence of 0.01 per 1000 live-births and these 11 patients accounted for 0.22% of all heart malformations encountered in this study.[15] The New England Regional Infant Cardiac Program identified 10 infants with this condition, 1 of the 10 with an additional ventricular septal defect, from the total of 2251 infants enrolled in the study.

Associated conditions

The anomaly usually occurs in isolation, but has been described with many other other cardiac malformations including patent arterial duct, ventricular septal defect, coarctation of the aorta, Shone's syndrome, tetralogy of Fallot, transposition of the great arteries, hypoplastic left heart syndrome, Ebstein's anomaly, atrioventricular septal defect, scimitar syndrome, partial anomalous pulmonary venous return, pulmonary valve stenosis, aortopulmonary septal defect, aortic atresia, etc.[16–24]

Morphological considerations

The anomalous left coronary artery usually connects to a facing pulmonary sinus (assuming the great arteries are normally related) (Fig. 10-1), but the connection may be to the main pulmonary artery or the proximal left or right pulmonary artery, or rarely from the non-adjacent sinus.[6–13,25,26] Based on the work of Bogers,[27,28] one can postulate that the developing epicardial coronary artery(s) become aligned with the PA rather than aortic root, then grow into the PA wall to establish the anomalous connection. In some patients ostial stenosis will be present at the point of connection with the pulmonary trunk or branch pulmonary artery. Beyond infancy and reflecting the additional flow through the right coronary artery, the right coronary artery becomes considerably dilated when compared to the dimension of the normal right coronary artery in an age and weight-matched control. Indeed, this feature has been used in the echocardiographic diagnosis of this condition and its differentiation from a dilated cardiomyopathy.[29,30] In an occasional adult with this condition the right coronary artery assumes aneurysmal dimensions.[31] When the anomalous left coronary artery connects to the right pulmonary artery, often there are associated cardiac malformations.[32] Yet in the four patients reported by Atik and colleagues,[32] the anomalous vessel had an unusual intramural aortic trajectory, but there were no important associated cardiac malformations.

Anomalous connection of the right coronary artery from the pulmonary trunk is very much rarer than the left coronary artery (Fig. 10-1, of upper panel, left-hand and middle diagrams).[33–41] Neufeld and Schneeweiss suggested that this anomalous connection may have hemodynamic importance in about a quarter of cases.[4] The often benign course has raised a controversy over the need for surgical treatment in these patients. Also very infrequently the left anterior descending coronary artery connects with the pulmonary artery (Fig. 10-1, upper panel, right-hand diagram).[42–44] An anomalous connection of both coronary arteries or a single coronary artery to the pulmonary trunk is even less common (Fig. 10-1, lower panel).[45–51] While this condition would seem incompatible with life, there are a number of reports of this anomaly in young children who have survived by virtue of associated abnormalities that maintained elevated pressure in the pulmonary trunk.[45,48] Furthermore the group from Ann Arbor reported the clinical and surgical course of two infants, ages 3 and 6 months, with this anomaly.[47] One patient had normal intracardiac anatomy with low pulmonary artery pressures (30/12 mmHg). The second patient had a restrictive subpulmonic ventricular septal defect with moderately elevated pulmonary artery pressure (50/13 mmHg). Left ventricular ejection and shortening fractions were severely depressed in both patients. The common coronary trunk arose from the right anterior facing sinus in one patient and from the left posterior facing sinus in the other.

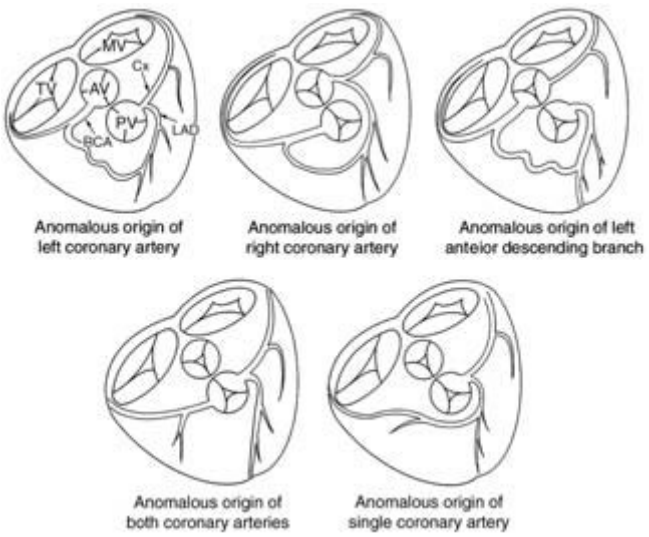


Fig. 10-1 Various types of anomalous coronary arterial origin from the pulmonary artery. AV, aortic valve; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; MV, mitral valve; PV, pulmonary valve; RCA, right coronary artery; TV, tricuspid valve.

Both patients underwent repair by direct coronary implantation to the aorta. Left ventricular function improved with shortening fractions near normal at a follow-up of 6 months for one patient and 1 year for the other.

Pathophysiology and clinical presentation

In broad terms, two forms, adults and infantile, are recognized clinically representing two ends of an "anatomic and physiologic continuum."[4,5–7,9–13,18,31,52–56] This continuum likely reflects at least in part the degree of collaterization that develops between the two coronary systems. From two-thirds to *c*. 90% of patients with this anomaly die during the first year of life due to myocardial ischemia and intractable heart failure,[10] but death is uncommon during the first 2 months. Roberts has suggested that this may well reflect the normal physiological situation of the diastolic pressures in the pulmonary trunk and aortic root being similar until the pulmonary vascular bed matures with regression of fetal muscularization.[5] The possibility that the presence of fetal hemoglobin, with its unique oxygen dissociation curve, may offer some protection from ischemia initially, has not to our knowledge been thoroughly investigated.

The affected myocardium may be rendered ischemic by the changes in coronary perfusion produced by this anomaly. Various papers have addressed the pathophysiology responsible for progressive myocardial ischemia and infarction, and these have been summarized elesewhere.[4,11–13] Initially the anomalously connected left coronary artery is perfused at systemic pressures by the pulmonary artery reflecting vasoconstrictive elements normally present in the perinatal pulmonary vascular bed. With normal regression of the muscular elements of the pulmonary vascular bed and with the subsequent fall in pulmonary artery pressures to a normal level, the pressure in the pulmonary artery is not sufficient for myocardial perfusion. Retrograde flow from the right coronary system to the anomalously connected left coronary artery occurs via collateral channels; a myocardial steal-like syndrome then develops, with resulting myocardial ischemia and infarction if collateral development is inadequate. The affected infant may have gross cardiac enlargement associated with the myocardial ischemia but at other times mitral regurgitation due to papillary muscle infarction may be the dominant lesion.[57] Some patients will develop an ischemic left ventricular aneurysm.

Anomalous coronary artery from the pulmonary artery should be suspected when the plain chest radiogram in a critically ill infant shows marked cardiomegaly with left side chamber dilatation and signs of left heart failure (Fig. 10-2). The mainstay of imaging diagnosis currently is echocardiography. By itself, two-dimensional echocardiography may produce false

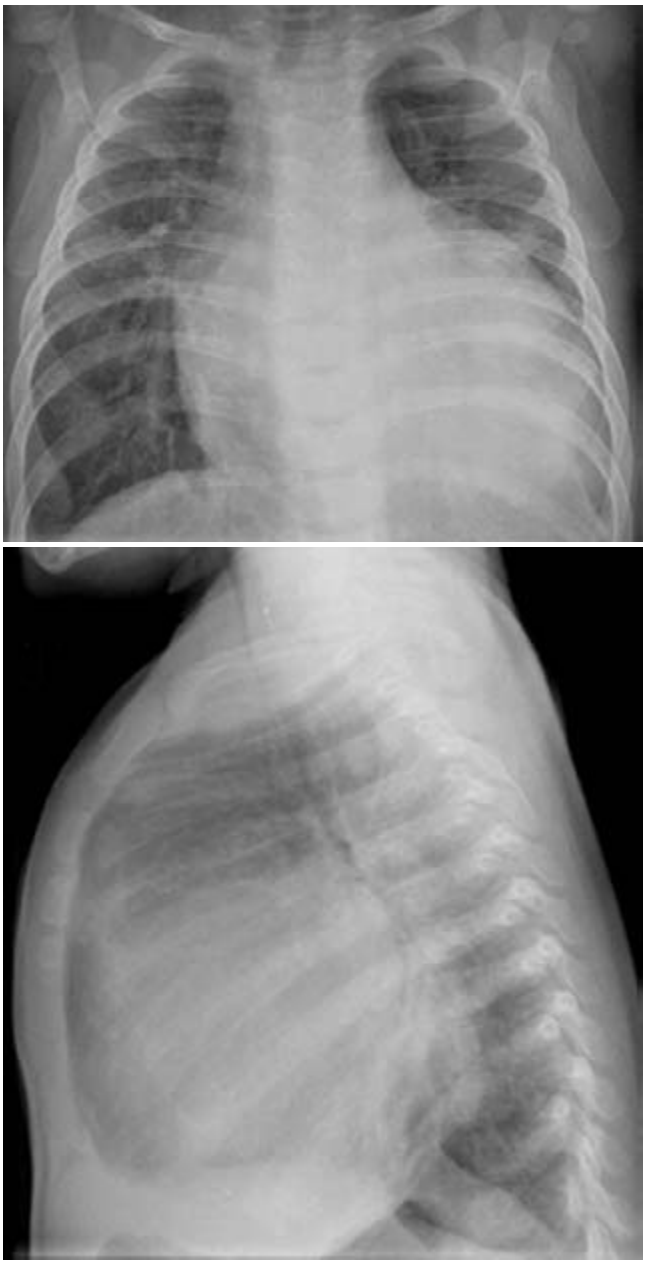


Fig. 10-2 Plain chest radiograms in frontal (**A**) and lateral (**B**) views show marked cardiomegaly with predominant left side chamber enlargement and pulmonary venous hypertension.

negatives, due to "drop out" of the wall separating the aortic root and left coronary artery.[58] However, the addition of both pulsed wave Doppler and color flow Doppler has resulted in a highly reliable diagnostic modality.[11–13,29,30,58–61] This imaging is based on identifying retrograde flow in segments of the anomalous coronary, a diastolic flow jet into the pulmonary artery, and an enlarged contralateral coronary artery. Echocardiographic diagnosis does, however, have its limitations. Where there is raised pulmonary artery pressure, as in a neonate or a child with left ventricular failure, there may in fact be antegrade flow into the anomalously connected vessel, and the coronary connections to the aorta may not be dilated. Similarly, in the neonate with an anomalously connected left coronary artery, the right coronary artery may not be dilated before the pulmonary artery diastolic pressures fall. Clearly, if there is any possibility of an anomalously connected coronary artery with a nondiagnostic echocardiographic or negative study in a young child, angiography is mandatory. The diagnosis may be confirmed angiographically by left ventriculography, aortic root angiography, selective coronary injections, or pulmonary artery injections. Selective right coronary arteriography will provide the most information, however (Fig. 10-3). In addition, selective coronary arteriography will provide more information about the status of the intercoronary collateral circulation.[6,7,9,11,12,17,18,62–65] In the older child these intercoronary collateral arteries may be recognized in the interventricular septum from echocardiography.[62A]

Outcome analysis

There is no fetal information about this condition. The older literature describes the poor prognosis of affected infants with frank myocardial infarction, with the majority of symptomatic infants dying in the first year of life. Indeed Perloff summarizing that literature suggests that 80–90% of infants with this condition if untreated die in the first year of life.[66] Sometimes spontaneous clinical improvement occurs, likely reflecting some degree of collateralization with time. Some patients with anomalous left coronary artery from the pulmonary artery may escape clinical detection in infancy, presenting later in childhood, adolescence, or as adults for evaluation of a heart murmur, mitral regurgitation, chest pain, or a cardiac rhythm disturbance. Such patients obviously have fairly well-developed collateral circulation.[66A] An occasional adult with this condition will present in the sixth, seventh, eighth, or ninth decades of life, and sometimes these elder individuals will be asymptomatic.[67,67A] In one asymptomatic adolescent girl, ostial stenosis of the anomalous left coronary artery was diagnosed by echocardiography and confirmed by angiography.[68] It is likely that the ostial stenosis reduced the steal into the pulmonary artery allowing for survival to adolescence. Similar observations about the relative protective effects of ostial stenosis have been reported by others.[69,70] It is uncommon for the patient to present as a neonate, much less succumb, for the normally elevated pulmonary vascular resistance usually maintains adequate flow into the anomalously connected left coronary artery.[10]

Some of the issues to be considered in patients with anomalous left coronary artery from the pulmonary artery include:

- Is it important to establish a two-coronary artery system?
- types of operative strategies
- specific maneuvers to enhance outcome
- ? recovery of left ventricular function
- mitral valve function
- reasons for re-intervention.

Gasul and his colleagues in 1966 and more recently Kirklin and Barratt-Boyes in 1993 and Dodge-Khatami and coworkers in 2002 summarized the surgical approaches to improve the status of the infant with inadequate collateralization and frank

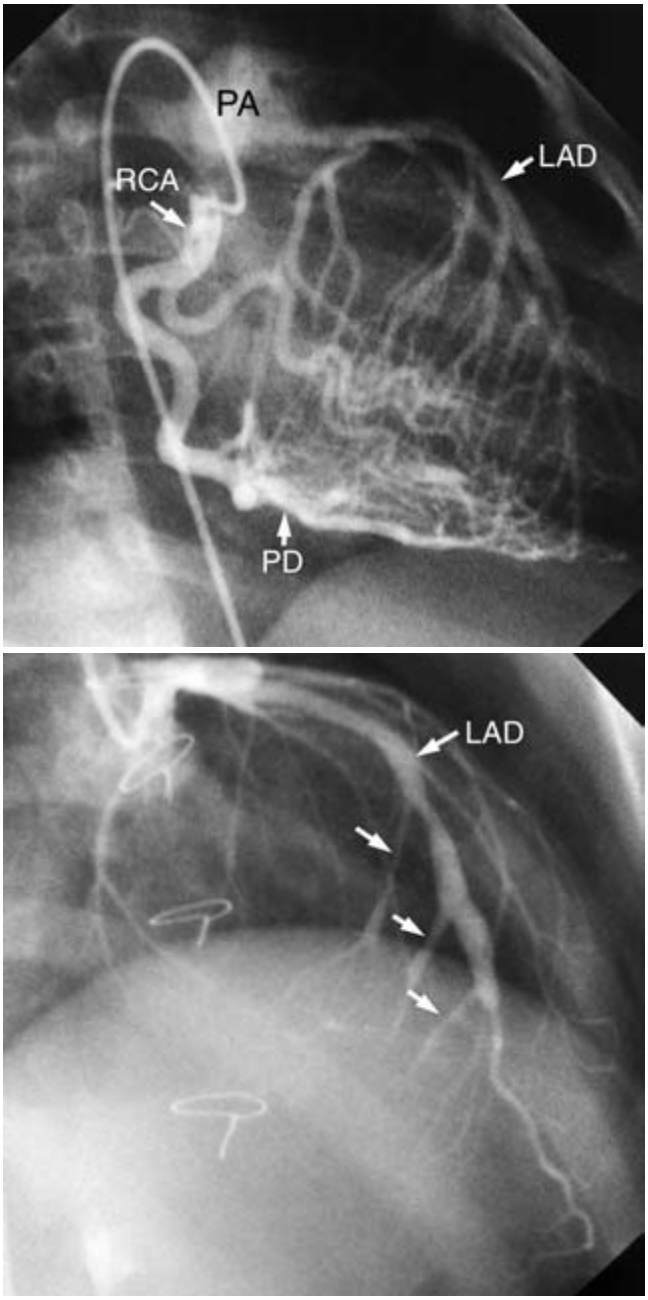


Fig. 10-3 Anomalous origin of the left coronary artery from the pulmonary artery. **A**. Selective right coronary arterial injection demonstrates filling of the left coronary arterial system through many collateral channels. The pulmonary artery (PA) is filled in a retrograde fashion. Left anterior descending coronary artery (LAD) shows irregularities. PD, posterior descending coronary artery; RCA, right coronary artery. **B**. Selective left coronary arteriogram after surgical implantation of the left coronary artery to the aorta. Note persistence of the irregularities of the left anterior descending branch and its septal branches (arrows).

myocardial ischemia.[7,13,71] These maneuvers included creation of an aortopulmonary anastomosis, designed to raise the pressure in the pulmonary trunk. This approach was unsuccessful primarily because of the large volume load it posed to the already damaged and failing left ventricle. Other approaches included banding of the pulmonary artery, but this too was unsuccessful. Pericardial poudrage, first performed by Paul and Robbins[72] or chemical epicardialization, both approaches designed to increase collateral flow to the left ventricular myocardium, had limited success in the few cases reported. Others tried to connect the divided anomalous left coronary artery to the left common carotid artery, but again most of the patients died, remembering the era in which this approach was taken. In the past few decades, a variety of operations have been performed to either close the shunt to the pulmonary artery and/or reestablish antegrade flow in the anomalous vessel.[13] In 1958, both Edwards[73] and Case and his colleagues[74] suggested that one could ligate the anomalously connected coronary artery to prevent the steal phenomenon, and this was accomplished a year later by Sabiston.[75] Sabiston and his colleagues also showed the direction of blood flow in anomalous left coronary artery from the pulmonary artery and as well used phenol painted on the epimyocardium to stimulate collateral formation.[75] Ligation of the left coronary artery had an appreciable mortality in the range of 30% or more, and late follow-up was not that encouraging.[10–13,76,77] Late sudden death was reported to occur in from 14% to 25% of these patients with a single coronary artery system.[10–13,76,78] In addition while some infants demonstrated improvement, years later some developed frank myocardial ischemia. Furthermore, the observations of Kececioglu and colleagues about patients who survived ligation of the anomalous left coronary artery were also quite concerning.[79] They studied left ventricular function and myocardial perfusion in 8 patients from 3 to 21 years (mean 16 years) after ligation of the anomalous left coronary artery from the pulmonary artery. While only 1 patient complained of exercise-induced chest pain, 4 patients had abnormal ST-segments in the exercise electrocardiogram and all 8 patients showed myocardial ischemia at exercise scintigraphy. At rest, the ejection fraction of the left ventricle was within normal range in all patients. But in 5 patients, the ejection fraction failed to increase adequately under exercise conditions, reflecting impaired ventricular function. Again, these results confirm the advantages of surgical procedures designed to establish a two-coronary system. Yet some patients seemingly do very well for many years after ligation as in the patient reported by Nakano and Konishi.[80]

A number of maneuvers were introduced to define a two-coronary artery circulation (Fig. 10-4). Some attempted to establish a two-coronary system by grafting a systemic artery into the anomalous left coronary artery or the use of a saphenous vein graft, and these approaches did have some success.[81] Clearly, the literature suggested that establishment of a two coronary system was the optimal approach,[13,82] preferably by reimplantation of the anomalous vessel to the aorta, or in those cases not favorable for reimplantation, by tunnel repair. With the advent of the Jatene operation and coronary transfer in the mid-1970s for transposition of the great arteries (see Chapter 25B), this experience likely served as the impetus for surgical reimplantation of the anomalous left coronary artery. In those patients where the anatomy seemingly did not allow this approach, Takeuchi devised a tunnel approach which has been used as an alternative.[83] Despite the fact that most now advocate establishing a two-coronary system, some still advocate ligation of the anomalous left coronary artery as an emergency when mechanical left ventricular support is not available.[84] Most attribute to Neches and colleagues the first successful

Fig. 10-4 Surgical maneuvers for establishment of a two-coronary artery circulation in patients with anomalous origin of the left coronary artery from the pulmonary artery. Reimplantation of the anomalous coronary artery to the aorta by using a technique similar to the arterial switch operation is the most commonly used and ideal method. A graft can be interposed when the anomalous coronary artery cannot be adequately mobilized. Takeuchi's procedure consists of creation of an aortopulmonary window, tunneling of the left coronary arterial route within the pulmonary artery by using the flap from the pulmonary arterial wall, and patch graft of the anterior wall of the pulmonary artery. Ao, aorta; AV, aortic valve; LV, left ventricle; MV, mitral valve; PA, pulmonary artery; PV, pulmonary valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

direct reimplantation of the anomalous left coronary artery into the aorta by transferring it with a button of pulmonary artery.[84A]

There is an extensive surgical literature which when scrutinized demonstrates the evolving surgical approaches.[13,85–88] Backer and his colleagues have reviewed their experience with a total of 20 of these patients undergoing surgical intervention at two institutions between 1970 and 1990.[89] The age at operation ranged from 3 weeks to 11 years (mean 26 months). Twelve patients had congestive heart failure, 3 were in cardiogenic shock, and 2 had cardiac murmurs. The operative techniques included ligation ($n = 9$), subclavian artery anastomosis ($n = 5$), aortic implantation ($n = 3$), internal mammary artery anastomosis ($n = 1$), intrapulmonary tunnel from aortopulmonary window to coronary artery ($n = 1$), and cardiac transplantation ($n = 1$). The 3 deaths in the series occurred at 3 weeks, at 2 months, and at 9 years after ligation. There have been no deaths after establishment of a two-coronary artery system or after transplantation. Two of the 5 patients who had subclavian artery anastomosis to the anomalous coronary artery have severe anastomotic stenosis and collateralization. From this experience with patients with anomalous origin of the left coronary artery from the pulmonary artery, they recommend direct aortic implantation of the anomalous coronary artery at the time of diagnosis. Intrapulmonary tunnel from aortopulmonary window to coronary artery, or aorta-coronary bypass with internal mammary artery are recommended for children in whom aortic implantation is not anatomically feasible. Furthermore they condemn left coronary artery ligation as not indicated for these patients and they recommend that those who have survived ligation should be considered for elective establishment of a two-coronary artery system because of the risk of late death. Complications form the Takeuchi operation include supravalvular pulmonary stenosis, baffle leaks creating a coronary artery–pulmonary artery fistula, and aortic valve regurgitation. Dodge-Khatmai and colleagues suggest that as many as 30% of patients will require catheter-based or surgical intervention to correct these complications.[7]

The Pediatric Cardiac Care Consortium has had considerable experience with the surgical treatment of anomalous left coronary artery reporting on 109 operations performed in infants and children from 1985 through 1994.[90] Sixty-eight operations were performed in infants and 41 in children. Four operations were in neonates, 47 in infants from 1 to 6 months, 17 in infants from 6 to 12 months. The total mortality in the infant group was 19 of 68 (28.4%). The distribution by type of operation in infants was as follows: left coronary artery transfer, 39 patients, ligation 5 patients, tunnel 13 patients, left subclavian artery to left coronary anastomosis, 6 patients. In the period from 1985 to 1989, the mortality for left coronary transfer was 18%, and for a tunnel procedure, 50%. From 1990 to 1994, the mortality for a left coronary transfer was 21% and for the tunnel procedure, 57%. Forty-one children and young adults with anomalous left coronary artery underwent an operation with a total mortality of 4.8%. In terms of the tunnel procedure, Amanullah and colleagues described a procedure by creating a tunnel using autogenous aortic and pulmonary arterial walls.[91] The advantage of this technique is that the new left coronary artery lies in the horizontal plane and in an anatomically correct axis running in the groove behind the pulmonary artery. It also provides tension-free endothelialized autogenous arterial walls with normal growth anticipated.[91] The exhaustive literature survey conducted by Dodge-Khatami and colleagues showed mortality rates of 75–80% in the early 1980s and 0–23% in the current era.[7] They suggest that in the present era mortality rates for direct reimplantation range from 0% to 16%, while mortality rates for the Takeuchi procedure are comparable, ranging from 0% to 23%. Moodie and his colleagues reported 20 years ago in a small series of adult patients an 80% saphenous vein graft patency at a mean follow-up of 5.8 years.[91A] For a number of reasons, vein grafting has fallen into disfavor.[7]

We have just recently completed a review of the Toronto Hospital for Sick Children's experience with anomalous left coronary artery from the pulmonary artery.[92] From 1952 to 2000, 67 patients presented with anomalous coronary artery from the pulmonary artery. Management of the 67 patients with anomalous left or circumflex coronary artery from the pulmonary artery included no surgical intervention in 5 patients, ligation of the anomalous coronary artery in 10 patients, and Takeuchi tunnel repair in 4. Forty-seven were repaired by aortic reimplantation, and these are the subjects of this study. Two patients had anomalous circumflex coronary artery from the pulmonary artery, and one had anomalous right coronary artery from the pulmonary artery. The left coronary artery originated from the left posterolateral sinus in 43 and from the right posterolateral sinus in 1. The median age at repair was 7.7 months. Before repair, 10 infants (21%) presented *in extremis* requiring ventilatory/inotropic support and 38 (80%) presented in heart failure. Electrocardiographic analysis ($n = 44$) demonstrated myocardial ischemia in 32 patients (anterolateral in 25 and posterolateral in 7) and combined with gross evaluation at the time of surgery myocardial infarction was confirmed in 35 patients (anterolateral wall $n = 13$, lateral wall $n = 10$, apex $n = 6$, posterolateral wall $n = 5$). The echocardiographic analysis showed the median preoperative ejection fraction ($n = 32$) was 33% (range 7–73%). Ten patients (23%) had a preoperative ejection fraction < 20%. The mean preoperative left ventricular end-diastolic diameter ($n = 36$) was 4.0 ± 0.73 cm, and when indexed to the 95th percentile of normal was 1.4 ± 0.3 cm (range, 0.8–2.2). Preoperatively, the degree of mitral valve regurgitation was: 0 in 1 patient (2%), mild in 18 (43%), mild to moderate in 7 (17%), moderate in 11 (26%), moderate to severe in 3 (7%) and severe in 2 (5%). Endocardial fibroelastosis as assessed by echocardiography ($n = 39$) was present in 36 patients (92%). Aneurysm formation or mural dyskinesis was evaluated in 27 patients and present in 13 (48%). Left ventricular wall motion abnormalities were evaulated in 32 patients and included: 0 wall motion abnormalities in 6 patients (19%), isolated anterior wall hypokinesis in 2 patients (6%), isolated lateral wall hypokinesis in 1 patient (3%), apical hypokinesis in 4 patients (13%), global hypokinesis in 12 patients (37.5%), posteroseptal hypokinesis in 2 (6%), posterolateral hypokinesis in 1 patient (3%), anterolateral and posterior wall hypokineis in 1 patient (3%), posterior, anterior and apical wall hypokinesis in 1 patient (3%), and anterolateral hypokinesis in 2 patients (6%). The mean preoperative diameter of the right coronary artery ($n = 16$) was 0.31 ± 0.12 cm (range, 0.19–0.6 cm). The mean preoperative diameter of the left coronary artery ($n = 7$) was 0.25 ± 0.14 cm. The mean ratio of the right to left coronary artery ($n = 7$) was 1.32 ± 0.4. Pericardial hood was used in 4; concomitant mitral valve repair was performed in 1 child. The hospital survival was 92% with 4 postoperative deaths. Five children required postoperative extracorporeal membrane oxygenation (ECMO) for a median of 4 days (2–8 days). Patients who had

ECMO were significantly more likely to present in critical condition (40% vs. 3% if no ECMO; $P = 0.006$) or with ventricular arrhythmias (67% vs. 7%; $P = 0.027$), have significantly lower pre-repair median ejection fraction (10%, $n = 5$ vs. 40%, $n = 38$, $P = 0.01$) or more severe left ventricular dilation ($P = 0.03$). With up to 15 years' follow-up (mean 4.71 years), there were no late deaths. Kaplan–Meier survival was 91% at 5 years; freedom from reoperation was 93% at 10 years. At late follow-up, echocardiography demonstrated significant improvements in mean ejection fraction (64 ± 9% vs. 33 ± 21% preoperative, $P < 0.0001$); the degree of mitral regurgitation (moderate + 9% vs. 38% pre-repair, $P < 0.02$); wall motion abnormalities (15% vs. 81% pre-repair, $P < 0.002$). The ratio of measured left ventricular end-diastolic dimension to the 95th percentile of normal declined from 1.4 ± 0.3 to 1.0 ± 0.1 ($P < 0.0006$). Children who had ECMO had normal ejection fractions and ventricular dimensions at follow-up ($n = 3$). Repeated measures mixed linear regression analysis demonstrated normalization of ejection fraction and left ventricular functional parameters occurred within 1 year of repair. Kaplan–Meier freedom from reoperation was 100% at 1 month, 98% (95% CI, 94% to 100%) at 1 year, 93% (95% CI, 84% to 100%) at 5 and 10 years. No patients required heart transplantation. Four patients required late reoperations: coronary ostial stenosis ($n = 3$), supravalvar pulmonary stenosis ($n = 1$) and severe mitral regurgitation ($n = 1$). Similar to the experience at the Toronto Hospital for Sick children with surgical therapy for this condition, there are a number of reports documenting excellent long-term follow-up with normalization, or nearly so, of left ventricular functional parameters, exercise testing, and resolution of the severe myocardial perfusion defects.[93–108]

Sauer and her colleagues were interested in identifying risk factors for perioperative mortality in children with anomalous origin of the left coronary artery from the pulmonary artery.[64] They reviewed the outcomes of 33 children (median age at initial cardiac catheterization 0.4 years [0.1–11.8]) with anomalous origin of the left coronary artery from the pulmonary artery, without other associated hemodynamically significant cardiovascular anomalies, who were treated throughout a period of 18 years. A two-coronary artery circulation was reestablished in 31 of 33 children. One child died before the intended operation, and in one child the left coronary artery was ligated. There were 6 operative deaths, 5 intraoperative and 1 at 12 h after operation. The following preoperative factors were associated with a statistically significant higher perioperative mortality: young age at operation ($P < 0.03$), left and balanced type of coronary circulation ($P < 0.01$), and electrocardiographic signs of extensive acute myocardial infarction, namely, marked ST elevation (≥ 0.2 mV in at least two leads) ($P < 0.03$). Left axis deviation on the electrocardiogram was associated with an extreme right dominant type of coronary circulation ($P < 0.005$). The latter was also linked with adequate perfusion of the posterolateral left ventricular wall ($P < 0.005$). At autopsy, severe increase of heart weight to two or three times the normal heart weight was found in six of seven children. As one might anticipate, the perioperative mortality was determined primarily by the extent of myocardial ischemia. This in turn is influenced by the dominant type of coronary circulation and the extent of interarterial collateralization. Young age, in addition, in their experience, proved to be a risk factor for mortality at corrective surgery.

Some infants are unable to be weaned from cardiopulmonary bypass after establishment of a two-coronary system because their left ventricle is so compromised by the ischemic process. The marked recovery of left ventricular function reported late after repair, however, suggests that an aggressive approach to repair should be undertaken. Del Nido and his colleagues have shown that a left ventricular assist device improves survival in children with left ventricular dysfunction after repair of anomalous origin of the left coronary artery from the pulmonary artery.[109] Of 31 children undergoing primary repair of anomalous origin of the left coronary artery from the pulmonary artery at Boston Children's Hoapital from 1987 to 1996, 26 were infants (6 weeks to 9 months old). All but 2 had severe left ventricular dysfunction, and 8 had moderate to severe mitral regurgitation. Seven children were unable to be weaned from cardiopulmonary bypass because of poor left ventricular function and elevated left atrial pressure. These 7 children were placed on mechanical left ventricular support using a centrifugal pump, with support ranging from 2.2 to 70.6 h. One child died shortly after the start of left ventricular assist (2.2 h), and another died of arrhythmia within 24 h after successful decannulation. All 5 survivors had significant improvement in left ventricular function, with 2 requiring late mitral valve repair.

Left ventricular function has been assessed with echocardiography and myocardial perfusion assessed with scintigraphy under dipyridamole stress in pediatric patients after repair for anomalous origin of the left coronary artery from the pulmonary artery.[83–108] Stern and colleagues reported on 23 patients who underwent operation for anomalous origin of the left coronary artery from the pulmonary artery.[63] These patients were reexamined with two-dimensional echocardiography and thallium-201 perfusion imaging.[63] Follow-up studies were performed 0.6–16.2 years (median 2.9 years) after operation. In 22 of 23 patients, a two-coronary artery system had been established by implantation of the left coronary artery into the aorta ($n = 8$) or by anastomosis of the left subclavian artery with the left coronary artery ($n = 14$). The left coronary artery had been ligated in only one patient. For stress testing, 0.8 mg dipyridamole per kilogram body weight was infused in a 10-min period in 20 of the 23 patients. High-dose dipyridamole infusion increased mean heart rate (98.1 ± 27.1 to 122.3 ± 19.2 beats/min, $P < 0.001$) and mean left ventricular ejection fraction (54.8 ± 11.8% to 61.3 ± 12.5%, $P < 0.05$) and decreased left ventricular end-diastolic volume index (38.8 ± 26.7 to 29.9 ± 8.3 mL/m^2, $P < 0.005$). At rest, left ventricular dimensions were abnormal in only 1 patient, in whom the anastomosis with the left coronary artery proved to be occluded, as seen with subsequent angiography. Left ventricular function seen with two-dimensional echocardiography was normal in 19 patients and was compromised in 3 (all of whom had major structural anomalies of the left ventricle, such as left ventricular aneurysm, occlusion of the anastomosis, or mitral valve prosthesis). Patients with R-wave loss as seen with preoperative electrocardiography tended to have larger left ventricular volumes at follow-up (69.2 ± 56.5 mL/m^2 vs. 32.4 ± 9.6 mL/m^2, $P < 0.07$). Ten of 20 patients had normal thallium-201 perfusion scans. In 9 of 20 patients, defects revealed by permanent thallium-201 perfusion were observed and determined to be myocardial scars. Transient perfusion defects under dipyridamole stress with redistribution at rest occurred in 3 children, 2 of whom also had permanent thallium-201 defects. None of the 3 patients had angina-like

symptoms or S-T segment changes during dipyridamole stress. Left ventricular ejection fraction, however, decreased severely during dipyridamole infusion in the single patient who had undergone ligation of the left coronary artery. These results are certainly reassuring! Indeed the majority of studies listed earlier show that the majority of patients normalize their ventricular function after the establishment of a dual coronary artery system. This is somewhat surprising considering that some of these infants have sustained transmural infarctions. In some patients with frank left ventricular aneurysms wall motion abnormalities will persist after repair. Singh and colleagues have studied myocardial flow reserve in long-term survivors of repair of anomalous left coronary artery from pulmonary artery.[93] Their studies showed that long-term survivors of repair demonstrate regional impairment of myocardial flow reserve. They suggest that this may contribute to impaired exercise performance by limiting cardiac output reserve.

Huddleston and his colleagues have focused attention on mitral valve function in infants presenting with anomalous left coronary artery off the pulmonary artery.[110] Although establishing a dual coronary circulation is the procedure of choice, there remains controversy as to how the mitral valve should be handled. They reviewed their 15-year experience with this lesion at St Louis Children's Hospital in 17 infants under 18 months of age who underwent repair, with all but 1 being treated with reimplantation of the left coronary artery into the aorta; the other underwent the Takeuchi procedure (intrapulmonary artery baffle) and was excluded from this evaluation. The average age and weight at operation were 0.5 ± 0.3 years and 6.1 ± 1.9 kg, respectively. All presented with varying degrees of heart failure and 9 patients also had either moderate or severe mitral regurgitation. There was 1 early and no late deaths after reimplantation of the left coronary artery. The left ventricular function post-repair improved from a preoperative shortening fraction of 0.19 ± 0.09 to 0.34 ± 0.08 ($P < 0.01$). Moderate or severe MR was present in 2 patients postoperatively, and both developed significant obstruction in the left coronary artery postoperatively as well. Both underwent mitral valve repair and revascularization of the left coronary artery with improvement. Rarely, mitral valve endocarditis will be the first clinical finding leading to the diagnosis of anomalous left coronary artery from the pulmonary artery.[111]

The Heart Institute of Japan has reported the importance of mitral annuloplasty on the long-term results after surgical repair of anomalous origin of the left coronary artery.[112] Between January 1982 and March 2000, 29 patients with anomalous origin underwent surgical intervention at their institution (direct aortic reimplantation in 19 and Takeuchi procedure in 10). The age at the time of operation ranged from 2 months to 24 years (median, 29.3 months), and 9 patients were infants. Twenty-four patients had varying degrees of mitral incompetence. Simultaneous mitral annuloplasty at the anterolateral commissure was performed in all 24 patients with incompetence. There were 2 hospital deaths among the infants, and no late deaths. The mean follow-up was 100 ± 57 months, and the actuarial survival was 93.1% at 10 years (70% CL, 87–99). Cardiothoracic ratio at discharge was not decreasing significantly ($P = 0.35$); however, this value 5 years after the operation showed a significant decrease ($P = 0.003$) vs. preoperative value. Preoperative mitral incompetence decreased in all but one of the operative survivors with mitral annuloplasty at the last follow-up. The left ventricular fractional shortening *Z*-score was not normalized at discharge but was normalized in the late period. Their data demonstrated that impaired left ventricular function normalized in the long term (even if it was below normal immediately after operation) after two-coronary repair. They went on to recommend that simultaneous mitral annuloplasty should be performed at the time of operation for patients who have mitral incompetence with anomalous origin of the left coronary artery. Mitral valve incompetence is a well-documented sequela of the myocardial ischemia caused by the anomalous left coronary artery originating from the pulmonary trunk. The severity can vary from mild to very severe, reflecting papillary muscle ischemia, infarction and rupture. Less commonly one may find a true congenital abnormality of the mitral valve. As we have discussed earlier, it is unusual to have to replace the regurgitant mitral valve.[13,97,113] Malignant ventricular rhythm disturbances may be the presenting findings in the adult with anomalous left coronary artery from the pulmonary trunk.[114] In other patients with this disorder, cardiac arrest has been documented with exercise.[115]

The data we have summarized from our institution and others indicate that most infants and children undergoing reimplantation of the anomalously connected left coronary artery have a very good functional recovery, including those requiring ECMO or a left ventricular assist device. Surgical mortality in the past decade has been substantially reduced and in many series, surgical mortality approaches zero.[11–13,89,92,94,98,109–111] In follow-up it is important to recognize that stenosis of the reimplanted vessel can occur and surveillance for this complication is important. Although the Takeuchi repair allows *in situ* rerouting of the left coronary artery, intrapulmonary baffling may result in supravalvar pulmonary stenosis, baffle leaks, tunnel stenosis and compromised long-term functional outcomes of patients with anomalous origin of the left coronary artery from the pulmonary artery.[11–13,18,97] Mitral valve function may return to normal, but some patients may require late attention to mitral valve function.[97] Patients old enough to exercise should undergo stress-testing periodically and Holter ambulatory recordings at regular intervals are important as well. Any number of nuclear medicine imaging modalities should be used to demonstrate the positive effects of revascularization including normalization of hibernating myocardium.[116] Aortic regurgitation has been documented as a long-term complication of coronary artery reimplantation.[117] In one patient who developed stenosis of the reimplanted coronary artery, treatment was accomplished by stent placement.[118] Others have reported successful percutaneous transluminal angioplasty of a stenotic internal thoracic artery used as a graft in the treatment of anomalous left coronary artery.[119] It should be mentioned that an anomalous left coronary artery from the pulmonary artery may be unmasked by ligation of a large arterial duct.[120] Sadly, this condition may be associated with sudden death.[121,122] Supravalvular pulmonary stenosis has been recognized as a late complication of surgery for anomalous left coronary artery.[123]

In summary:

- The anomalous left coronary artery from the pulmonary artery is the most common congenital etiology for myocardial infarction in the pediatric age population.
- Surgical techniques have evolved to establishing a two-coronary artery circulation.
- Almost every pattern of anomalous origin can be transferred from the pulmonary artery to the aorta.

- ECMO or other left ventricular assist devices may be required pre- and postoperatively.
- Surgical results are now excellent for reimplantation strategy.
- A minority of patients require mitral valve surgery because of papillary muscle ischemia and infarction.
- Left ventricular function seemingly recovers fully in the short-to-medium term follow-up.
- Life-long cardiac surveillance is required, with particular attention to coronary artery and myocardial function.

All references can be found at the end of the book. See pp. 641–4 for Chapter 10.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

11A

Robert M. Freedom and Shi-Joon Yoo

Ebstein's Malformation of the Tricuspid Valve

Dr Wilhelm Ebstein, then in his 30th year, published the report of a 19-year-old laborer with pronounced cyanosis, Mr Joseph Prescher, with the focus of this report on Prescher's congenitally malformed heart.[1] Ebstein described the very peculiar malformation of the tricuspid valve now bearing his name, and his contribution has been subsequently translated into the English language.[2–5] In the > 130 years since this publication, the definition of the tricuspid valve as demonstrating features of the Ebstein malformation conveys the physiology of a regurgitant valve of varying severity.[6–8] This is partly true, but there is now ample morphological as well as clinical data indicating that an imperforate valve, a stenotic valve, as well as a regurgitant valve are embraced by the designation of Ebstein's malformation of the tricuspid valve.[9–24] Thus, this morphological heterogeneity translates into a diverse clinical experience. In an editorial comment to the paper by Celermajer and colleagues,[25] Mair states: "Perhaps no other congenital heart lesion encompasses as broad a spectrum of clinical significance as does Ebstein's malformation."[26]

Incidence

This is an uncommon disorder occurring in about 1 in 20 000 livebirths, and we have estimated its prevalence amongst patients with congenital heart disease at the Hospital for Sick Children in Toronto to be *c.* 0.5%.[27] The New England Regional Infant Cardiac Program identified 18 patients with Ebstein's disease from 2251 infants with congenital heart disease, but 5 of these 18 had associated pulmonary atresia.[28] The Baltimore–Washington Infant study enrolled 4390 infants with congenital heart disease from 1981 to 1989, and 43 (1%) had Ebstein's malformation.[29,30] The Baltimore–Washington study indicates the prevalence of Ebstein's anomaly was 5.2 per 100 000 livebirths.[30] The recently completed prospective Bohemia Survival study identified 22 children at birth with Ebstein's anomaly of the tricuspid valve. This gave a prevalence of 0.03 per 1000 livebirths and these 22 accounted for 0.38% of all heart malformations encountered in this survey.[31] The Pediatric Cardiac Care Consortium identified from 1985 to 1993, 215 patients with Ebstein's malformation of the tricuspid valve among 27 678 patients whose details were entered into the Consortium's database who underwent surgery.[32] There are reports of an unexpectedly high frequency of Ebstein's anomaly of the tricuspid valve among infants born to mothers who ingested lithium during pregnancy.[33–35] However, a review of infants born with the disorder and examined at our institution has not supported these observations.[36]

Morphology of Ebstein's malformation of the tricuspid valve

The essence of Ebstein's malformation of the tricuspid valve is displacement of part of the origin of its leaflets from the atrioventricular junction into the cavity of the right ventricle, and this displacement is accompanied by varying degrees of valvular dysplasia and abnormal attachments of the valvular distal margins.[7–14,16,24,27,37–39] While the hallmark of Ebstein's anomaly is displacement from its annulus of part of the tricuspid valve into the cavity of the right ventricle, the degree of displacement is variable, from just minimal displacement to extremely severe. As Becker and his colleagues[39] and others[7–14,16,24,27,37,38] have pointed out, other confounding features include dysplasia of the tricuspid valve and more recently attention has been focused on the abnormal distal attachments of the tricuspid valve as well. Indeed, Zuberbuhler and Anderson[14] indicate that displacement, dysplasia, and abnormalities of distal attachment are all integral aspects of Ebstein's anomaly. The normal tricuspid valve has three leaflets, the posterior or mural leaflet, the septal leaflet, and the anterosuperior leaflet. There are numerous observations showing that it is the posterior or mural and septal leaflets of the tricuspid valve that are usually displaced, while the anterosuperior leaflet retains its normal annular attachment (Fig. 11A-1). The observations of Zuberbuhler and Anderson[14] about displacement of the tricuspid valve indicate that in some hearts the mural leaflet is not displaced, but displacement is confined to the septal leaflet. The septal leaflet displays considerable variability from displacement, to virtual absence, to resembling a supernumerary hammock-like structure which fuses with the leaflet. Becker and his colleagues[39] and the more recent observations of Anderson point out that some degree of dysplasia of the tricuspid valve is virtually always present in the neonatal expression of this disorder.[10,12–14,24] In some hearts the displaced mural and septal leaflets are plastered to the wall of the right ventricle, while in others the valve tissue is recognizable as excrescences marking the level of the displaced orifice. The nondisplaced anterosuperior leaflet is usually large, redundant, and sail-like. Finally, the distal attachment of the anterosuperior and/or mural leaflets to the junction between the inlet and trabecular components of the right ventricle may exhibit what Zuberbuhler and Anderson[14] characterize as linear attachments. When such linear attachments are extensive, this may result in functional tricuspid stenosis, as well as posing a degree of functional obstruction to pulmonary blood flow (Fig. 11A-2).[12,13,15,16,24] The most florid manifestation of these linear attachments is the so-called imperforate type of Ebstein's,

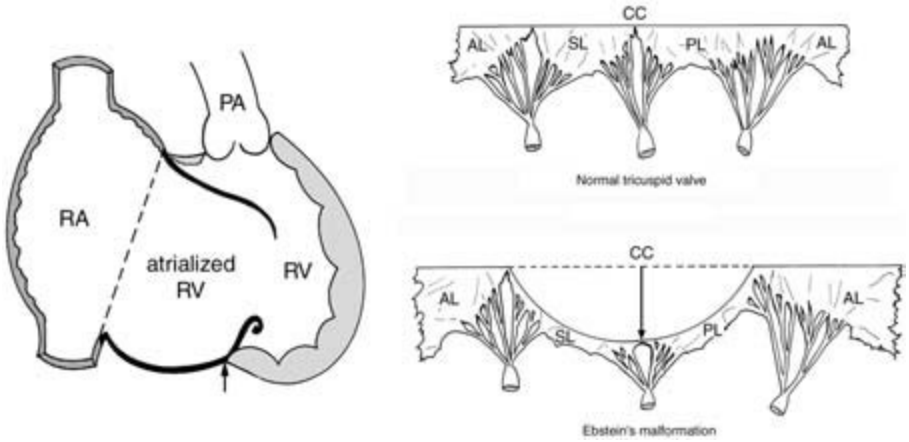


Fig. 11A-1 Pathological features of Ebstein's malformation of the tricuspid valve. Left, atrialization of the right ventricle (RV) owing to apical displacement of the tricuspid valve attachment (arrow). Interrupted line indicates the tricuspid annulus. Right, patterns of the tricuspid valve attachment in normal heart and in Ebstein's malformation. Note that the septal (SL) and posterior (PL) leaflets have displaced attachment and that the maximal displacement is at the crux cordis (CC). The anterior leaflet (AL) is usually enlarged, although it does not show displaced attachment. PA, pulmonary artery; RA, right atrium.

producing in effect functional tricuspid atresia.[12,13,18–20,40–42] For the majority of affected patients, however, the displacement of the tricuspid valve results in atrialization of a portion of the right ventricle, a process that reduces the size of the functional right ventricle. The impact of this disorder in the severely affected neonate can be profound. The atrialized portion of the right ventricle may be very thinned, virtually devoid of myocardium, and consistent with Uhl's malformation of the right ventricle.[7–14,16,25,41–50] Abnormalities of left ventricular form and function are also present, although perhaps less frequently recognized in the neonate. These include angiocardiographic evidence of an abnormal contour and wall motion, as well as mitral valve prolapse and other mitral valve anomalies including orificial, leaflet, chordal, and papillary muscle anomalies.[51–53] More recently, Celermajer and his colleagues have found increased left ventricular fibrosis in neonates dying with Ebstein's anomaly when compared to a similarly-aged normal.[54] The pulmonary arteries are small, reflecting the small lungs, a consequence of intrauterine compression by the very much enlarged right heart chambers.[7,10,11,14,16,55–61]

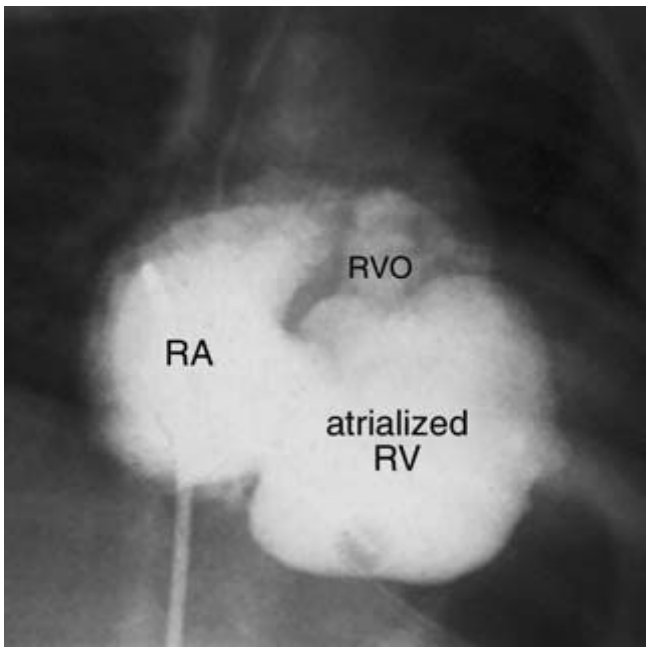


Fig. 11A-2 Stenotic Ebstein's malformation of the tricuspid valve. The tricuspid valve leaflets are adherent to each other and form a sac of atrialized right ventricle (RV). The right atrium (RA) is dilated. RVO, right ventricular outlet.

Associated anomalies

Ebstein's malformation of the tricuspid valve can be found with a wide variety of congenital cardiac malformations. These include an ovale foramen; a secundum atrial septal defect; aneurysm of the atrial septum; pulmonary stenosis or atresia; coarctation of the aorta; congenital pulmonary valvular regurgitation; divided right ventricle; mitral stenosis; ventricular septal defect, single or multiple; tetralogy of Fallot; complete transposition; atrioventricular discordance. Ebstein's malformation of the tricuspid valve has also been seen in the patient with an atrioventricular septal defect, occasionally with a double-orifice left atrioventricular valve; an overriding and straddling tricuspid valve.[62–77] Duplication of the tricuspid valve with Ebstein's malformation has been reported in the Japanese literature.[78] Bashour and colleagues have described a patient with an apical left ventricular diverticulum and Ebstein's malformation of the tricuspid valve.[79] The relationship between Ebstein's abnormality of the tricuspid valve and an unguarded tricuspid orifice has been explored. There are obvious similarities between these two conditions, and in severely affected neonates, it may be difficult to differentiate between these conditions even with echocardiography.[80–84] When Ebstein's malformation is associated with atrioventricular discordance, the affected valve is the left atrioventricular valve (Fig. 11A-3). In an occasional patient with right-sided Ebstein's malformation, the mitral valve may also be displaced.[85–90]

Extracardiac anomalies

A wide variety of extracardiac anomalies have been described with Ebstein's malformation. These include trisomy 18, chromosome 2p-, CHARGE association, Noonan's syndrome, Apert

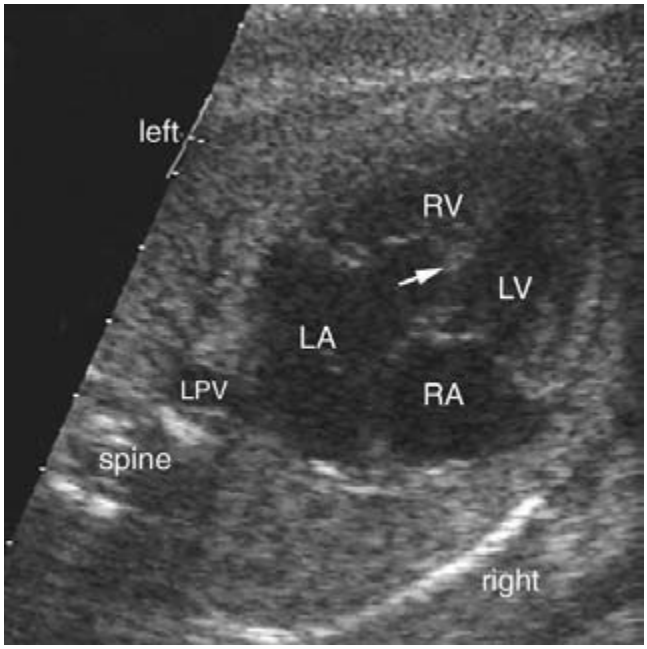


Fig. 11A-3 Ebstein's malformation of the left-sided tricuspid valve in corrected transposition of the great arteries. Fetal echocardiogram in four-chamber view shows apically displaced attachment (arrow) of the tricuspid valve of the left-sided right ventricle (RV). Note that there is mesocardia and the apex points the midline. LA, left atrium; LPV, left pulmonary vein; LV, left ventricle; RA, right atrium.

syndrome, biliary atresia, cleft lip and palate. There does not seem to be predilection for any specific extracardiac malformation.

Outcome analysis

The fetal diagnosis of Ebstein's anomaly of the tricuspid valve has been extensively reviewed.[55–61,91–94] Hornberger and her colleagues in a multi-institutional study identified 27 fetuses with severe tricuspid regurgitation, including 17 with Ebstein's anomaly.[57] From the data provided in this paper, most of these babies with Ebstein's anomaly died, either from termination of pregnancy, spontaneous fetal death or neonatal death and in 11 of these the diagnosis was confirmed at post-mortem. Lang and his colleagues have also commented on the outcome of fetuses diagnosed with Ebstein's anomaly.[60] Of 10 fetuses identified, death occurred during fetal life or the pregnancy had been terminated in 7, and the other 3 died at a median age of 2 days. Pavlova and colleagues have attempted to identify those factors influencing the outcome of fetuses with Ebstein's anomaly.[94] They found that the prognosis of Ebstein's anomaly during fetal life is not influenced by criteria described for postnatal life and may be related to factors that control the volume load of the left ventricle, namely the size of the ovale foramen.[94] Those reported fetal outcomes tend to be poor, but as pointed out by Sharland, Ebstein's malformation is well represented in any compilation of fetal heart disease because the worst end of the spectrum is preferentially detected in the fetus, with most cases notable for striking cardiomegaly and severe tricuspid incompetence.[93] These fetuses may present with hydrops or fetal tachycardia. In the series reported by Sharland, there were 54 cases of Ebstein's with normal segmental connections. Right ventricular outflow tract obstruction was identified as well in 23, aortic atresia in 1 and atrioventricular discordance and a ventricular septal defect in 4. Twenty-four families chose termination of pregnancy; there were 6 spontaneous intrauterine deaths, 8 neonatal and 2 deaths in infancy. Thus of the 54 cases diagnosed prenatally, only 14 survived. There is limited experience with the prenatal diagnosis of the imperforate Ebstein's variant.[94A]

A number of papers have addressed the postnatal natural history of patients with Ebstein's anomaly of the tricuspid valve and those morphological features influencing outcome.[5,6,10,11,14,16,17,22–27,31,32,95–97,97A,97B] To determine which morphologic features are associated with early death, the complete echocardiograms and medical records of 16 consecutive patients with Ebstein's anomaly and concordant atrioventricular connections who presented in the fetal ($n = 5$) or neonatal ($n = 11$) period were reviewed by Roberson and Silverman.[59] The cohort was classified into two groups on the basis of survival at 3 months. Group 1 consisted of 7 patients who died at ″ 3 months of age, and group 2 consisted of the 9 surviving patients. Comparing groups 1 and 2, the respective incidence rates of morphologic features that correlated with early death ($P < 0.05$) included tethered distal attachments of the anterosuperior tricuspid leaflet (86% vs. 11%), right ventricular dysplasia (86% vs. 0%), left ventricular compression by right heart dilation (71% vs. 11%) and the area of the combined right atrium and atrialized right ventricle being greater than the combined area of the functional right ventricle, left atrium and left ventricle (57% vs. 0%) measured in the apical four-chamber view. Right ventricular dysplasia was present in all patients with marked right atrial and atrialized right ventricular enlargement, in 86% of patients with tethered anterior leaflets and in 83% of those with left ventricular compression; 86% of patients with right ventricular dysplasia had tethered distal attachments. These authors suggest that echocardiography defines those specific morphologic features in the fetus and neonate that are highly predictive of death by 3 months of age. One must always urge some caution in these retrospective studies. Pavlova and colleagues have also studied those factors affecting fetal outcome.[94] The index of severity based on the surfaces of the right atrium and atrialized portion of the right ventricle and the cardiothoracic ratio had a significant impact only on neonatal survival. The smallest fossa ovalis was found in two fetuses with hydrops. In this analysis, fetuses who reached term without difficulties had a higher left ventricular output. A positive score was found between the *Z*-score of the left ventricular output and the size of the fossa ovalis. Russo and his colleagues have addressed those factors affecting mortality of babies with Ebstein's anomaly diagnosed in infancy.[96] Analysis of survival of 42 patients symptomatic at a mean age of 6 days demonstrated 69% survival at 14 days, 52% at 1 year, and only 37% at 5 years. Their data showed that early death was most influenced by morphological features including absence or hypoplasia of the trabecular portion of the right ventricle, a small and tethered anterior tricuspid leaflet, and associated anomalies.

Yetman and her colleagues from Toronto have reviewed the outcome in 46 cyanotic neonates with Ebstein's anomaly seen between 1954 and 1996.[98] Functional pulmonary atresia was found in 25 (54%) and anatomic pulmonary atresia in 11 patients (24%). The total mortality was 70% vs. 14% in 50 acyanotic patients with Ebstein's diagnosed during the same time interval. Kaplan–Meier estimates of survival were 61% at age 1 week, 48% at 1 month, 36% at 1 and 5 years, and 30% at

Fig. 11A-4 Data from the Toronto Hospital for Sick Children based on 100 patients with Ebstein's anomaly of the tricuspid valve seen from 1954 to 1995. This Kaplan–Meier survival curve shows percent survival with increasing age. Solid line, percent survival; dashed lines, 95% CL. (Reprinted from Yetman *et al.*,[98] Copyright (1998), with permission from Exerpta Medica, Inc.)

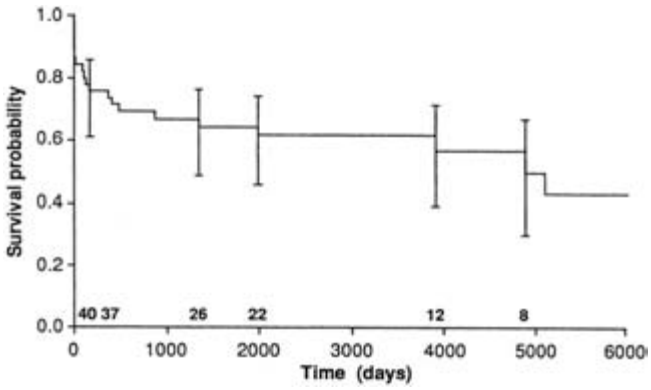


Fig. 11A-5 Kaplan–Meier survival analysis for 50 neonates with Ebstein's anomaly. Survival probability refers to freedom from cardiac death. (Reprinted from Celermajer *et al.*,[25] Copyright (1992), with permission from The American College of Cardiology Foundation.)

20 years (Fig. 11A-4). Mortality declined from 81% in 1956–85 to 47% in 1986–96. Significant predictors of mortality were reduced left ventricular function and either functional or anatomic pulmonary atresia. In our study, an atrial septal defect > 4.0 mm was an independent predictor of mortality. An echocardiographic ratio of the combined right atrial and atrialized right ventricular area to the area of the functional right ventricle and left heart > 1.0 was 100% predictive of death.[98] Others have suggested that early cyanosis with associated lesions conveys a poorer prognosis.[99] Celermajer and his colleagues have published similar findings (Figs 11A-5, 11A-6).[25]

In another multi-institutional review, Celermajer and his colleagues reviewed the outcome of 220 cases of Ebstein's anomaly from fetal to adult life between 1958 and 1991, with 1–34 years of follow-up.[100] The most common presentation in each age group was an abnormal routine prenatal scan for fetuses (86%), cyanosis in neonates (74%), heart failure for infants (43%), incidental heart murmur for children (63%), and arrhythmia for adolescents and adults (42%). The earliest presentation was frequently associated with other cardiac lesions, usually pulmonary stenosis or atresia. Cardiac surgery was required at some stage in 86 (39%) of the 220 patients. Actuarial survival for all liveborn patients was 67% at 1 year and 59% at 10 years. Of the entire cohort of 220 patients, 58 (26%) died, 7 fetuses were electively terminated and 155 patients were alive at last follow-up. The annual hazard for death was 36% for the first year of life, 4% for the second year, 1% from ages 2 to 10 years, and 1.4% from ages 10 to 40 years. Of 21 fetuses, there were 7 terminations, 5 intrauterine and 6 postnatal deaths, with 3 surviving. Univariate analysis showed that a significant risk for death was associated with a more severe echocardiographic grade of the disease, cardiothoracic ratio > 60%, associated important pulmonary outflow tract obstruction, and presentation in fetal life. In the 32 patients requiring tricuspid valve surgery, the risk was more related to age at presentation than age at operation. The perioperative mortality was 50% for those diagnosed in the first year of life and 0% for those diagnosed after age 1 year. Twenty-eight neonates with initial resolution of cyanosis later developed heart failure, cyanosis, or both, 2–18 years after presentation. Eleven of these had evidence of left ventricular dysfunction. Of the 220 patients, 74 (34%) have had rhythm disturbances at some stage and they identified 13 patients with pre-excitation, but without symptoms. Death was attributed to congestive heart failure in 26 (45%) of the 58 patients, was perioperative in 19 (33%), sudden and unexpected in 8 (14%), related to cardiac catheterization in 4, and of noncardiac origin in 1 child.

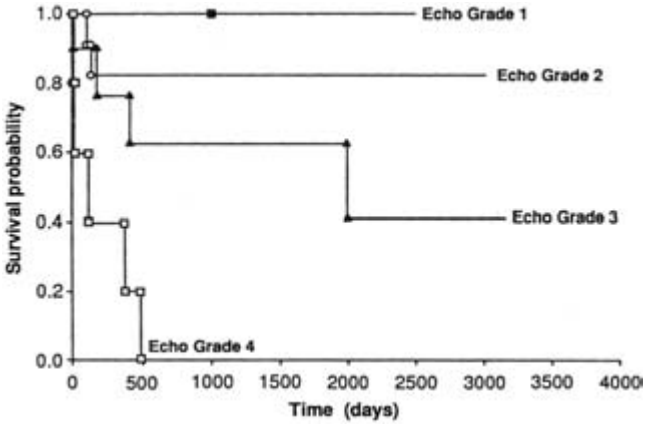


Fig. 11A-6 Kaplan–Meier survival analysis for 28 neonates with Ebstein's anomaly who had echocardiographic (Echo) grading of severity of tricuspid valve anoamly. Grade 1, least severe to grade 4, the most severe. Survival probability refers to freedom from cardiac death. (Reprinted from Celermajer *et al.*,[25] Copyright (1992), with permission from The American College of Cardiology Foundation.)

Attie and his colleagues have reviewed the course of 72 unoperated patients with Ebstein anomaly aged over 25 years from 1972 to 1997 and followed up from 1.6 to 22.0 years.[101] Patients were classified in three groups of severity according to the echocardiographic appearance of the septal leaflet attachment of tricuspid valve. The mean age at diagnosis was 23.9 ± 10.4 years, and the most common clinical presentation was an arrhythmic event (51.4%). There were 30 (42%) deaths, including 6 from arrhythmia, 12 related to heart failure, 7 sudden, 2 unrelated, and 3 unascertained. According to Cox regression analysis, predictors of cardiac-related death included age at

diagnosis (hazard ratio 0.89 for each year of age, 95% confidence intervals (CI)(0.84–0.94), male sex (3.93, 95% CI, 1.50–10.29), degree of echocardiographic severity (3.34, 95% CI, 1.78–6.24), and cardiothoracic ratio ≥ 0.65 (3.57, 95% CI, 1.15–11.03). During follow-up, morbidity was mainly related to arrhythmia and refractory late hemodynamic deterioration. The magnitude of tricuspid regurgitation, cyanosis, and the New York Heart Association (NYHA) functional class at time zero were significant risk factors according to the univariate analysis, but not after multivariable confrontation. The results of this study suggested that pattern of presentation, clinical course, and prognosis of unoperated adult patients with Ebstein anomaly are influenced by several factors. Although the initial symptoms are usually mild and commonly related to supraventricular arrhythmias, these are not associated with the long-term outcome. The severity of the morbid anatomy was the main determinant of survival only in extreme cases, but not in those with mild or moderate deformations, which are more common in adults. Other independent risk factors such as cardiothoracic ratio, sex, age at diagnosis, and the echocardiographic evaluation may help to determine the therapeutic approach. Adult patients with Ebstein anomaly should not be considered as a simple low-risk group.

For those patients requiring surgical repair or replacement of the tricuspid valve there is now considerable experience, cross-sectional echocardiography, both pre- and intraoperatively, has contributed to better understanding of valve function and along with improving surgical techniques has contributed to improved surgical results,[102–105] and for the most part has supplanted angiographic imaging.[11,41,42,106–110] Surgical experience with Ebstein's anomaly has been extensive.[38,111–121] Chavaud has reported on the outcome of 111 patients operated on at Hôpital Broussais in Paris.[111,112] The mean age of the patients in this series was 25 ± 15 years of age, ranging from 4 to 65 years. The most commonly associated lesion in this series was either an atrial septal defect or patent foramen ovale. Eighty percent were considered to have at least moderate to severe tricuspid regurgitation, and tricuspid valve stenosis was present in 25 patients. A valve-sparing operation was possible in 108 patients (97%) and the valve was replaced in three patients. The operative mortality was 10%. This group identified a subset who died within 24 h of operation with an akinetic right ventricle, all with very severe disease. In 1992, recognizing this subgroup, Chavaud and his colleagues began unloading the right ventricle with a bidirectional cavopulmonary shunt. The mean follow-up was 5 ± 3.6 years (0.19–16 years). Actuarial survival was 88.5% at 1 year, and 85 ± 7% at 5, 10, and 15 years. Freedom from reoperation was 87.5% ± 7% at 14 years.

Danielson has reported on the surgical results from the Mayo Clinic for this condition, analyzing the results in 189 patients operated upon from 1972 to 1991.[117,120] Closure of an atrial septal defect was performed in 169 patients and ablation of an accessory pathway(s) in 28 patients and repair of ventricular septal defect in 7, etc. The perioperative mortality included 12 patients (6.3%). Tricuspid valve replacement was required in 69 patients, with four early deaths, and eight early deaths in the 110 patients undergoing plication and valvuloplasty. They were able to provide follow-up on 151 (85.3%) of the operative survivors. Ten late deaths occurred In those who survived > 1 year after surgery, 92.9% were in NYHA class I or II. Reoperations were required in 4 of the 110 patients who had undergone primary valve repair. This represented 3.6% in a follow-up extending to 19 years. This group has reviewed the late results of bioprosthetic tricuspid valve replacement in 158 patients with Ebstein's anomaly, extending their observations from 1972 to 1997.[121] They had follow-up information on 149 patients (94.3%) who survived 30 days ranging up to 17.8 years (mean 4.5 years). The 10-year survival was 92.5 ± 2.5% (SE). One hundred and twenty-nine late survivors (92.1%) were in NYHA class I or II, and 93.6% were free of anticoagulation. Freedom from bioprosthesis replacement was 97.5 ± 1.9% at 5 years and 80.6 ± 7.6% at 10 and 15 years. Marianeschi and his colleagues have reported on a small series of 10 children (median age 9 years) operated upon from 1995 to 1997 in whom a valve-sparing operation was combined with a bidirectional cavopulmonary shunt.[113] There were no early deaths, and this group advocates right ventricular unloading as an adjunct to improve ventricular function and tricuspid valve function.

The Pediatric Cardiac Care Consortium identified 215 patients with Ebstein's malformation who underwent 250 various types of surgical procedures.[32] Six of 17 neonates died, and of 27 infants identified with Ebstein's malformation undergoing surgery, 10 (37%) died. Among these 250 operations were 112 tricuspid valve replacements which had an operative mortality of 8.0%, and an operative mortality of 5.4% for those undergoing tricuspid valve repair. Renfu and his colleagues have recently summarized their experience in corrective surgery of Ebstein's anomaly.[118] A total of 139 patients operated on between June 1980 and January 2000 were studied retrospectively. Among these patients, 111 underwent atrialized ventricle plication, tricuspid valve reconstruction and DeVega tricuspid annuloplasty, 27 underwent tricuspid valve replacement, and 1 patient with right ventricular hypoplasia underwent an additional total cavopulmonary connection. Overall, there were 12 operative deaths (mortality rate 8.6%); however, between 1990 and 2000, the mortality rate was 3.3%. Among the reconstruction patients, 10 cases were reoperated on for valve replacement, and all survived. These authors concluded that surgery for Ebstein's anomaly should be defined according to the pathologic/anatomic features of the condition. Tricuspid valve reconstruction should be performed in the mild condition; in medium A type, reconstruction should be performed, while for medium B type, reconstruction or valve replacement should be selected, albeit with caution. Valve replacement should be performed in the severe conditions.

Some patients with Ebstein's anomaly of the tricuspid valve, often the stenotic type have been treated with univentricular palliation of the Fontan type. One group of patients continues to have an unfavorable outlook, namely those neonates with gigantic cardiomegaly and profound hypoxemia. Some of these babies may have functional pulmonary atresia and indeed some had undergone unnecessary operation. We demonstrated *c.* 25 years ago the role of aortography in differentiating functional from organic pulmonary atresia[121A] and others later have demonstrated the utility of color Doppler in making this differentiation.[121B-D] More recently Atz and his colleagues have demonstrated the efficacy of inhaled nitric oxide in making this differentiation in neonatal Ebstein's anomaly.[121E]

The cardiopulmonary function in this group is also compromised by the small volume of the lungs resulting from intrauterine compression. Tricuspid valve repair and replacement in the neonate is almost always disappointing, reflecting in part the grossly disadvantaged right ventricle that is diffusely thinned with its functional component grossly underdeveloped. Some

have advocated the innovative approach of Starnes and his colleagues and now others of closing the tricuspid valve and constructing a systemic-to-pulmonary artery shunt.[122,122A,123,123A] Some success has been achieved with this approach, although the experience of the Pediatric Cardiac Care Consortium reported four of six babies dying using this operation.[32] There is one report of successful biventricular repair in a number of severely affected neonates.[124] This approach uses tricuspid valve repair, reduction atrioplasty, relief of right ventricular outflow tract obstruction if present and partial closure of the atrial septal defect.[124] Finally, the outcome of some patients with Ebstein's anomaly of the tricuspid valve is linked to the substrate for pre-excitation, and as we have noted surgical or catheter-based intervention may have to address interruption/ablation of these pathways.[23,27,32,38,41,42,111,112,125,126]

In summary:

- This is a complex disorder with a wide range of clinical expression, affecting the fetus and allowing yet other patients to survive into the eighth and ninth decades of life.
- Fetuses with severe tricuspid regurgitation do not fare well, with spontaneous fetal loss.
- Patients presenting beyond infancy with increasing heart size, cyanosis, or symptoms may benefit from valve reconstruction with or without plication of the atrialized portion of the right ventricle.
- Tricuspid valve replacement is a reality at the primary operation or because of late, recurrent tricuspid regurgitation.
- Patients, especially children, may benefit from right ventricular unloading with a bidirectional cavopulmonary shunt.
- The predilection to pre-excitation will require intervention, surgical or catheter-based, in many patients.
- The neonatal expression of severe Ebstein's anomaly of the tricuspid valve has a poor prognosis, especially those with functional pulmonary atresia.
- Some of the most severely affected neonates will demonstrate spontaneous improvement as the pulmonary vascular bed matures and pulmonary resistance falls.
- Some of the most severely affected neonates may benefit from conversion to tricuspid atresia and univentricular palliation.

All references can be found at the end of the book. See pp. 645–8 for Chapter 11A.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

11B

Robert M. Freedom and Shi-Joon Yoo

Uhl's Anomaly of the Right Ventricle

Uhl's anomaly of the right ventricle is a most uncommon condition characterized by near or complete absence of the myocardium of the right ventricle (Fig. 11B-1).[1,2] According to Gerlis and his colleagues,[3] they attribute to Osler the first description of a parchment heart in which all the chambers were greatly dilated and the walls were very thin.[4] It was almost 50 years later when in 1952 Uhl described a heart in which the wall of the right ventricle was described as paper thin, almost devoid of muscle fibers, an appearance suggestive to him also of a parchment heart.[1] This is but one of the so-called dysplastic conditions of the right ventricle, one form now bearing the appellation of Uhl's anomaly of the right ventricle, and also one that seemingly shares some features with arrhythmogenic right ventricular dysplasia or cardiomyopathy.[3,5–10]

Incidence

Uhl's anomaly is most uncommon and is not catalogued in any of the studies of the prevalence of congenital heart disease. There does seem to a familial predilection for this uncommon disorder, although the apparent overlap between Uhl's anomaly and arrhythmogenic right ventricular dysplasia is common to these and other similar reports.[3,11–13] According to data summarized by Ikari and colleagues, the male sex slightly predominates in Uhl's anomaly, with 56% of reported cases in males.[14]

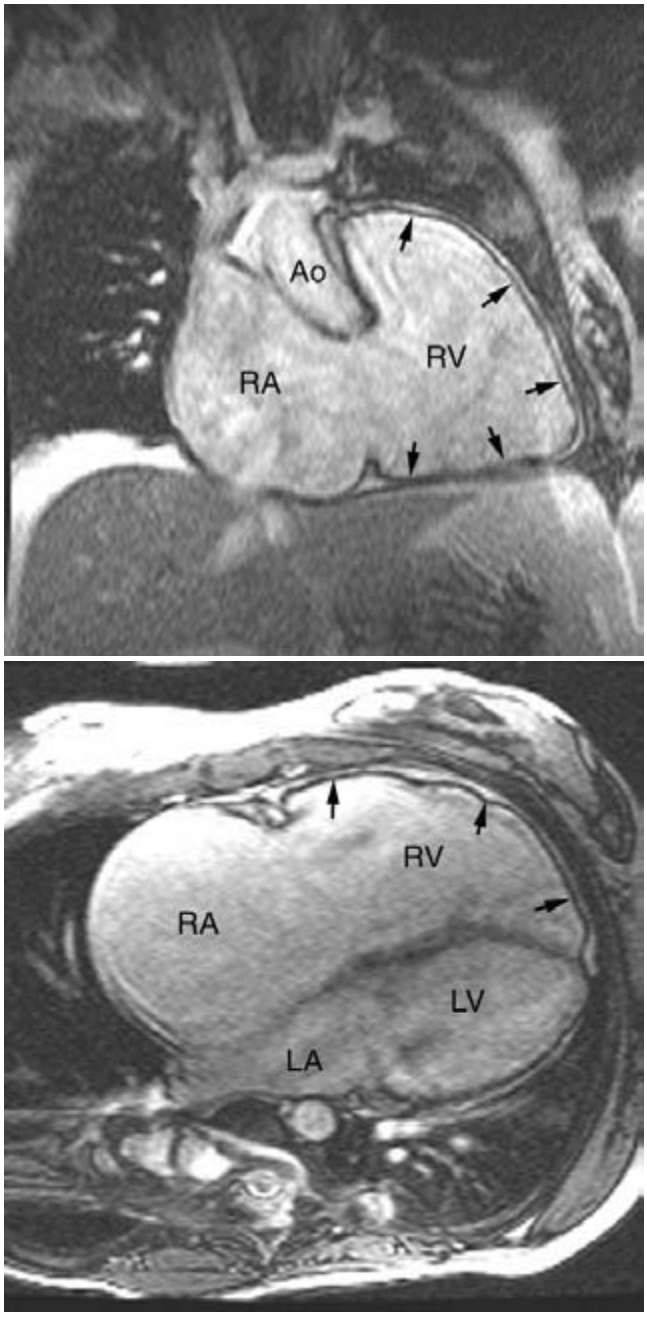
Morphology

Despite the relative infrequency of this disorder, there is an ample literature addressing the morphology and histopathology of the malformation designated as Uhl's anomaly of the right ventricle.[1–3,7–10] What is so characteristic of Uhl's anomaly and as Uhl himself revisited in his editorial[2] to the case report of James and his colleagues[15] is the "sharp demarcation between normal left ventricular myocardium and the abnormal myocardium of the right ventricle, the limitation of the abnormality to the right ventricle itself, the absence of any significant degree of associated inflammation, and the similar absence of any infiltrative process." The etiology of hearts devoid of the myocardium of the right ventricle remains uncertain.[2] There is little evidence to suggest a primary inflammatory process, and Uhl in his more recent editorial does not believe the process results from a congenital developmental failure in the human embryo in its early stages.[2] Uhl seems supportive of the suggestion of James that the pathogenesis of Uhl's anomaly is predicated on massive apoptosis of the right ventricle and crista supraventricularis.[15–18] In 1979, Fontaine and his colleagues described an entity which they called arrhythmogenic right ventricular dysplasia, an entity characterized by localized deficiency or fibrofatty replacement of the right ventricular myocardium.[19] As Gerlis points out, the term arrhythmogenic, or right ventricular, dysplasia has been used increasingly often, and references to Uhl's anomaly have noticeably decreased.[3] What is the inference of this changing nosology? Do these two conditions represent two different conditions, or are they variants of a single underlying congenital malformation?[3] On the basis of an exhaustive review of the literature and examination of five cases with a primary deficiency of the right ventricular myocardium, Gerlis and his colleagues conclude that Uhl's anomaly of the right ventricle and arrhythmogenic right ventricular dysplasia are likely separate and distinct morphological entities.[3] James and his colleagues submit that Uhl's anomaly and arrhythmogenic right ventricular dysplasia have in common their pathogenesis as apoptotic dysplasia, but that they differ in that Uhl's anomaly is an incessant process concluding in complete destruction of the right ventricle, whereas arrhythmogenic right ventricular dysplasia represents focal and episodic apoptosis within the right ventricle, beginning at any time, including later in life.[15]

Any number of congenital heart malformations may demonstrate marked thinning of the morphologically right ventricle including Ebstein's anomaly of the tricuspid valve with or without pulmonary atresia; aortic atresia with a discordant atrioventricular and ventriculoarterial connection, etc. How much of the thinning in these cases represents acquired changes secondary to the primary anatomic disturbance, and how much is a fundamental disturbance of the right ventricular myocardium? The signal case described by Uhl did not have any associated cardiac anomalies,[1,2] and Taussig felt that this diagnosis should exclude associated cardiac malformations.[20] This of course is arbitrary, but we will follow Taussig's suggestion, confining our discussion to cases without major associated cardiac anomalies.[20]

Outcome analysis

There is only sparse data on outcomes of fetuses recognized to have Uhl's disease of the right ventricle.[13,21] With a morphologically right ventricle grossly devoid of myocardium, it is not surprising that the fetus may tolerate poorly the hemodynamic burden placed on the right ventricle. This may be manifested as fetal heart failure, hydrops, and death.[13,21] A poorly functioning right ventricle with gross tricuspid regurgitation in the fetus may suggest Ebstein's anomaly of the tricuspid valve or gross tri-



A

B

Fig. 11B-1 Uhl's anomaly of the right ventricle. Coronal (**A**) and axial (**B**) MR images show that the heart is markedly enlarged with dilatation of the right atrium (RA) and right ventricle (RV). The right ventricular free wall (arrows) is paper thin and surrounded by a thin layer of epicardial fat. Ao, aorta; LA, left atriium; LV, left ventricle.

cuspid valve dysplasia, conditions certainly more common than Uhl's anomaly.[13,21–25]

From the cases in the literature designated as Uhl's anomaly of the right ventricle, patients have presented as fetuses, neonates, infants and into the adult age group.[1,3,4,12–15,21,26–43] Clinical presentations have been heralded by findings of heart murmur, heart failure, enlarged heart on chest radiography, cardiac palpitations, syncope, near and sudden death. It is the presentations of cardiac palpitations, syncope, near and sudden death in the older child and adolescent that raise the spectre of arrhythmogenic right ventricular dysplasia.[3,5–12,19] In this regard, there are increasing data from clinical, histopathological and genetic markers that Uhl's anomaly and arrhythmogenic right ventricular cardiomyopathy or dysplasia are fundamentally different disorders.[3] None the less, some literature considers arrhythmogenic right ventricular cardiomyopathy a less severe form of Uhl's anomaly, or at least related conditions.[10,11,44]

Just as the clinical findings are diverse, so are the outcomes. We described in 1978 a newborn with Uhl's anomaly and functional pulmonary atresia.[45] This baby was managed with a prolonged course of prostanoid therapy and with maturation of the pulmonary vascular resistance, the baby gradually improved. In 1998, Tumbarello and his colleagues reported the same patient, then a 14-year-old boy who denied any cardiac symptomatology.[46] The remarkable finding was that he had developed Doppler findings consistent with right ventricular restriction.[46] For those patients with right ventricular failure, some have advocated a one-and-a-half ventricle repair,[47,48] and in the infant reported by Yoshii and colleagues this was successfully combined with a partial right ventriculectomy.[49] Azhari and colleagues reported a 5-month-old infant who underwent a staged repair concluding in a total cavopulmonary connection.[50] Cardiac transplantation has been successfully carried out in an infant with Uhl's anomaly.[14] Finally, one patient with Uhl's anomaly and severe hypokinesia of the right ventricle and tricuspid insufficiency completed successfully a pregnancy, delivering by elective cesarean a healthy 2.7 kg girl.[39] From the authors' own characterization it is likely this mother suffered from arrhythmogenic right ventricular dysplasia.[39]

All references can be found at the end of the book. See pp. 648–9 for Chapter 11B.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom, Shi-Joon Yoo, and John G. Coles

Congenital Abnormalities of the Mitral Valve

Congenital mitral stenosis

Congenital mitral stenosis is a rare malformation,[1–34] and this anomaly was not catalogued in the New England Regional Infant Cardiac Program, nor in those more recent studies of the prevalence of congenital heart disease carried out in Alberta, Canada, nor in the Baltimore–Washington Infant study.[35–37] Collins-Nakai and her colleagues citing several sources indicate that congenital mitral stenosis occurs in about 0.6% of autopsied patients with congenital heart disease, and in from 0.21% to 0.42% of a clinical series.[3]

Ruckman and Van Praagh in 1978 characterized the anatomic types of congenital mitral stenosis based on 49 autopsy cases (Figs 12-1, 12-2).[30] They defined four anatomic types of mitral stenosis: (1) so-called typical mitral stenosis with short chordae tendineae, obliteration of interchordal spaces and reduction of interpapillary distance; (2) hypoplastic congenital mitral stenosis; (3) supravalvular stenosing mitral ring; (4) parachute mitral valve.[54] These forms are not mutually exclusive, and indeed, we as well as others have seen a number of patients with so-called typical mitral stenosis and a supramitral stenosing ring.[7–16,20–26] The parachute mitral valve and the supravalvular mitral stenosing ring are well associated in Shone's complex in which left ventricular inflow obstruction occurs in association with obstruction of the left ventricular outflow and aortic arch.[10,16,22] The developmental complex bearing Shone's name is characterized by left ventricular subaortic obstruction, coarctation of the aorta, parachute mitral valve, and the supravalvular stenosing ring of the left atrium. In the Ruckman and Van Praagh compilation of the anatomic types of congenital mitral stenosis based on autopsy specimens, the hypoplastic congenital mitral stenosis was primarily identified in those patients with the hypoplastic left heart syndrome.[30] The median age of death of these patients was only 5 days, consistent with this diagnosis. We and others have defined a hypoplastic but otherwise normal mitral valve in patients with bilaterally total anomalous pulmonary venous connections and in coarctation of the aorta, amongst other conditions. More interest has been devoted to the forms of congenital mitral stenosis as one determines which pathologic substrate is amenable to either balloon intervention or to aggressive surgical intervention, including the left ventricular approach.[14,24,31,38] Congenital mitral stenosis has been identified in isolation, but can complicate patients with coarctation of the aorta; ventricular septal defect; tetralogy of Fallot; aortic stenosis; double-outlet right ventricle; anomalous origin of the coronary artery from the pulmonary trunk, and rarely, those with atrioventricular discordance.

The parachute form of congenital mitral stenosis can occur in isolation, but this anomaly of the papillary muscles has been identified in association with a wide variety of congenitally malformed hearts,[3,4,7–16,18,20–26] but particularly in patients with the atrioventricular septal defect (see Chapter 5). It has also been observed in patients with coarctation of the aorta, aortic stenosis, left ventricular outflow tract obstruction, Shone's complex, transposition of the great arteries, ventricular septal defect, tetralogy of Fallot, double-inlet ventricle, etc. Tandon and his colleagues reviewed some years ago 52 specimens of congenitally malformed hearts with a parachute mitral valve.[15] The ventriculoarterial connection was concordant in 35 cases (67.3%), double-outlet right ventricle in 8 (15.4%), and discordant ventriculoarterial connections in 4 (7.7%). The most common intracardiac malformation in this large series was a ventricular septal defect identified in 37 specimens (71.1%). In 28 of the 35 specimens with concordant ventriculoarterial connections, at least two of the four obstructive anomalies of the Shone syndrome coexisted.

Oosthoek and colleagues have examined in detail the parachute-like asymmetric mitral valve and its two papillary muscles.[39] This study was carried out to characterize the morphologic features of parachute-like asymmetric mitral valves and to discriminate this anomaly from parachute mitral valves. Mitral valves with unifocal attachment of chords have been called "parachute valves," independent of the number of papillary muscles. The anomaly involving two papillary muscles has not received separate attention. The gross anatomy of 29 mitral valves with focalized attachment of chords was studied. In 28 of the autopsy specimens asymmetric mitral valves with two papillary muscles were present, and one of the muscles was elongated, located higher in the left ventricle with its tip reaching to the annulus, and attached at both its base and lateral side to the left ventricular wall. The valve leaflets could be directly attached to this abnormal muscle that received few chords or, in three hearts, no chords at all, resulting in an oblique and eccentric orifice. Because of the focalized attachment of chords to one of the two papillary muscles, we call this malformation "parachute-like asymmetric mitral valve." They found only one "true parachute mitral valve," that is, one having a single papillary muscle that received all chords. The morphologic features of asymmetric mitral valves are essentially different from those of true parachute valves. They suggest that a distinction between these two anomalies will contribute to recognition by the pediatric cardiologist and surgeon.

The supravalvular stenosing mitral ring is an uncommon form of left atrial outflow obstruction.[3,4,7,8,10–16,22–26,40–49] Rarely

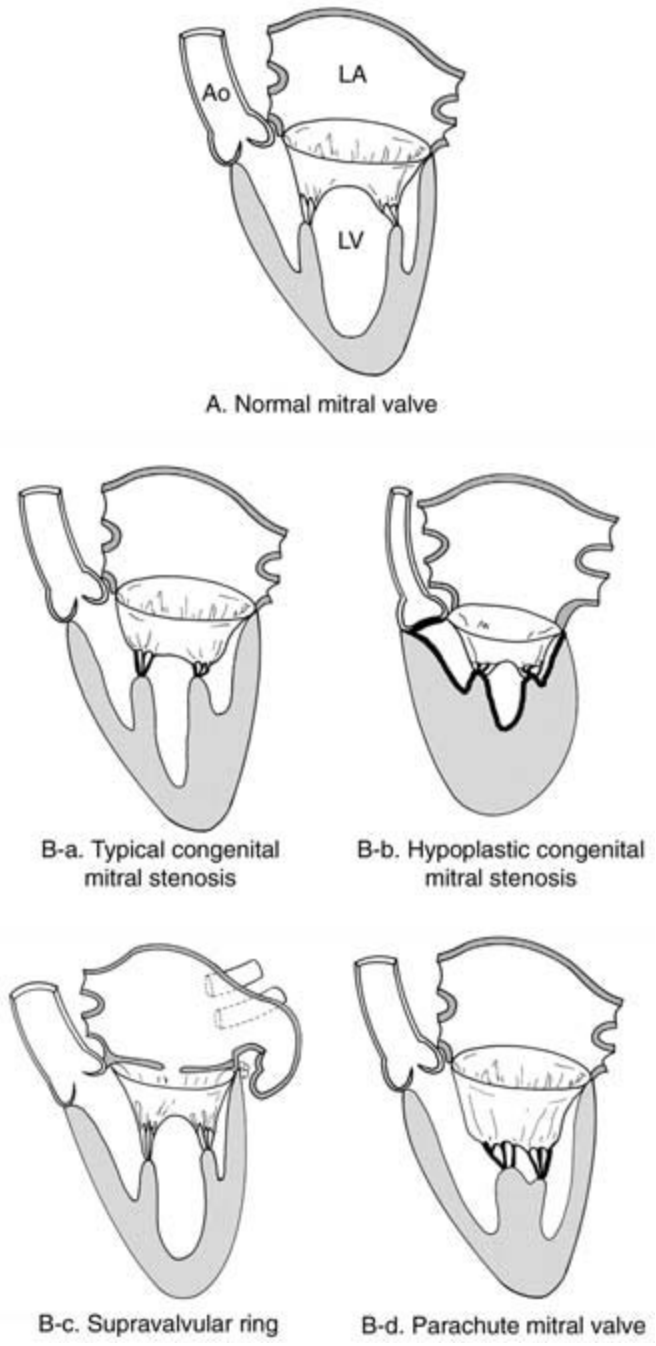


Fig. 12-1 Normal mitral valve and various forms of congenital mitral stenosis. **A.** Normal mitral valve. The delicate leaflets are supported by two widely spaced papillary muscles and long and thin chordae tendineae. Ao = aorta; LA = left atrium; LV = left ventricle. **B.** Congenital mitral stenosis (Ruckman and Van Praagh).[30] (a) Typical congenital mitral stenosis. The papillary muscles are large and close together. The chordae tendineae are thick and short, compromising the interchordal spaces. (b) Hypoplastic congenital mitral stenosis. This form is seen in association with aortic atresia or severe stenosis and intact ventricular septum. The left ventricle is hypertrophied. Endocardial fibroelastosis is commonly associated. The mitral valve and its tension apparatus are all small and show variable degree of deformity and hypotrophy. (c) Supravalvular stenosing mitral valve. A diaphragm is formed above the mitral valve annulus. In contrast to cor triatriatum, the dividing diaphragm or membrane is below the orifice of the appendage (see Fig. 12-3A for cor triatriatum). (d) Parachute and parachute-like mitral valve. In classical form, a single papillary muscle supports the mitral valve. More commonly, there are two papillary muscles but the posteromedial papillary muscle is very hypoplastic, resulting in a feature similar to a parachute.

occurring in isolation, its most frequent association is with the Shone's complex.[10,16] The stenosing supravalvular mitral ring is distinguished from the classic subdivided left atrium of cor triatriatum sinistrum (Fig. 12-3A). The subdividing membrane of cor triatriatum sinistrum is found superior to the ostium of the left atrial appendage, while the supravalvular stenosing mitral ring, classically a fibrous tissue, is found with a few millimeters superior to the mitral valvular annulus, and unequivocally inferior to the ostium of the left atrial appendage. While recognition of the supravalvular stenosing mitral ring has been achieved by left atrial angiocardiography, this left atrial structure is best recognized and its severity assessed by cross-sectional echocardiography with Doppler and color flow interrogation. A supramitral stenosing ring has also been seen in association with a classically divided left atrium.[50]

Tulloh and colleagues reviewed those risk factors for recurrence or death after resection of a supravalvular stenosing mitral valve in 23 consecutive patients.[45] Firstly, their data showed that supravalvar mitral stenosis is part of a spectrum of obstructive lesions affecting the left heart. The prognosis in those requiring resection within the first 18 months of life is poor, with a high mortality and the risk of recurrence in the survivors is high because of continuing turbulent flow across a small left ventricular inflow tract. Older age (> 18 months) at resection of supravalvar mitral stenosis was the only variable

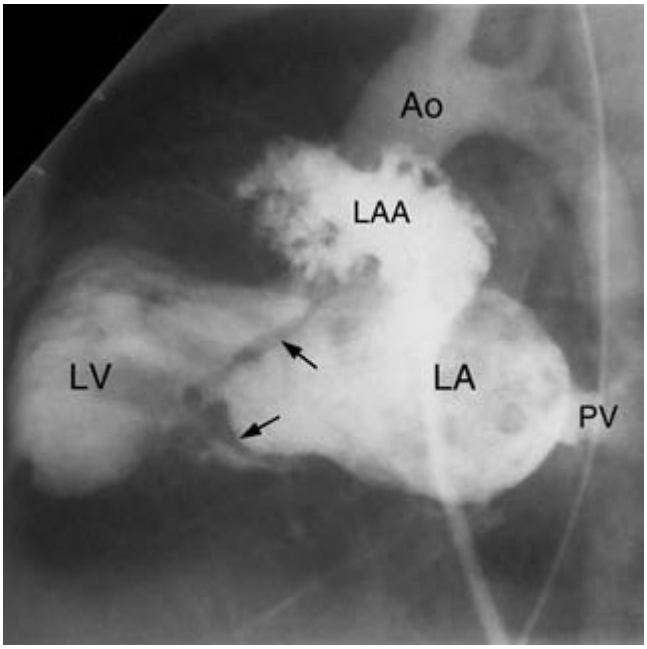


Fig. 12-2 Lateral left atriogram shows doming of the thickened mitral valve leaflets (arrows) during ventricular diastolic phase. There is regurgitation of contrast medium into the dilated pulmonary vein (PV). Ao, aorta; LA, left atrium; LAA, left atrial appendage.

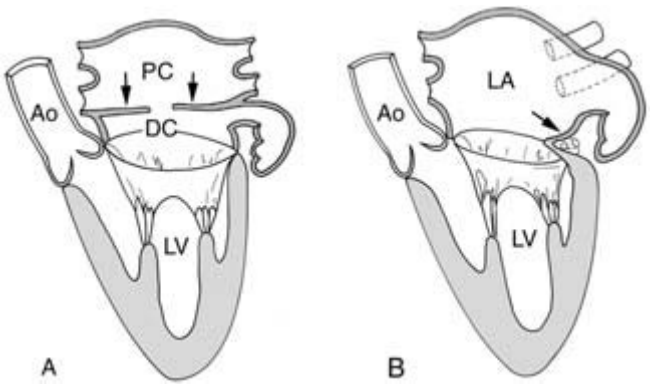


Fig. 12-3 Lesions simulating supramitral ring. **A**. Cor triatriatum. The obstructing membrane (arrows) divides the left atrium into the proximal (PC) and distal (DC) chambers. The membrane is above the orifice of the atrial appendage in cor triatriatum, while it is below the appendageal orifice in supramitral ring (see Fig. 12-1Bc). Ao, aorta; LV, left ventricle. **B**. Eccentric supramitral ridge. It is formed by exaggerated invagination of the atrioventricular groove (arrow). The circumflex coronary artery is incorporated into the ridge. LA, left atrium.

predictive of survival free of recurrent supravalvar mitral stenosis on multivariable analysis.

Rarely, the supravalvular ridge may contain a dominant left circumflex coronary artery as reported by Huhta and his colleagues.[46] This ridge departed from the classical circumferential supravalvular stenosing mitral ring in that the ridge was not fibrous, rather being eccentric and non-circumferential (Fig. 12–3B). The ridge was apparently formed by exaggerated invagination of the left atrioventricular groove. Therefore, the circumflex coronary artery is incorporated into the ridge together with the epicardial fat.

Congenital mitral valve regurgitation

Congenital mitral regurgitation is uncommon, being identified in only 6 of the 2251 infants enrolled in the New England Regional Infant Cardiac Program.[35] In the morphological assessment of the congenitally regurgitant mitral valve, virtually all aspects of the mitral valve, including abnormalities of the free valve margin, chordal apparatus, and papillary muscles have been identified in the etiology of the regurgitation.[2,4,5,7,8,13,18,25,47,51–68] Such abnormalities include dysplasia of the valve, double-orifice, deficient leaflet tissue, isolated anterior and/or posterior cleft of the mitral valve, polyvalvular disease, displacement of the mitral valve of the Ebstein type, an unguarded mitral orifice, and the so-called anomalous mitral arcade. Mitral regurgitation can occur in the newborn period reflecting a disordered transitional circulation, i.e. transient myocardial ischemia of the newborn.[65–68] Papillary muscle ischemia and infarction in the baby with critically severe aortic stenosis has been well described.[54,55] Mitral regurgitation has also been identified in the newborn infant with myocarditis as well as other primary endomyocardial disorders. Usually beyond the newborn period, those babies and young infants with anomalous left coronary artery originating from the pulmonary artery or those babies with atresia of the left coronary artery ostium and inadequate coronary artery collateralization will develop papillary muscle ischemia or frank infarction with resultant mitral regurgitation. Mitral regurgitation has been observed in patients with coarctation of the aorta, and this represents either functional impairment of the left ventricle, or congenital abnormalities of the mitral valve.[28,51] One cannot forget those patients with Marfan's syndrome in whom mitral regurgitation may be conspicuous.[69, 70] In the older patient with Marfan syndrome, mitral regurgitation has been attributed to prolapse, but in the infantile presentation of Marfan syndrome and severe mitral regurgitation, the mitral valve may exhibit features of dysplasia as well as prolapse.[69] Mitral regurgitation can occur in the patient with Kawasaki disorder; infective endocarditis; following trauma; and in the patient with chronic anemia.

Freed and his colleagues have addressed the frequency of congenital mitral regurgitation in patients with coarctation of the aorta.[51] Amongst 861 infants and children with coarctation of the aorta examined between 1950 and 1973, 18 (2.1%) had congenital mitral regurgitation. The mechanisms responsible for the mitral regurgitation were diverse including chordal rupture and congenital perforations. We have identified double-orifice mitral valve; isolated anterior mitral clefts; and deficient leaflet tissue as causal for mitral regurgitation in patients with coarctation of the aorta.[25,33,47]

Anomalous mitral arcade

Layman and Edwards in 1967 called attention to a specific pathologic condition of the mitral valve responsible for congenital mitral insufficiency: the so-called anomalous mitral arcade.[71] The arcade is characterized by connection of left ventricular papillary muscles to the anterior mitral leaflet, either directly or through the interposition of unusually short chordae (Fig. 12-4).[25,33,47,71–78] This malformation has also been called the "hammock" valve. In our experience, the pathology of an anomalous mitral arcade is not inconsistent with severe mitral stenosis, or a mixed functional disturbance. Castaneda and his colleagues reported a 10-month-old infant with congenital mitral stenosis resulting from an anomalous mitral arcade.[77] In addition, the heavy papillary muscles of this abnormal mitral valve contributed to subvalvar obstruction. Similar pathologic findings have been observed by Frech and his colleagues in two patients with mitral stenosis and regurgitation.[76] Enlarged,

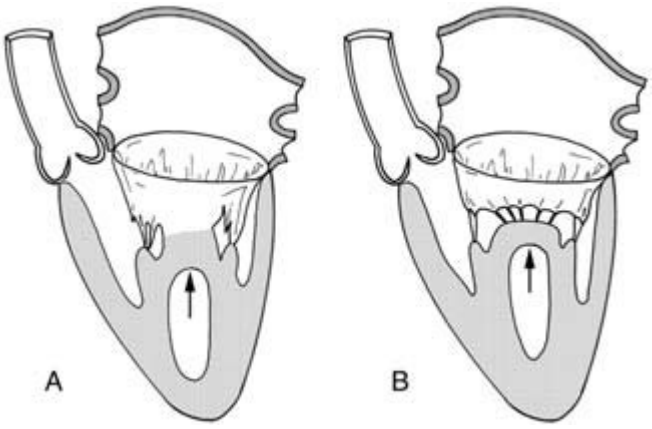


Fig. 12-4 Mitral arcade. The tips of the papillary muscles are fused to form an arcade that is attached to the mitral valve leaflets either directly (**A**) or through the interposition of short chordae tendineae (**B**).

thickened papillary muscles in close approximation to the free valve margin of the mitral valve contribute to subvalvular obstruction. While the anomalous mitral arcade is considered a disorder of the pediatric age-group, Myers and her colleagues have documented this anomaly in a 36-year-old man with clinical, hemodynamic, and angiocardiographic evidence of mitral stenosis and mild mitral regurgitation.[73] Perez and his colleagues report a 28-year-old woman with congenital mitral insufficiency secondary to an anomalous mitral arcade.[75] An anomalous arcade of both atrioventricular valves has been described in an infant with massive tricuspid and mitral insufficiency.[74] It is of interest that this patient also had so-called myocardial non-compaction. The patient reported by Balfour and colleagues also had an anomalous left coronary artery originating from the pulmonary trunk.[78]

Isolated cleft of the anterior mitral leaflet

Amongst the causes of the congenital mitral regurgitation is the isolated cleft of the anterior leaflet of the mitral valve.[2,4,5,7,25,47,79–91] This disorder is very different from the so-called cleft left atrioventricular valve in the patient with an atrioventricular septal defect (Fig. 12-5). The anomaly of the isolated cleft of the anterior mitral leaflet is characterized by a cleft dividing the anterior leaflet of the mitral valve into two portions with a normally-positioned mitral annulus and intact atrioventricular muscular and membranous septum.[80–93] Sigfusson and colleagues have provided a thorough morphological analysis of why an isolated cleft of an otherwise normal mitral valve should not be considered part of an atrioventricular canal malformation.[90] These authors also do not consider a so-called isolated cleft a forme-fruste of an atrioventricular canal malformation. One of the more important reasons to make this differentiation is the disposition of the specialized atrioventricular conduction tissue that differs so importantly between these two lesions. This

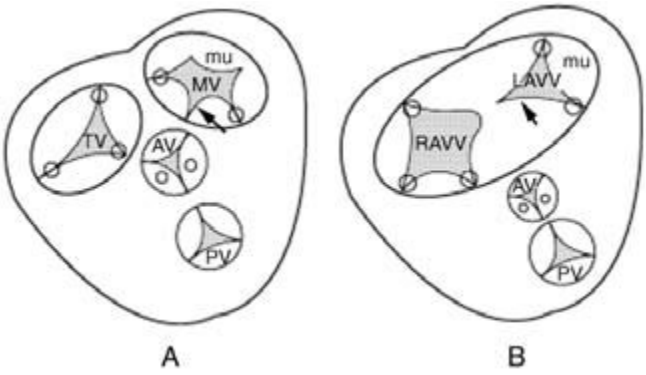


Fig. 12-5 Difference between the isolated cleft of the anterior leaflet of the mitral valve (**A**) and the cleft of the left atrioventricular valve (LAVV) in atrioventricular septal defect (**B**). Notice that the cleft (arrow in A) of the anterior leaflet of the mitral valve (MV) in an otherwise normally formed heart points the aortic valve (AV), while the cleft (arrow in B) of the left atrioventricular valve in atrioventricular septal defect points the interventricular septum. Also note the disposition of the papillary muscles (circles) and extent of the mural leaflet (mu). The papillary muscles in atrioventricular septal defect are more closely spaced and arranged more anteroposteriorly than in an otherwise normally formed heart. PV, pulmonary valve; RAVV, right atrioventricular valve; TV, tricuspid valve.

deformity of the mitral valve is an uncommon cause of congenital mitral regurgitation, but has been identified in patients with ventricular septal defect, tetralogy of Fallot, tricuspid atresia, etc. The cleft of the anterior leaflet of the mitral valve points towards the left ventricular outflow tract, while the so-called cleft of the left atrioventricular valve in atrioventricular septal defect points towards the right ventricle (Fig. 12-5).[80–91] Barth and his colleagues reported the autopsy findings of an isolated cleft in the anterior mitral leaflet in a 27-year-old man.[86] An accessory mitral valve leaflet has been associated with a solitary mitral cleft.[88] There is now considerable surgical experience dealing with the so-called isolated cleft of the aortic or anterior leaflet of the mitral valve.[85,91–93]

Double-orifice mitral valve

Double-orifice mitral valve is that condition in which two complete orifices are supported by their own tension apparatus (Fig. 12-6).[25,33,47,94–101] This should be distinguished from a simple fenestration of a valve leaflet not supported by its own tension apparatus. The basic morphology is either presence of an accessory orifice at a commissure (commissural type) or in a leaflet (hole type), or central division into two orifices of equal size by a bridge of leaflet tissue (central type). Among these, the commissural type is the most common.[99] The double-orifice mitral valve is a well-known morphological finding in the patient with an atrioventricular septal defect (see Chapter 5), but a number of cases of double-orifice mitral valve have been documented in patients with a normal atrioventricular septum.[94–101] This condition does not invariably result in a regurgitant valve, although severe regurgitation in the setting of a double-orifice mitral valve has been observed in the pediatric patient as well as in the adult in the seventh decade of life. A double-orifice mitral valve has been observed in a two-day-old baby with type-1 truncus arteriosus, and the mitral abnormality was beautifully demonstrated by cross-sectional echocardiography. Bano-Rodrigo and his colleagues reported 27 post-mortem cases of double-orifice mitral valve.[99] In this study, an anomaly of the tensor apparatus was always identified, including chordal rings; accessory papillary muscle or muscles; fused papillary muscles or parachute deformity; crossing chordae tendineae; or central fibrous subdivision. Double-orifice mitral valve almost always consisted of abnormal holes demarcated by the functioning valve leaflets and supported by the chordae, rather than of abnormal fibrous bridges or adhesions between normal leaflets. Since these fibrous "bridges" between the smaller accessory orifice and the larger main orifice are composed of mitral leaflet tissue and chordae, not fibrous adhesions, these bridges should not be transected surgically, to avoid iatrogenic mitral regurgitation. The atrioventricular canal was normally divided in 44% and a common atrioventricular canal was present in 56%. Functionally, the mitral valve was normal in 48%, regurgitated in 26% and stenotic in 26%.

Mitral valve prolapse

Prolapse of the mitral valve has been identified in the newborn and in the individual in the 10th decade of life or older.[102–124] This common condition has been recognized in individuals with a wide range of congenital heart malformations, Marfan's syndrome, annuloaortic ectasia, ischemic heart disease, hypertrophic cardiomyopathy, pectus excavatum, and in those whose

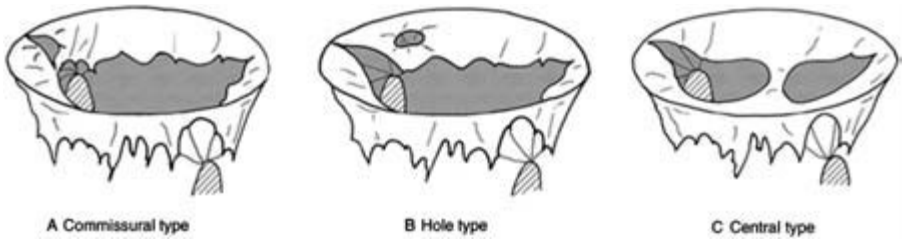


Fig. 12-6 Double-orifice mitral valve. **A**. Commissural type: presence of an accessory orifice at the commissure. **B**. Hole type: presence of an accessory orifice in a leaflet. This type should be differentiated from a simple fenestration that is not supported by its own tension apparatus. **C**. Central type: division of the mitral valve orifice into two equal parts by a bridge of leaflet tissue.

body habitus is asthenic. It has been observed in those with pectus excavatum, straight back, and scoliosis. The etiology of mitral valve prolapse is not clear, and probably is multifactorial. Myxomatous degeneration, myocardial factors, and ischemic heart disease have been suggested as causal to mitral valve prolapse. First identified on the basis of a late systolic murmur of mitral regurgitation and a mid systolic click, or honk, mitral valve prolapse soon became identified with mitral regurgitation of variable severity, and some data demonstrated progression from mild to more severe degrees of mitral incompetence. In the evolution of imaging modalities, it is clear that cross-sectional echocardiography with color Doppler is the modality of choice, and angiographic imaging is of historical interest only.

Outcome analysis

There is virtually no information on the fetal diagnosis of isolated congenital mitral stenosis or regurgitation, and most surgical series in the pediatric age range consist of < 50 patients accumulated over two or more decades. Cross-sectional echocardiography with color Doppler flow mapping and more recently three-dimensional reconstruction has proven invaluable in the pre- and intraoperative management of patients with congenital mitral valve disease.

Moore and his colleagues from the Children's Hospital in Boston have had an extensive experience with the management, both surgical and balloon valvuloplasty, in infants and young children with congenital mitral stenosis.[14] They reviewed the records of 85 infants with congenital mitral stenosis to assess the severity, associated cardiac lesions, echocardiographic morphological appearance of the mitral valve, treatment, and outcome. They described five valve morphologies: "typical" hypoplastic mitral valve with symmetric papillary muscles (SYMM, 52%), supravalvar mitral ring (SVMR, 20%), double-orifice mitral valve (DOMV, 11%), hypoplastic mitral valve with asymmetric papillary muscles (ASYMM, 8%), and parachute mitral valve (PARA, 8%). Of the 85 infants, 31 (36%) were severely symptomatic, requiring intervention within the first 2 years. Balloon dilation was performed in 18 infants (age, 8.7 ± 5.7 months; weight, 5.9 ± 1.9 kg) and valve surgery in 13 (age, 10.9 ± 5.9 months; weight, 6.7 ± 2.1 kg). Balloon dilation decreased the peak transmitral gradient (LAa-LVED) > 30% in 15 of 18 initial attempts, from 20.3 ± 8.2 to 10.9 ± 4.9 mmHg ($P < 0.001$), and the mitral valve area increased from 0.7 ± 0.3 to 1.0 ± 0.5 cm^2/m^2 ($n = 10$, $P = 0.01$). No infant died during the initial balloon dilation, although 2 of 3 died during a repeat procedure for restenosis. Other complications included significant mitral regurgitation in 7 of 18 patients (39%), 4 of whom had SVMR. Of the 18 infants, 8 (44%) had persistent symptomatic improvement at a mean follow-up of 14 months (range 2–32 months). The 2-year survival after balloon dilation was 70%; 40% remained free of repeat intervention. Mitral valve surgery in 13 infants consisted of SVMR resections in 7, mitral valve replacements in 4, and LA-to-LV aortic valved homografts in 2. The operative mortality was 30%. Sustained improvement occurred in 8 (6 with SVMR) at 11–62 months of follow-up (mean, 30 months), with a 2-year survival of 60%. This group found that infants with severe congenital mitral stenosis have a 2-year mortality rate approaching 40% regardless of treatment modality. Balloon dilation significantly reduces the transmitral gradient in the majority, but symptomatic improvement persists in only 40%. Procedure-related mortality was associated with repeat balloon dilation in patients with left ventricular hypoplasia. Balloon dilation of "typical" congenital mitral stenosis can provide symptomatic relief in many infants, allowing postponement of valve replacement, although infants with SVMR do better with surgical management.[14]

Endo and his colleagues have studied the effects of pulmonary venous obstruction (PVO) on the histopathology of the pulmonary vascular bed.[125] Pulmonary venous obstruction induces pulmonary arterial hypertension, as well as pulmonary venous hypertension, and jeopardizes the repair of cardiac lesions. Four cases of congenital mitral stenosis and four cases of cor triatriatum (Lucas type A), ages ranging from 2 months to 16 years, were histologically examined on pulmonary vasculature. Histometrical analysis was performed on medial thickness and intimal changes of both pulmonary arteries and veins. For comparison, the examination of pulmonary vasculature in ventricular septal defect (VSD) cases was also performed. Medial thickening and intimal fibrosis, in both pulmonary arteries and veins with widespread lymphangiectasia, were characteristic vascular changes of PVO cases. Medial thickness of pulmonary arteries was correlated with preoperative pulmonary arterial pressure (PAP) ($r = 0.77$, $P = 0.03$ for systolic PAP), and greater than that of VSD cases. Medial thickness of pulmonary veins was also greater in PVO cases. Intimal fibrosis of pulmonary arteries and veins was seen extensively at the advanced ages, whereas no plexiform lesions or more advanced stages of pulmonary vascular disease were present. While congenital PVO induced progressive medial thickening and intimal fibrosis in pulmonary arteries and veins accompanied by lymphangiectasia, no plexiform lesions or more advanced stages of pulmonary vascular disease were present, which may explain the reversibility of pulmonary hypertension due to congenital PVO.

Stellin and his colleagues reported on 34 consecutive children (20 male and 14 female) with a mean age of 5.9 years (range 45 days to 18 years) treated surgically for congenital mitral valve

disease between January 1987 and June 1999.[126] Four patients (11.7%) were under 12 months of age, while 21 patients (62%) were younger than 5 years. Twenty-two patients presented with MV incompetence, while 12 presented with stenosis. Associated cardiac lesions were identified in 22 patients (62.8%). Mitral valve reconstruction was possible in all. There were no operative deaths. Three patients required reoperation for MV restenosis (a re-repair in one and MV replacement with mechanical prosthesis in two) 4 months, 27 months and 5.6 years after repair with no operative deaths. There was only one late death for prosthetic valve thrombosis. Follow-up data reveal that the 33 surviving patients are asymptomatic and well 4 months to 12 years (mean 72 months) after surgery. At 12 years, actuarial survival and freedom from reoperation are 96.8% and 85.9%, respectively. Echocardiography performed in all of them shows no or mild incompetence or stenosis in 26 (78%), while residual moderate MV incompetence persists in six. Their experience indicates that MV reconstructive procedures in infants and children with congenital MV dysplasia are effective and reliable with low mortality and low incidence of reoperation rate.

Chauvaud and his colleagues have a very extensive experience with congenital mitral valve anomalies.[127] Between 1970 and 1995, 145 patients younger than 12 years old underwent surgery for congenital mitral valve insufficiency. The mean age at repair was 5.7 ± 3.1 years, ranging from 0.17 to 12 years. Mitral valve insufficiency associated with atrioventricular defect, atrioventricular discordance, straddling mitral valve, acquired diseases, Marfan syndrome, and degenerative disease were excluded from this study. According to Carpentier classification, 31 patients had type I mitral valve disease (normal leaflet motion), 79 patients type II (leaflet prolapse), and 35 type III (restricted leaflet motion), with 15 having normal papillary muscles and 20 abnormal papillary muscles. Associated lesions were present in 51 patients (35%). A conservative operation was possible in 138 patients (95%). Among them, 70 patients required a prosthetic annuloplasty and 21 patients valve extension with a pericardial patch. Mitral valve replacement was necessary in only seven patients (5%). In-hospital mortality was 5% (95% CL: 2.5% to 9.9%) (7 patients). No early death was observed in the group of patients who underwent valvular replacement. In-hospital mortality was as follows: type I, 9.6%; type II, 2.5%; and type III, 13%. No statistically significant difference was noted among patients with the different types of disease. The mean follow-up was 9.3 ± 6.9 years (1–26 years), and cumulative follow-up was 1142 patient-years. Ten late deaths occurred. Actuarial survival at 10 years was 88% in patients who underwent valve repair and 51% in patients who underwent valve replacement. Late reoperation was required in 15% ($n = 21$) of patients who had undergone valve repair and 28% ($n = 2$) in patients with valve replacement. Causes of reoperation were recurrent left ventricular failure ($n = 1$), residual or recurrent mitral valve insufficiency ($n = 17$), mitral valve stenosis ($n = 3$), and calcification of the bioprosthesis ($n = 2$). No failure resulting from leaflet extension was observed. In the repair group, actuarial freedom from reoperation was 68% (95% CL: 80.5% to 51.5%) at 15 years, and the linearized rate of exposure to reoperation was 1.9% per patient-year. No thromboembolic event was observed in any group. This distinguished group found that congenital mitral valve insufficiency can be repaired in infancy with a low mortality. Furthermore, conservative surgery with Carpentier's techniques was feasible in the majority of cases of congenital mitral valve insufficiency. This technique offers stable long-term results with a low rate of reoperation. Leaflet extension associated with prosthetic ring annuloplasty could prevent reoperations in selected cases.

Uva and colleagues addressed surgical results in 20 patients < 1 year of age who underwent operations for congenital mitral valve disease between 1980 and 1993.[128] Ten patients had congenital mitral incompetence and 10 had congenital mitral stenosis. The mean age was 6.6 ± 3.4 months and mean weight was 5.6 ± 1.5 kg. This group excluded patients with atrioventricular canal defects, univentricular heart, class III/IV hypoplastic left heart syndrome, discordant atrioventricular and ventriculoarterial connections, and acquired mitral valve disease. Indications for operation were intractable heart failure or severe pulmonary hypertension, or both. Associated lesions, present in 90% of the patients, had been corrected by a previous operation in seven. In congenital mitral incompetence there was normal leaflet motion ($n = 3$), leaflet prolapse ($n = 2$), and restricted leaflet motion ($n = 5$). In congenital mitral stenosis anatomic abnormalities were parachute mitral valve ($n = 4$), typical mitral stenosis ($n = 3$), hammock mitral valve ($n = 2$), and supramitral ring ($n = 1$). Mitral valve repair was initially performed in 19 patients and valve replacement in the patient with the hammock valve. Concurrent repair of associated lesions was performed in 12 patients. There was no operative mortality rate. There were six early reoperations in five patients for mitral valve replacement ($n = 4$), a second repair ($n = 1$), and prosthetic valve thrombectomy ($n = 1$). One late death occurred 9 months after valve replacement. Late reoperations for mitral valve replacement ($n = 2$), aortic valve replacement ($n = 1$), mitral valve repair ($n = 2$), subaortic stenosis resection ($n = 1$), and second mitral valve replacement ($n = 1$) were performed in five patients. Actuarial freedom from reoperation was 58.0% ± 11.3% (70% confidence limits, 46.9% to 68.9%) at 7 years. After a mean follow-up of 67.6 ± 42.8 months, 94% of living patients were in New York Heart Association class I. Doppler echocardiographic studies among the 13 patients with a native mitral valve showed mitral incompetence of greater than moderate degree in one patient and no significant residual mitral stenosis. Overall, six patients had mitral prosthetic valves with a mean transprosthetic gradient of 6.2 ± 3.7 mmHg. These results showed that surgical treatment for congenital mitral valve disease in the first year of life can be performed with low mortality. Valve repair was a realistic goal in about 70% of patients and would possibly be more with increased experience. The reoperation rate was still appreciable and was related to complexity of mitral lesions and associated anomalies, but late functional results were encouraging.

Ohno and his colleagues from the Department of Pediatric Cardiovascular Surgery, The Heart Institute of Japan, Tokyo Women's Medical University have reviewed their clinical results for mitral valve repairs for congenital mitral insufficiency.[129] Forty-nine consecutive patients aged 2 months to 34 years (mean, 4.4 years) had mitral valve repair between June 1984 and December 1996. Forty-one patients (83.7%) had associated cardiac anomalies. The predominant pathologies for the regurgitations were chordal anomalies in 34 patients (69%), annular dilatation in 8 (16%), and leaflet anomalies in 7 (14%). Mitral valve repair included commissure plication annuloplasty in 43 patients (88%), modified DeVega in 11, cleft closure in 5, plication of the anterior leaflet in 3, triangular resection of the ante-

rior leaflet in 2, chordal shortening in 1, and placement of artificial chordae in 1. Several combined techniques were required in 19 patients. There were no early or late deaths. The follow-up period was from 6 to 166 months (mean 88.4 months). Forty-seven patients (95.9%) were in New York Heart Association class I. The long-term echocardiographic studies showed that 2 of 30 patients without reoperation had moderate regurgitation. The actuarial freedom from reoperation was 85.6% (95% confidence limits, 72.8%, 98.4%) at 13 years. Five patients (10.2%) required valve replacement from 13 days to 75 months after the valve repair. Their experience showed that valve repair for congenital mitral insufficiency gave adequate results in combination with commissure plication annuloplasty and other techniques with excellent long-term functional status.

Zias and colleagues from the Children's Memorial Hospital in Chicago have reported on mitral valve remodeling techniques as applied to 26 infants and children (mean age 6.0 years, range 0.4–15.9 years) with various forms of congenital mitral valve disease over a 7-year period.[130] They excluded patients with atrioventricular canal, L-transposition and single ventricle. Intraoperative transesophageal echocardiography was utilized to assess the repair and guide the need for immediate intervention. Twenty-one patients had mitral regurgitation: 10 with cleft anterior mitral leaflet, 7 with annular dilatation, 1 with normal leaflets with an obstructing cord, 2 with prolapsed leaflets and elongated cords, and 1 with restricted leaflet motion, normal papillary muscles, and shortened cords. Of the 5 patients with mitral stenosis, 3 had supravalvular mitral ring, 1 had midvalvular mitral ring, and 1 had a parachute valve. Three of the mitral stenosis patients had additional stenotic lesions. Concurrent repair of associated lesions was performed in 21 patients (78%). The operative mortality was 3.8% ($n = 1$). There were no late deaths. Immediate re-repair in four patients resulted in improved function. All mitral stenosis patients improved. A total of 20 mitral regurgitation patients (95%) improved; one required mitral valve replacement. The mean follow-up is 31 months (range 2–81 months). All patients are in New York Heart Association functional class I or II. They found that assessment using transesophageal echocardiography can guide the necessity for immediate re-repair to achieve improved function an outcome

Tamura and colleagues reviewed the outcome of twenty patients (9 male, 11 female) diagnosed with an isolated cleft of the mitral valve.[131] Seven patients had associated cardiac lesions. The median age of diagnosis was 5.2 years (range 0.4 to 13.6 years). Echocardiography aided by color Doppler demonstrated the cleft in all patients. However, an incomplete diagnosis was made in 4 of 20 patients before surgery. The severity of the mitral regurgitation at presentation was mild in 11, moderate in 8, and severe in 1 patient. In the 13 patients without associated cardiac lesions, 5 underwent mitral valve repair at median age of 5.2 years (range 1.2 to 7.7 years) for moderate to severe mitral regurgitation, 4 being symptomatic. The severity of the mitral regurgitation in seven of the eight unoperated patients has remained unchanged over the follow-up period (median 8.3 years, range 0.7 to 14.4 years). In total, 10 patients underwent mitral valve repair (median 6.4, range 0.4 to 13.8 years). No patient required valve replacement. None of the 10 patients had more than mild mitral regurgitation over the follow-up period (median 0.6, range 0.2 to 11.0 years). Surgery is indicated in those patients with moderate to severe mitral regurgitation and probably should be done early following diagnosis.

Hisatomi and colleagues examined the results of intermediate and long-term follow-up of 25 patients aged 3 months to 11 years (mean 2.6 ± 2.3 years) who initially underwent conservative mitral valve repair for mitral regurgitation associated with ventricular septal defect between April 1973 and March 1991.[132] The preoperative degree of mitral regurgitation was 2+ in 3, 3+ in 17, and 4+ in 5 patients, and the major causes of mitral regurgitation were annular dilatation and prolapse of the anterior leaflet.

Annuloplasty was performed in all except 2 patients, suturing of the cleft was done in 3 patients, and posterior mitral leaflet advancement was done in 2 patients. In addition, the papillary muscle was incised and adhesive chordae were removed in 1 patient, and adhesive fused chordae were detached from a leaflet in 1 other patient. There were no early deaths. Two patients with residual mitral regurgitation with or without mitral stenosis underwent reoperation for mitral valve replacement 2 months and 6 years after the mitral repair, respectively. Late death occurred in 2 patients, and the actuarial survival rate was 92.0% at 15 years after operation. The freedom from reoperation was 91.3% at both 10 and 15 years after the initial operation. Postoperative color Doppler flow imaging was performed in 22 of the 23 survivors, and results showed no mitral regurgitation in 4, mild regurgitation in 14, and moderate regurgitation in 4 patients. When they completed their study, 4 patients had mitral stenosis, with a mean transmitral pressure gradient > 10 mmHg. The residual lesion of moderate mitral regurgitation with or without mitral stenosis developed in 6 of 11 patients in whom bilateral mitral annuloplasty was applied after the initial operation. Nineteen of the 22 survivors without reoperation were in New York Heart Association class I, and 3 were in class II. Their data demonstrated clinical improvement after conservative mitral repair in most pediatric patients with ventricular septal defect. They suggested that a careful follow-up for growth potential still appears to be needed to detect changes in mitral regurgitation and the development of mitral stenosis after valve repair, especially after bilateral annuloplasty.

One of the more complex groups of patients includes those with Shone's syndrome, a syndrome of multiple levels of left ventricular inflow and outflow tract obstruction.[10–16,22,25,43,47,48] Bolling and his colleagues from Ann Arbor reviewed the records of 30 consecutive patients seen with Shone's anomaly at our institution between 1966 and 1989. Anatomical diagnoses in these patients were supravalvar mitral ring (22 patients), mitral valve abnormalities including parachute mitral valve, fused chordae, or single papillary muscle (26 patients), subaortic gradients (26 patients), and coarctation (29 patients). Nineteen patients had all four lesions. Other common defects were bicuspid aortic valve (19 patients) and ventricular septal defect.[20] Two patients were treated medically. The other 28 patients required 84 procedures with 18 patients undergoing more than one procedure. Operations included coarctation repair (28 patients), mitral valve repair or replacement (11), ventricular septal defect closure (8), subaortic resection (8) and complex left ventricular outflow tract reconstruction or bypass (4). Age at first operation ranged from 7 days to 7 years (median age, 3 months). There were no operative deaths at the first operation. However, mortality rose to 24% (4/17) after the second operation. All operative deaths were secondary to severe mitral

valve disease. The survivors have been followed from 1 to 16 years (mean follow-up 6 ± 1 years). There were no late or sudden deaths. Morbidity has included stroke (1), gastrointestinal bleeding (2), permanent heart block (1), and persistent congestive heart failure (6).[22]

Brauner and colleagues from UCLA presented their surgical results in 19 consecutive patients with Shone's anomaly, with a median follow-up of 8 years.[48] Mitral stenosis was present in all, with parachute deformity in 12 patients. Supramitral rings were found in 9 patients. Other features included subaortic stenosis (15 patients), valvar aortic stenosis (9), bicuspid aortic valve (16), and coarctation (13 patients). The patients underwent 46 surgical procedures, including 18 mitral operations (9 replacements, 9 repairs). There were 3 in-hospital (16%) and 2 late (10.5%) deaths. Of the 5 nonsurvivors, 4 patients (80%) had predominant mitral disease and moderate to severe pulmonary hypertension, vs. 4 (28.5%) and 5 (36%) survivors, respectively (P = not significant). Valve repair was the final procedure in 9 survivors. The other 5 patients had repeated valve replacements (1), aortoventriculoplasty with valve replacements (2), or no mitral operation (2). Freedom from mitral reoperation was 78% (7 of 9 patients) after repair procedures and 43% (3 of 7 patients) after replacement. At follow-up, 10 patients (71.4%) are in New York Heart Association functional class I and the other 4 in classes II and III. Six (43%) await reoperation due to recurrent aortic (4) or subaortic (1) stenosis and recoarctation (2). Echocardiography reveals mild mitral stenosis or regurgitation in 3 patients after repair (33%). Four are considered free of residual disease (21% of all). In this experience, late outcome in Shone's anomaly seems to correlate with the predominance of mitral valve involvement and the degree of pulmonary hypertension. Valve repair is indicated whenever feasible and should be considered before the occurrence of pulmonary hypertension.

Serraf and his colleagues have reviewed their clinical experience with 72 patients with congenital mitral stenosis, with or without associated defects operated on between 1980 and 1999.[133] Thirteen patients had isolated congenital mitral stenosis, while in 59, it was associated with other heart defects, either ventricular septal defect (n = 28) or multilevel left ventricular obstruction (n = 41). In this group of patients, 23 had a staged approach and 26 underwent a single-stage repair. Early mortality was 12.5%. No deaths occurred in the patients with isolated congenital mitral stenosis or in those undergoing single-stage repair. Logistic regression revealed that early mortality was influenced by association with left ventricular outflow tract obstruction ($P < 0.001$) and by the use of a staged approach ($P < 0.01$). There was no late mortality in the group with isolated congenital mitral stenosis, but there were 2 late deaths in the group of single stage repair and 6 late deaths in the staged surgical approach group. Reoperation was required in 24 patients, mainly for residual mitral valve dysfunction or left ventricular outflow tract obstruction. Including the reoperations, 10 patients received a prosthetic mitral valve.[133] At 15 years after surgery, survival was 69.6 ± 7.5%, freedom from reoperation was 70.8 ± 6.3%, and freedom from mitral valve replacement was 69 ± 6.0%. In this regard there is increasing experience with mitral valve replacement in infants and young children.[134,135] Annular hypoplasia and small size of the patient continues to make this a challenge, and some have advocated for supra-annular positioning of the mitral prosthesis, but the results are not encouraging.[136]

The Pediatric Cardiac Care Consortium reviewed their small experience with the supramitral stenosing ring.[137] Their experience encompassed only 11 patients, 5 infants and 6 children. The two youngest patients, 8 and 31 days, both died. Sullivan and his colleagues reported that in the 14 infants and children operated on at the Great Ormond Street Sick Children's Hospital in London[43] there were no deaths. In the 8 patients reviewed by Collins-Nakai, there were no surgical deaths.[3]

While there is now considerable experience with balloon valvuloplasty for rheumatic mitral stenosis, there is relatively little information about this technique when applied to patients with congenital mitral stenosis.[14,38,138,139] It is difficult to be enthusiastic for balloon mitral valvuloplasty. As one surveys the literature, the initial enthusiasm for this procedure has evaporated and there is relatively little published on this methodology subsequent to the report from Boston in 1994.[138,139] From the surgical results reviewed thus far, and with exposure of the mitral valve from the left atrium and left ventricle,[31,140] surgical remodeling of the mitral valve seems to have deflated the balloon.

In the long-term follow-up of these patients they must be surveyed for:

- residual mitral stenosis
- residual mitral regurgitation
- pulmonary artery hypertension
- left ventricular function
- systemic outflow tract obstruction
- aortic regurgitation
- atrial flutter/fibrillation.

All references can be found at the end of the book. See pp. 649–52 for Chapter 12.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

13A

Robert M. Freedom and Lee Benson

Congenital Pulmonary Stenosis and Isolated Congenital Pulmonary Insufficiency

Congenital pulmonary stenosis

Pulmonary valvar or valvular stenosis is one of the more common forms of congenital heart malformations and it has been extensively studied since the original description of pulmonary valve stenosis by John Baptist Morgagni in 1761.[1] The terms valvular and valvar both refer to "a valve" and are and have been used interchangeably.[2] Designations that have been used to define the stenosis as an isolated lesion include pure or uncomplicated valve stenosis and pulmonary stenosis with normal aortic root or with an intact septum. Isolated pulmonary valve stenosis is a form of an acyanotic congenital heart malformation with normal or diminished pulmonary blood flow. The atrial septum is usually intact; if not, the defect is usually in the form of a patent foramen ovale, although an actual atrial septal defect of the secundum type may coexist. Interestingly, Abbott speculated in her atlas about the etiology of pulmonary stenosis stating: "This condition is practically always inflammatory, the result of an endocarditis running its course in fetal life after septation has been completed."[2A]

Incidence

About so-called pure pulmonary stenosis, Taussig stated in her 1947 *Congenital Malformations of the Heart*: "pulmonary stenosis as an isolated malformation with no defect in the ventricular septum, is rare." She goes on to say "the author has not had the opportunity to study a proven case of pure pulmonary stenosis."[2B] The reasons for this are uncertain. Abrahams and Wood in 1951 found the incidence of pulmonary stenosis to be 11.6% amongst 689 patients, and Campbell in 1954 reported the incidence to be 10%, similar to the 9.9% reported from the Toronto Hospital for Sick Children.[3–5] The New England Regional Infant Cardiac Program published in 1980 found a prevalence for pulmonary valvular stenosis of 0.073 per 1000 live births,[6] while the Baltimore–Washington Infant Study published in 1985 found a prevalence of 0.189 per 1000 live births.[7] The higher prevalence in the more recent study certainly reflects the role of echocardiography in the diagnosis of the more mild expressions of the disorder. The more recently completed Bohemia Survival survey identified 292 children with pulmonary stenosis from a population of 815 569 children born between 1980 and 1990.[8] This gave a prevalence of 0.36 per 1000 live births and these accounted for 5.81% of all congenital heart malformations encountered in this survey.[8] Data from the geographically confined country of Malta found the prevalence at birth of pulmonary stenosis from 1990 to 1994 to be 1.65/1000 live births, with 1.11/1000 mild lesions and 0.54/1000 lesions requiring intervention.[9] Hoffman and Kaplan recently reviewed 39 studies on the incidence of congenital heart disease.[10] The mean of these studies provided an incidence for congenital pulmonary stenosis of 729 per million live births.[10] From the study published by Ryan and colleagues, 2% of patients with 22q11 microdeletion had pulmonary stenosis.[11] In this regard, the interested reader will find valuable *Progress in Pediatric Cardiology* **16**(2), August 2002, which is devoted to the velocardiofacial syndrome.[12]

Recurrence risks

Driscoll and his colleagues using data collected for the report from the Second Joint Study on the Natural History of Congenital Heart Defects found that definite congenital heart disease occurred in 1.7% of the 177 children of the male probands and 3.8% of the 210 children of the female probands.[13] Overall the occurrence of congenital heart disease in children of patients with pulmonary stenosis from this study was 2.8%. Two of the eight occurrences of congenital heart defects in children of maternal parents were siblings, both of whom had pulmonary stenosis.[13] Nora and Nora found a recurrence risk of 3.6% for an affected parent with pulmonary stenosis.[14,15] Data provided by Whittemore and her colleagues about recurrence was even more striking with 20% of the progeny of an affected parent with pulmonary stenosis having congenital heart disease, and 55% of these were concordant for pulmonary stenosis.[16] In this study, there was no difference between the maternal and paternal offspring.[16] Tynan and Anderson have recently summarized the literature addressing the familial incidence of pulmonary stenosis.[17] Udwadia and colleagues have described a family with familial congenital valvar pulmonary stenosis with autosomal dominant inheritance.[17A]

Morphological observations

Pulmonary obstruction at the valve level is manifest in two distinct patterns, so-called typical valve stenosis, and dysplastic pulmonary valve stenosis.[17–19] Typical pulmonary valve stenosis is characterized by a thin, pliant, conical or dome-shaped valve with a restricted orifice (Fig. 13A-1). The valve is formed with three leaflets or cusps[17–19] though it may be bicuspid[20] or four raphes may be evident.[20] Morphologically in the neonatal expression of critical pulmonary stenosis, the fused raphes extend from a central opening to the pulmonary artery wall (acommissural) creating an eccentric (rarely circular) hemody-

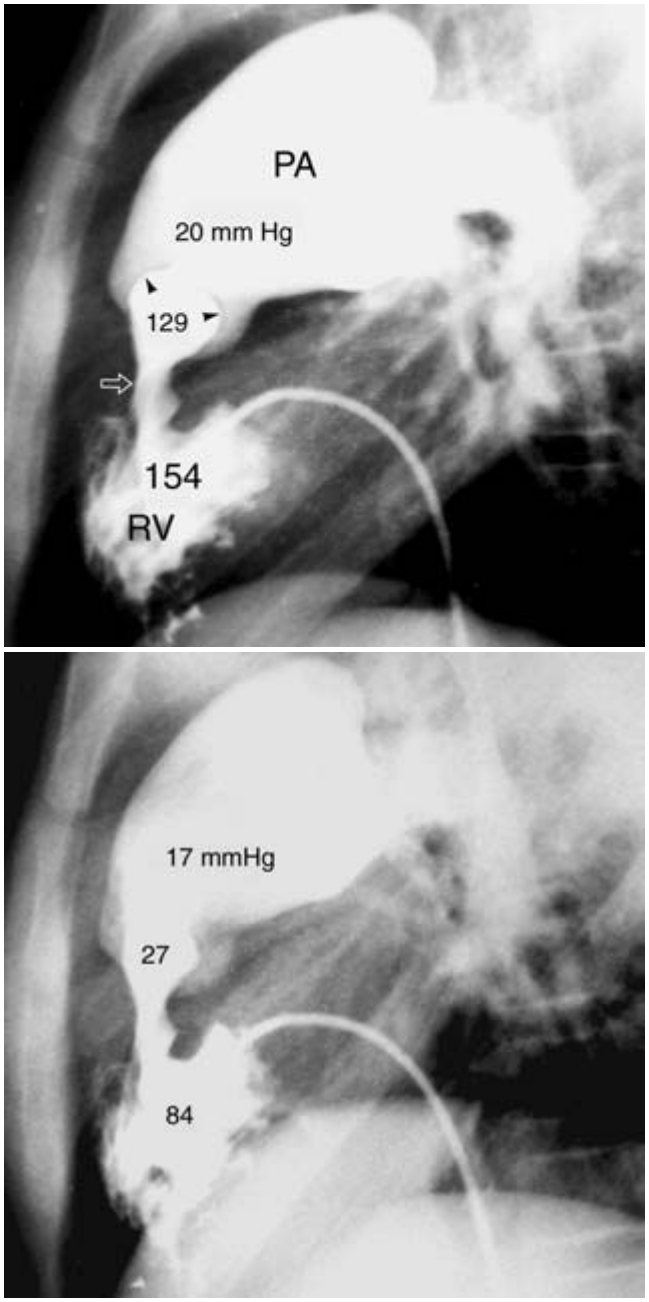


Fig. 13A-1 Typical pulmonary valve stenosis. **A.** Systolic frame of right ventriculogram in lateral projection shows mildly thickened, dome-shaped pulmonary valve leaflets (arrowheads). The right ventricular infundibulum (open arrow) shows dynamic narrowing. Note the post-stenotic dilatation of the main pulmonary artery. **B.** After balloon dilatation, the pulmonary valve is widely open and the leaflets are not domed. Dynamic stenosis of the right ventricular infundibulum persists in this immediate post-procedural angiogram. The numeric numbers are the pressures in mmHg. PA, pulmonary artery; RV, right ventricle.

namic orifice of varying diameter, depending on the extent of commissural fusion. No separate leaflets are present and although angiographically they may appear thin, histologically they appear as disorganized myxomatous tissue throughout.[19] Secondary changes occur in the right ventricle and pulmonary artery as a result of the profoundly after-loaded ventricle. The right ventricle hypertrophies, particularly the infundibular region with muscular encroachment on the size of the cavity. This may be quite extensive and in the neonate suggests the appearance of true hypoplasia of the chamber. However, few newborns, after effective relief of the valve obstruction, require additional sources of pulmonary blood flow, as the chamber as well as the annulus will both enlarge and become more compliant with time.[21–26] However, some babies despite a prolonged course of prostaglandin will require some surgical maneuver to augment pulmonary blood flow despite what is seemingly adequate relief of the outflow tract obstruction. This may reflect a poorly compliant ventricle, at times aggravated by a slightly restrictive tricuspid valve annulus, with right-to-left atrial shunting. The tricuspid valve is generally well formed and competent, although right atrial enlargement can develop with significant tricuspid insufficiency secondary to right ventricular hypertension and myocardial ischemia.[27,28] In this regard right ventricular myocardial necrosis and infarction has been well-documented in neonates with critical pulmonary stenosis.[28A,28B] In the absence of an intrinsic tricuspid valve anomaly (displacement and/or dysplasia of the leaflets, clefts, abnormal chordal attachments) this too resolves with relief of the obstruction. The tricuspid valve may be congenitally abnormal especially in the neonatal expression of the disorder, although perhaps less severely disordered than in the patient with pulmonary atresia and intact ventricular septum.[27,28] Kirklin and Barratt-Boyes state that about 50% of neonates with pulmonary stenosis have normal tricuspid valve dimensions while in the remainder the diameter is smaller than normal.[29] In their experience only in 10% is the tricuspid valve truly hypoplastic.

In the older infant and child post-stenotic dilation of the main pulmonary trunk is the rule,[30] although rarely a supravalvar hourglass deformity has been described.[31] Such enlargement of the pulmonary artery trunk can be seen at all stages of disease expression, from newborn through adult and pulmonary artery aneurysms, although rare, have been described.[32–34] There is disproportionate dilatation of the left pulmonary artery branch, due to the leftward orientation of the right ventricular outflow tract, and the parallel takeoff of the left pulmonary artery from the main trunk. Additionally, it is thought that the alterations in fluid dynamic forces with dispersion of the kinetic energy of the jet beyond the stenotic valve increases the systolic pressures toward the left pulmonary artery.[35] Calcification may occur within the pulmonary valve, but is exceptional in any but the adult with longstanding usually severe disease.[36–40] The aortic arch is usually but not invariably left-sided, when pulmonary valve stenosis is present with an intact ventricular septum. This is in contrast to the situation in Fallot's tetralogy when a right-sided aortic arch is present in 30% of cases. A right-sided aortic arch has been reported rarely[4,41,42] in critical pulmonary valve stenosis. While the expression of pulmonary valve stenosis is usually but not invariably an isolated malformation, in its "typical" presentation, when the mechanism of right ventricular outflow obstruction is due to valve dysplasia there is a greater incidence of associated cardiac and non-cardiac malformations (e.g. Noonan's syndrome);[43–49] Williams syndrome;[40–52] and Alagille's syndrome,[53,54] although peripheral pulmonary arterial stenoses, are frequently more prominent features (Fig. 13A-2). Indeed it was Becu and colleagues who quite early suggested that isolated pulmonary valve stenosis may be part of a more widespread systemic process.[55]

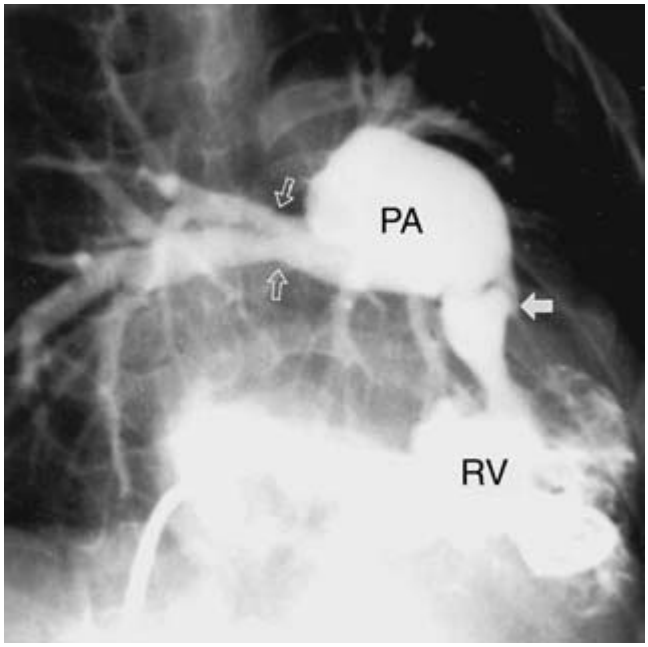


Fig. 13A-2 Pulmonary valve stenosis in a case of William's syndrome. Systolic frame of right ventriculogram in right anterior oblique view shows thickened and domed pulmonary valve (arrow). The right pulmonary artery shows mild narrowing (open arrows). PA, pulmonary artery; RV, right ventricle.

The dysplastic form of pulmonary valve stenosis occurs much less frequently (about 20% of cases with pulmonary valve stenosis) than that of typical valve stenosis[44–48,56] (Fig. 13A-3). In this setting, obstruction to right ventricular outflow reflects the reduced mobility of the thickened valve leaflets with the often associated hypoplasia of the valve annulus, supravalve tethering, a small or short main pulmonary artery and frequently peripheral pulmonary artery stenosis. The three leaflets are distinct and composed of disorganized myxomatous tissue and generally have little or no commissural fusion.[19,44,45] However, the response to balloon valvotomy would suggest that in some, a commissural element exists.[56–63] Valve thickening generally involves the entire leaflet through to the attachments to the annulus.[19,56] The expression of pulmonary valve stenosis in the neonate has the appearance of such dysplasia angiographically. However medium-term studies after successful balloon dilation have documented the valve to become pliant and then with time[21,22] or spontaneously normalize, or nearly so.[64]

Stamm and his colleagues have addressed the clinical anatomy of the normal pulmonary root compared with that in isolated pulmonary valvular stenosis.[65] These observations are perhaps germane to surgery of the pulmonary root or valve, but are applicable to balloon valvuloplasty as well. The normal pulmonary valve is enclosed in a proximal sleeve of free-standing right ventricular infundibulum supporting the fibroelastic walls of the pulmonary sinuses at the anatomic ventriculoarterial junction. The valvular leaflets are attached in semilunar fashion across this junction, delimiting the extent of the valvular sinuses. The stenotic valves can be separated into dome-shaped valves, dysplastic valves and a third group of less typical cases. In the dome-shaped valves, which have a relatively circular origin of their leaflets, three raphes were tethered to the arterial wall at the sinutubular junction, producing a waist-like narrowing. The leaflets of the dysplastic valves are attached in a relatively normal semilunar fashion, but stenosis results from thickening of the leaflets at their free edges. Serial histologic sections through normal and abnormal valves failed to demonstrate any well defined fibrous "annulus" that could be of clinical relevance. Unlike the normal and the dysplastic valves, the dome-shaped valves have circular rather than semilunar lines of attachment of the valvular leaflets. Liberation of the fused zones of apposition of the leaflets within the dome is unlikely to restore such abnormal valves to normal structure, even if this procedure relieves the stenosis.[65] We have stated earlier that in some patients with severe valvar pulmonary stenosis, infundibular hyertrophy may be conspicuous[66,67] (Fig. 13A-4). With adequate relief of the valvar obstruction either surgically or with balloon valvuloplsty, the infundibular obstruction usually regresses.[68–76] Infrequently, the site of the obstruction is primarily infundibular.[17,20,22,28,29,66,67,77] This form of obstruction does not lend itself to balloon intervention, and surgery will be required for important obstruction. It is conceivable that subvalvar obstruction in some patients represents a divided right ventricle with spontaneous closure of an associated perimembranous ventricular septal defect[78] (see also Chapter 19A).

Pulmonary valvar stenosis may be a component of a number of more complex intracardiac anomalies, and include these patients with tetralogy of Fallot, so-called divided right ventricle; obstructive anomalies within the pulmonary arteries; or other right ventricular inlet or outlet anomalies. Diffuse infundibular obstruction within the right ventricle may also be a manifestation of a hypertrophic cardiomyopathy as an expression of a diffuse myocardial process particularly seen in the young.[79] Ventriculocoronary connections have been seen in an occasional patient with critical pulmonary stenosis, but we are

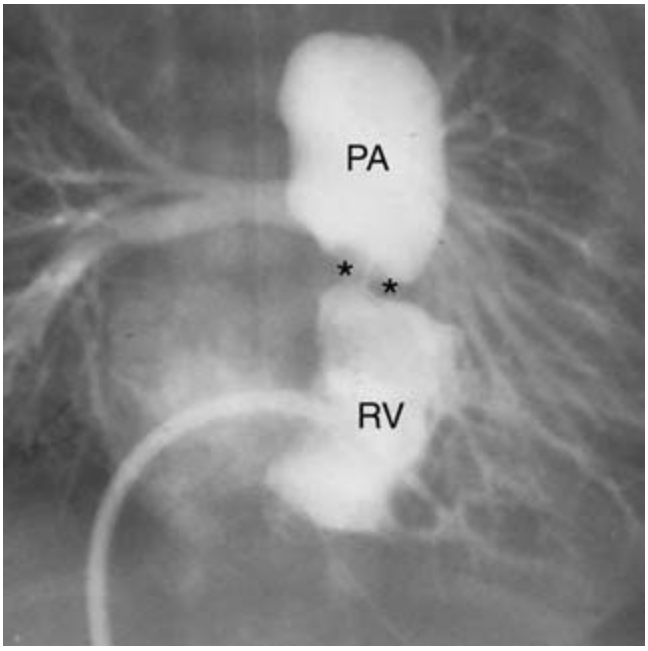
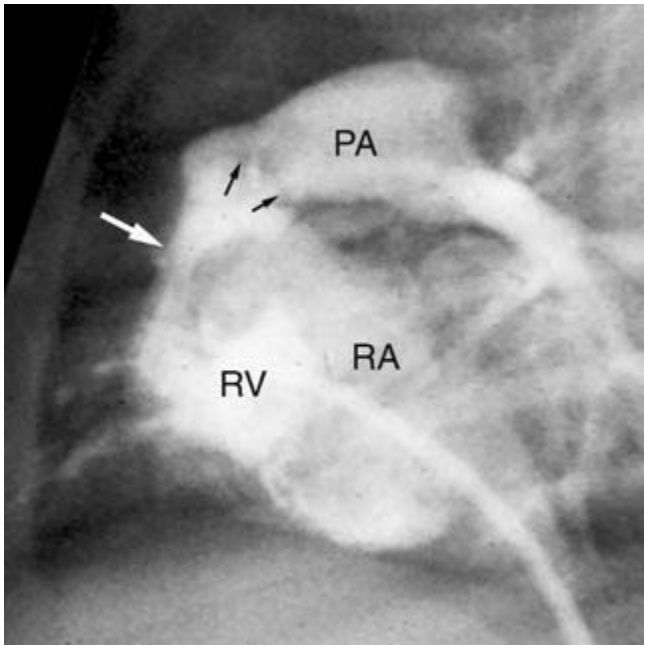
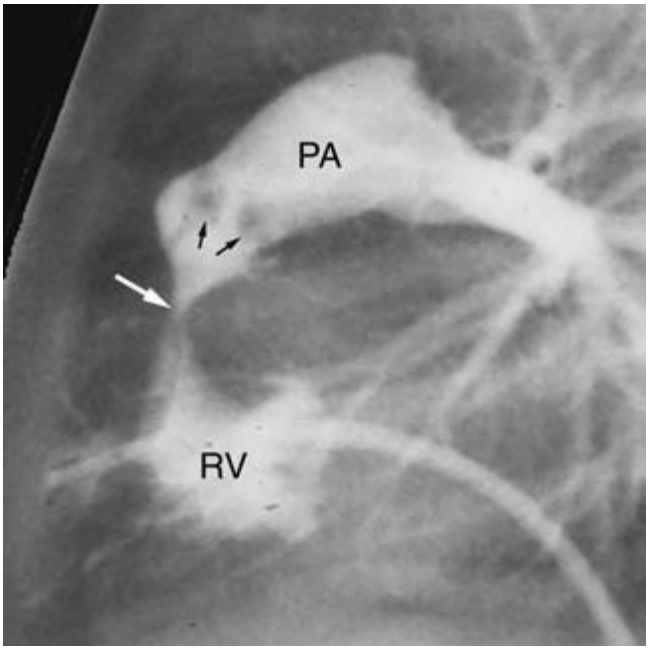


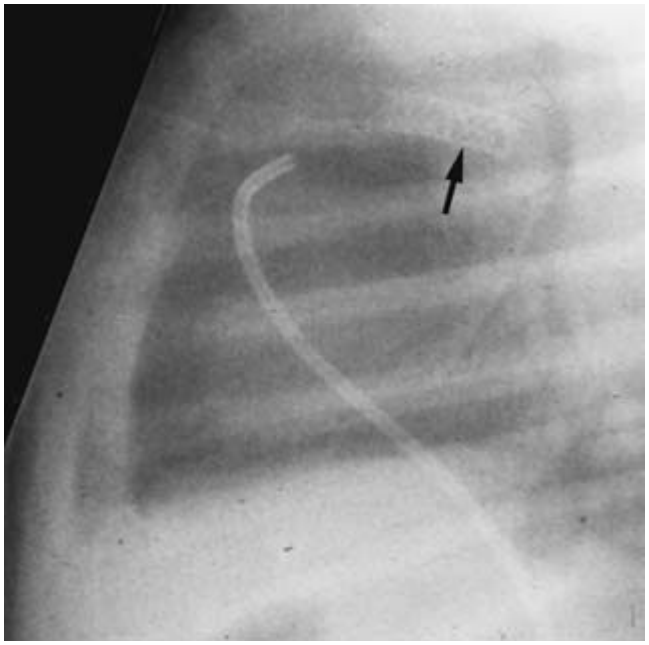
Fig. 13A-3 Dysplastic pulmonary valve stenosis. Right ventriculogram in right anterior oblique view shows very "lumpy," thickened pulmonary valve leaflets (asterisks). PA, pulmonary artery; RV, right ventricle.



A



B



C

Fig. 13A-4 Critical pulmonary valve stenosis treated by balloon dilatation. **A**. Right ventriculogram obtained before balloon dilatation of the pulmonary valve shows thickened pulmonary valve leaflets (arrows) and dynamic narrowing (arrow) of the right ventricular infundibulum. **B**. Right ventriculogram obtained after balloon dilatation shows improved excursion of the pulmonary valve leaflets (arrows). The patient developed desaturation with closure of the ductus and so-called "suicidal contraction" (arrow) of the right ventricular infundibulum immediately after balloon valvuloplasty. **C**. The ductus arteriosus was dilated by placing a stent (arrow).

not aware of a patient with critical pulmonary stenosis in whom the coronary circulation is right ventricular-dependent.[80,81]

Outcome analysis

Fetal outcome

There is considerable information on the fetal expression of pulmonary valvar stenosis, and the progression from moderate to severe obstruction including acquired atresia of the pulmonary outflow tract.[82–91] Sharland indicates that isolated pulmonary stenosis represents *c*. 0.8% of cases of structural heart disease diagnosed during fetal life in their combined series.[91] Termination of pregnancy was the choice of about 20% of families once the diagnosis was made, acknowledging that in most of these the obstruction was critical. Sharland indicates that as fetal recognition of mild pulmonary stenosis increases, the percentage of families choosing termination of pregnancy will likely decrease.[91] In sequential fetal studies, one can document lack of growth of right heart structures with important progression in severity in some.[89,91] Fetal pulmonary stenosis has been shown to develop in the recipient of a twin-to-twin transfusion.[84,88]

Postnatal outcome

Patients with trivial or mild pulmonary stenosis can survive to the eighth or ninth decade of life and survival into the eighth decade has even been reported in the patient with severe disease, although admittedly such longevity with serious disease is uncommon.[36,38,39,92–95] Johnson and his colleagues summarized the literature to 1972 addressing longevity in patients with pulmonary stenosis.[93] The natural history of the patient with congenital pulmonary valvar stenosis has been analyzed in detail.[96–108] Campbell suggested in 1969 that the mortality rates

for congenital pulmonary stenosis rise from 2% per annum in the first decade to 3.4% in the third, 6% in the fourth, and 7% per annum in the fifth and later decades.[96] He further comments that up to the age of 40, deaths are 20 times as many as would be anticipated in the general population. From his observations he speculated that only 19 ± 7% live to the age of 40 years. These observations were overly pessimistic. While clinical findings combined with the electrocardiogram facilitated non-invasive assessment of severity, the earlier studies relied on serial cardiac catheterizations to confirm the severity of the obstruction as well as to provide information about progression.[108A] But over the past nearly two decades such hemodynamic information has been afforded non-invasively from cross-sectional echocardiography and Doppler interrogation.[104–108] The earlier studies that required cardiac catheterization likely excluded those with very mild or minimal disease, especially the young infant and the advantage of the more recent studies is that such patients are included. Samanek has studied the probability of natural survival of children born in central Bohemia.[109] His data on children born with pulmonary stenosis showed the 1-year, 2-year, and 15-year actuarial survival rate to be 97%, 96% and 94%, respectively. Observations from the Baltimore–Washington Infant Study showed that the mean birth weight of singleton live births with pulmonary stenosis was 3021 g, with 19.8% < 2501 g and only 3.0% < 1501 g.[110] The mean gestational age was 38.7 weeks, with 14.4% small for gestational age and 9.6% large for gestational age.[110] As subsequent discussion of the natural and modified natural history of the patient with pulmonary stenosis will show, pulmonary stenosis may remain stable, progress, or rarely with natural remodeling of the valve, the severity of pulmonary stenosis may seemingly improve.[64,111]

Beginning in the early to mid 1950s experience with surgical pulmonary valvotomy rapidly accumulated. Swan and his colleagues in 1954 citing the earlier literature stated that the transventricular blind instrumental manipulation of the deformed pulmonary valve can be performed at low risk.[112] Yet they also expressed concern that this approach provided neither uniform nor adequate results and they reported their early experience with a transarterial pulmonary valvotomy. Campbell reported in 1959 his cumulative experience with 76 operated patients, and of these 30 were cyanosed.[113] There were 12 deaths in this overall experience, with 5 deaths occurring in the first 6 patients operated on.[113] Steinbicker and his colleagues published in 1966 the results of the first 100 surgically treated cases of pulmonary stenosis at the University of Colorado Medical Center, extending the earlier observations of Swan *et al.*[114] The average age of the patients was 9.75 years. There were 6 operative deaths in this experience. Tandon, Nadas and Gross reported in 1965 their institutional results of surgical pulmonary valvotomy in 108 patients operated from 1957 to 1961 using cardiopulmonary bypass and a pump oxygenator.[115] Only 5 patients were 1–2 years of age, 68 were between 5 and 15 years of age, and 23 were from 16 to 30 years of age. Twenty-eight patients were asymptomatic and 47 were cyanotic. The total mortality of this experience was 2.77%. The majority of the patients reported in these series were described as much improved following valvotomy. Mirowski and his colleagues from Johns Hopkins reported the 10- to 13-year follow-up of 53 patients operated on using a transventricular pulmonary valvotomy between 1949 and 1952.[116] The mean age at surgery was 11 years and the median age 8.8 years. There were 7 deaths. According to the authors, about 75% had excellent to good long-term results, while the remainder had poor results. They commented that results were better in the younger age than in older patients, an observation also made by Campbell.[113] Johnson and his colleagues in 1972 reported the long-term follow-up results in the adult, concluding that the benign course suggests that surgical correction is indicated only in the presence of symptoms or complications of pulmonic stenosis.[117] The many surgical series were complemented by some observations on the natural history of patients with pulmonary stenosis,[118,119] all setting the stage for the First Joint Study on the Natural History of Congenital Heart Defects. This was a huge undertaking with the participation of six institutions, including the University of Colorado Medical Center in Denver, Columbia-Presbyterian Medical Center, Mayo Clinic, Boston Children's Hospital, Children's Hospital of Buffalo, and Johns Hopkins Hospital and Medical Center.[101] The report emanating from the first study was dedicated to Edward C. Lambert (1915–74), chairperson of the Joint Study on the Natural History of Congenital Heart Defects, and the second report to Richard D. Rowe (1923–88), both men of remarkable vision and dedication to all aspects of pediatric cardiovascular medicine.

The First Report from the Joint Study on the Natural History of Congenital Heart Defects was published in 1977,[101] just about three decades after Brock's early experience. There had been considerable discussion throughout the 1950s as to the systolic pressure gradient, particularly in the asymptomatic child, on which surgery should be based. While there was not unanimity, most favored a pressure gradient of 50 mmHg and higher. This study published as The First Report from the Joint Study on the Natural History of Congenital Heart Defects was carried out in the era of cardiac catheterization for evaluation of severity and cardiac surgery as the form of intervention. Enrolling patients with pulmonary stenosis from the participating institutions who had been catheterized as early as 1958, we reported on the 565 patients with pulmonary stenosis included in this study. There were 298 males and 267 females. Eight-one were < 2 years of age; 364 between 2 and 11 years of age; and 120 from 12 to 21 years of age. Of the 261 patients followed medically (46% of the total), most had mild or at most moderate obstruction, and none of those older than 12 years of age had a gradient ≥ 80 mmHg. Almost none of these 261 patients had cyanosis, or congestive heart failure and only 6% had symptoms. There were no cardiac deaths among the 261 patients treated without surgery. One hundred and eighty-four patients had two cardiac catheterizations 4 or 8 years apart. The pressure gradients remained stable in the majority, but in 14% there was a significant increase and in another 14% a significant decrease. There were only 3 patients with initial gradients of < 40 mmHg who at follow-up study had gradients of 60 mmHg or more. Increases almost never occurred in patients over 12 years of age and most were likely to occur in patients under 4 years with initial gradients > 40 mmHg. All age groups included a few patients in whom a low initial gradient (40 mmHg or less) decreased through the years. There were no deaths, episodes of bacterial endocarditis, or central nervous system problems in those patients followed medically.

Of the 304 patients treated surgically, only 23 (7.5%) had gradients < 50 mmHg while 196 (65%) had gradients of 80 mmHg or more. More than 25% of the older children who underwent surgery were symptomatic and almost two-thirds had significant right ventricular hypertrophy on the electrocardiogram. In the era of this study, almost half the infants and 80% of the children were operated upon using cardiopulmonary bypass. There were

8 cardiac deaths (3%), all within the first 2 postoperative days. Six of these deaths occurred in patients < 1 week of age at surgery and only 1 was beyond infancy. All had severe pulmonary valvar stenosis with right ventricular pressure > 100 mmHg. Other than these deaths, surgery was successful in all but 10 patients. Of these 10, only 3 had been operated upon using cardiopulmonary bypass. For those who experienced significant relief of the obstruction, the postoperative drop in pressure gradient was both immediate and lasting, indicative of a gratifying surgical result. Thirty-eight patients experienced significant postoperative problems, the most frequent being the post-pericardiotomy syndrome. Persistent central nervous system complication was noted in one patient. No patient experienced postoperative bacterial endocarditis. We did not comment in this initial study on the effect of postoperative pulmonary regurgitation.[101]

The Report from the Second Joint Study on the Natural History of Congenital Heart Defects was published in 1993.[105,108] This follow-up study revealed that the probability of 25-year survival was 95.7%, similar to that of general population. The probability of survival was less (80%) in a subgroup of patients entering the first study > 12 years of age with cardiomegaly. Less than 20% of patients managed medically during the first study subsequently required intervention, and only 4% of operated patients required a second operation. Bacterial endocarditis was a rare complication.[120] Ninety-seven percent of patients were in New York Heart Association class I. Patients with gradients < 25 mmHg did not experience an increase in gradient, but it was recommended that those with gradients > 50 mmHg should undergo intervention. It was less clear about the need for intervention for those with gradients between 40 and 49 mmHg. Pulmonary regurgitation was assessed both clinically and by Doppler. In 310 patients in whom this assessment was made, 84 (27.1%) had no Doppler evidence of pulmonary regurgitation. Yet the clinicians labeled 184 patients (59.4%) as not having pulmonary regurgitation, thus underestimating its frequency. Among the 113 patients managed medically, the corresponding percentages were 51.3% and 89.4%, whereas among 197 surgically managed patients, they were 13.2% and 42.1%. No information was provided about the need for pulmonary valve replacement. Serious arrhythmias were uncommon in the pulmonary stenosis patients. Sudden unexpected death occurred in 0.5% of the patients, and this complication was substantially lower than in patients with aortic stenosis or with ventricular septal defect.[121]

Clearly one aspect of the more contemporary methodologies for assessing severity is the ability to assess serially changes in severity in patients, with pulmonary stenosis, especially young infants and children. Rowland and his colleagues have studied the natural history of 147 patients with pulmonary stenosis using serial Doppler examinations.[106] The age at the initial echocardiogram ranged from 2 days to 15 years, with a mean age of 14 months. The mean follow-up was 2.4 years. Seventy-one patients were aged ″ 2 months at presentation. Thirty-four of the 147 patients (34%) underwent an intervention, primarily a balloon valvuloplasty. Six of the 106 patients with trivial or mild pulmonary stenosis developed gradients > 60 mmHg. In most patients the final gradient of those followed medically was not significantly different from the initial evaluation. Twenty-one patients had an increase of > 20 mmHg. Sixteen of the 56 patients initially evaluated under 1 month of age had a ≥ 20 mmHg increase in their gradient. Only 4 of 59 patients evaluated initially between 1 month and 1 year and 3 of 32 evaluated over the age of 1 year had a 20 mmHg increase in their pulmonary stenosis gradient. Moderate gradients in the newborn infants were also likely to increase into the severe range, while such progression was less common in older infants and children with moderate obstruction on initial evaluation.

Anand and Mehta studied the natural history of asymptomatic valvar pulmonary stenosis in 51 infants diagnosed in infancy using two-dimensional echocardiography and Doppler method.[104] Of 40 infants, 6 asymptomatic infants (15%) showed rapid progression of pulmonary stenosis over a relatively short period of time. Within the first 6 months of life, 3 of the 6 infants showed worsening of the stenosis needing intervention (1 had surgical valvectomy and the others had percutaneous balloon valvuloplasty). The 3 other infants showed a more gradual increase of pulmonary stenosis over the first 2 years of life. This study showed that pulmonary stenosis even when mild can worsen in infancy, and it was not possible to predict which patients will follow this course. In their group of asymptomatic infants with initial mild pulmonary stenosis, 15% developed significant stenosis that needed intervention. On the basis of their observations they recommend frequent follow-up of asymptomatic infants with mild pulmonary stenosis during the first 2 years of life to detect rapid progression that may need intervention.

The natural history of moderate and severe pulmonary stenosis was forever changed by Russell Claude Brock (1903–80) who in 1948 reported 3 patients with pulmonary stenosis treated successfully by closed transventricular pulmonary valvotomy.[122,122A] These observations were then extended by Brock and Campbell in 1950 to 33 patients with ever-improving results, despite substantial mortality especially in those patients in congestive heart failure at presentation.[123] While the child and older patient could be managed with closed and then the open pulmonary valvotomy, the neonate with critical pulmonary stenosis presented what seemed like a formidable challenge. These babies were palliated with a variety of open and closed procedures, often in combination with a systemic-to-pulmonary artery shunt, but in the era before prostaglandin therapy, surgical mortality remained high.[27–29,66,67] In some neonates with critical pulmonary stenosis, mortality was attributed to the size of the right ventricle or infundibulum.[27] Yet most surgical series were relatively small, but over time surgical results did improve. Gersony and his colleagues reported in 1967 the results of surgical treatment of infants with critical pulmonary outflow obstruction.[124] The mortality for operated patients with pulmonary atresia and intact ventricular septum was 13 of 15 (87%) and 5 of 19 (26%) patients with critical pulmonary stenosis died.[116] Freed and his colleagues, also from the Boston Children's Hospital, extended these observations in 1973 to another 13 neonates, all with a diminutive right ventricle.[125] The results were considerably better in this experience, with only 1 late death. Most of the patients had been treated with either a transventricular or transpulmonary valvotomy, although several patients were treated with shunt alone, or a shunt following the valvotomy. Litwin and his colleagues also from Boston and also in 1973 reported their experience with 29 infants with critical pulmonary stenosis seen over the preceding decade.[126] All patients underwent a pulmonary valvotomy. In the initial part of the experience 12 babies underwent a blind valvotomy via a ventriculotomy and the remainder underwent a pulmonary valvotomy through a median sternotomy during a brief period of

normothermic inflow occlusion. Ideally the period of inflow occlusion is 2 min or less, and Litwin *et al.* stated that in most the inflow occlusion times ranged from 60 to 90s.[126] One infant required early in the postoperative period a Waterston anastomosis and a second baby required also early an infundibular resection and a right ventricular outflow patch. All patients survived the operation and there was late death $2^1/_2$ months postoperatively attributed to digitalis intoxication in the setting of hypokalemia.[126] In this center results were certainly excellent. Our experience was not as satisfactory. Coles and his colleagues reported in 1984 the results of surgical intervention in 36 consecutive neonates with critical pulmonary stenosis seen at the Toronto Hospital for Sick Children between January 1968 and March 1982.[127] A variety of surgical procedures were used, but the overall mortality was high at 42%. Caspi and his colleagues also from the Toronto Hospital for Sick Children extended these observations in 1990 to 39 neonates with critical pulmonary stenosis treated between 1982 and 1988 comparing the outcomes of surgical valvotomy to balloon valvuloplasty.[128] Thirty-nine patients (aged < 3 months) were treated initially by operation (group A, $n = 19$) or with balloon pulmonary valvotomy (group B, $n = 20$). Patients in group A were younger (5 (1.3 vs. 18 ± 4 days in group B) (mean ± standard error of the mean) and had a greater degree of hypoxia (oxygen tension, 55 ± 4 vs. 80 ± 6 mmHg) ($P < 0.05$ for all variables). Ten patients in group A and 8 patients in group B had right ventricular hypoplasia, based on an angiographically determined index. Balloon pulmonary valvuloplasty was attempted in 20 patients at the time of the initial catheterization but was unsuccessful in 9 owing to inability to catheterize the hypoplastic right ventricular outflow tract ($n = 8$) and severe infundibular stenosis ($n = 1$). Patients with failed balloon valvotomy were subsequently operated on within 24 h. The early operative mortality (< 30 days) was 25% (7 of 28); 1 death (9%) occurred after successful balloon valvotomy owing to associated critical aortic stenosis. The early postoperative gradient was 20 ± 2 mmHg; the post-balloon valvotomy gradient was 18 ± 3 mmHg. On the basis of this experience we concluded that balloon pulmonary valvotomy yields good results in patients with critical pulmonary stenosis with essentially normal-sized right ventricle, whereas surgical pulmonary valvotomy is required for patients with right ventricular hypoplasia. In retrospect this latter observation is incorrect as subsequent experience in Toronto and elsewhere with neonatal pulmonary valvuloplasty has shown.

Kirklin and Barratt-Boyes have reviewed in detail the surgical history of congenital pulmonary stenosis, presenting those closed and then open techniques to widen the congenitally stenotic pulmonary valve.[29] They mentioned the early experiences of Doyen in 1913 and Sellors in 1947 using the methodology of Doyen. Kirklin and Barratt-Boyes's data have shown nearly zero mortality in the current era for surgical pulmonary valvotomy for the infant and child or adult, excluding those with advanced congestive heart failure.[29] Surgical intervention for the child and older patients evolved from closed procedures to valvotomy performed using the technique of inflow occlusion to open techniques.[29,129] Gradually these techniques were applied to the critically ill neonate as well.[29] Intervention has evolved from the surgical theater to the catheter laboratory. Rubio-Alvarez *et al.*[130] initially described the technique by which pulmonic stenosis could be relieved by a catheter technique. Twenty-one years later Semb in 1979[131] using an inflated balloon-tipped angiographic catheter ruptured the valve when withdrawn from the main pulmonary artery to the right ventricle, reducing the outflow gradient. However, it was the introduction of the static balloon dilation by Kan *et al.*[132] in 1982 which fostered the application of this therapeutic modality to a greater audience. The technique has over the past two decades, become the "treatment of choice" for pulmonary valve stenosis at any age and with any valve morphology (Figs 13A-1, 13A-3).[133–171] The safety and efficacy of the technique in infants, children and adolescents has been confirmed by numerous studies summarized by McCrindle and Kan.[134] Thus the technology both to assess patients with pulmonary stenosis and the methodologies to treat this disorder continue to evolve.[141,166]

The Pediatric Cardiac Care Consortium has had considerable experience with the treatment of pulmonary stenosis.[103] Johnson has provided considerable information about the 1099 procedures carried out in the participating institutions between 1985 and 1993.[103] Of these 1099 procedures, 416 were operative procedures and 683 were percutaneous balloon pulmonary valvuloplasties. Of the 416 operative procedures, 215 were in infants < 12 months of age, 191 were children aged 1–21 years, and 10 were adults > 21 years of age. Overall, there were 18 deaths within 30 days following surgery, a mortality rate of 4.3%. At the time of operation the 215 infants ranged from 1 to 361 days, with a median age of 13 days. Operations were performed in 86 infants (40%) less than or equal to 1 week of age, 34 (16%) from 1 to 4 weeks, 36 (18%) from 1 to 3 months of age, 29 (13%) from 3 to 6 months of age, and 30 (14%) from 6 to 12 months of age. Overall mortality in the infants was 6.1% (13 of 215), and 8 of these were < 1 week of age. The mortality in this subgroup was 9.3%. Five of 129 infants operated on at an age > 1 week died (mortality = 3.9%). All the deaths in the infant group occurred in infants weighing < 5.0 kg, and mortality in those weighing < 3.0 kg was 15.4%. One hundred and ninety-one operative procedures were performed in children with a primary diagnosis of valvar pulmonary stenosis. In these 191 children a variety of operative interventions were performed, and 4 children died within 30 days of operation for a mortality in this group of 2.1%. One adult of the 10 patients over 21 years of age died. This was in a nearly 22-year-old individual with a dysplastic pulmonary valve who had undergone previous operations for complex left ventricular outflow tract obstruction. Pulmonary valve balloon valvuloplasty was performed in 683 patients, including 245 infants < 12 months of age, 391 children 1–21 years of age, and 19 adults. The overall mortality attributable to valvuloplasty in patients with isolated pulmonary stenosis was 0.15%. Some of the infants required a second procedure. Freedom from a second procedure for pulmonary stenosis treated in the first week of life was 66.1% and for those treated between 1 and 3 months of age, freedom from a second procedure was 82.6%. For those initially treated between 3 and 6 months, 92.7% did not require further intervention. A somewhat larger percentage of infants initially treated between 6 and 12 months of age required a second intervention (21.3%). Among the children 1–21 years of age, 391 patients underwent 407 balloon valvuloplasties from 1985 to 1994. There was 1 death among the 407 procedures, a 35-month-old infant who died secondary to cardiac perforation. Overall, freedom from a second pulmonary valve procedure was 93.5%. These data show that the majority of patients treated either surgically or with balloon valvuloplasty do very well. The surgical mortality of patients treated by members of the Pediatric Cardiac Care Consortium is comparable to other reports. As in

this and other reports, most of the mortality occurred in the younger patients, especially those under 4 weeks of age. Mortality rates for pulmonary balloon valvuloplasty are also very low, and these data are consistent with other contemporary reports. As we and others have demonstrated, balloon valvulopasty is less efficacious in those with dysplastic pulmonary valves, and many of these patients will require a further intervention, pulmonary valvectomy ± a transannular patch. McCrindle and his colleagues of the VACA Registry Investigators have assessed those independent predictors of long-term results after balloon pulmonary valvuloplasty.[148] When they compared patients with suboptimum results to those in whom the long-term outcome was good, they concluded that accurate prognostication after balloon pulmonary valvuloplasty depends on the careful determination of valvar anatomy. They go on to conclude that the use of an appropriate ratio of balloon to valve hinge point diameter in the setting of typical valve morphology should optimize the chance of long-term success.[148]

Kopecky and his colleagues reported in 1988 on the long-term outcome at 20–30 years of 191 patients who underwent surgical pulmonary valvotomy for isolated pulmonary valve stenosis at the Mayo Clinic between 1956 and 1967.[172] The mean age (± SD) at operation was 13.6 ± 13.1 years. An atrial septal defect was found in 42 patients and a patent foramen ovale in 30 patients. Eight patients died within 30 days of operation and 7 of these were 7 years old or younger. Of the 183 patients discharged from the hospital, the mean duration of follow-up was 23.9 ± 3.9 years. Late death occurred in 17 patients giving a mortality rate of 9.25% among survivors. Kaplan–Meier estimates of survival, excluding hospital mortality, were 99%, 96%, 95%, 92% and 90% at 5, 10, 15, 20, and 25 years, respectively. The mean age at death was 38 years, ranging from 5 to 65 years. Predictors of late death by univariate analysis were older age, higher preoperative right ventricular pressure, history of preoperative syncope, edema, or cyanosis, and the requirement for preoperative medical treatment. On multivariate analysis, only older age at operation and preoperative right ventricular pressure achieved statistical significance for late death. Multiple operative techniques were used in this series which was conducted well before the era of pulmonary balloon valvuloplasty, and certainly in the older patients with longstanding right ventricular hypertrophy, myocardial protection issues are germane.

Most of the surgical mortality and morbidity was identified in those neonates especially in the earlier eras of surgical intervention and before routine administration of prostaglandin. Mortality in these babies was substantial, no matter what therapy was employed. We have already commented on the contemporary management of the neonate with critical pulmonary stenosis, especially those patients who are prostanoid dependent before intervention. With adequate relief of the obstruction, most can be weaned from prostin therapy within a few days to 1–2 weeks. A few babies, despite adequate relief of the obstruction, will profoundly desaturate as the prostanoid therapy is weaned. This right-to-left shunting at atrial level has several potential etiologies: a stiff, non-compliant right ventricle; or perhaps a slightly small tricuspid valve orifice in the face of a muscle-bound right ventricle. For whatever reason, a few patients will require construction of a systemic-to-pulmonary artery shunt to alleviate the hypoxemia.[29] Hanley and his colleagues reported in 1992 for the Congenital Heart Surgeons Study the outcomes of 101 neonates enrolled in the 27 participating institutions between January 1, 1987 and January 1, 1991.[173] Numerous techniques were used to improve these critically ill neonates including balloon pulmonary valvuloplasty. Just before the first intervention, 70% of the patients were receiving prostaglandin therapy. The right ventricular–pulmonary trunk junction was severely narrowed in 15%. The right ventricular cavity size was severely reduced in 4%. The tricuspid valve was small in 15% of patients; its diameter was poorly correlated with right ventricular cavity size. Eighty-nine percent and 81% of patients survived 1 month and 4 years, respectively, after the initial surgical procedure. Multivariable analysis identified no patient-specific risk factors for death. Only open pulmonary valvotomy without a support technique was uniformly a procedural risk factor; under some circumstances, transannular patching without a shunt was a risk factor. The right ventricular-pulmonary trunk gradient immediately after valvotomy was < 30 mmHg in 81% of patients and was similar after surgical and balloon valvotomy. In 74% of patients, no intervention was required after the first accomplished intervention. This study demonstrated that marked variation in morphology is uncommon in neonates with critical pulmonary stenosis. (See Fig. 13.5.) Percutaneous balloon valvotomy and certain types of surgical valvotomy are optimal initial proce-

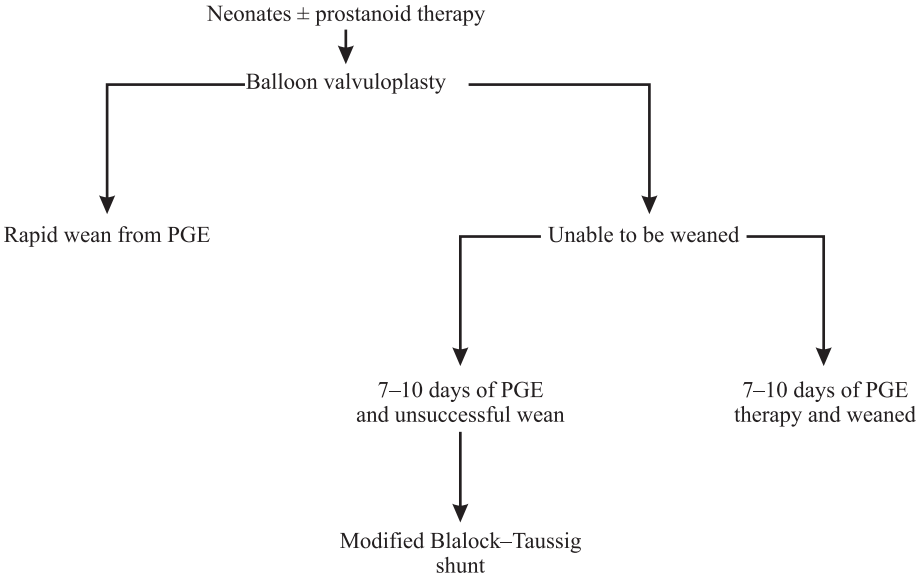


Fig. 13A-5 Course of neonates with critical pulmonary stenosis.

dures. The unusual situation of a small pulmonary "annulus" may initially require a transannular patch and a systemic-pulmonary artery shunt. Kirklin and Barratt-Boyes stated in 1993 survival for at least 4 years after birth in heterogeneous groups of neonates born with critical valvular pulmonary stenosis is about 80%.[29] They go on to state that in their experience at least 75% of neonates undergoing an accomplished pulmonary valvotomy require no further procedure. A few patients require a repeat valvotomy and about 10% require a transannular patch. In their experience about 2% cannot sustain a two-ventricle repair and a Fontan-type of operation or one-and-a-half ventricle repair will be required.[29]

Gildein and his colleagues reported on 18 neonates in whom pulmonary valvuloplasty was attempted.[174] The procedure was accomplished in 14 patients. The angiographically determined diameters of the pulmonary and tricuspid valves at the time of procedure were 5.6 ± 1.5 mm and 14.0 ± 5.4 mm. The mean Doppler gradient decreased from 71 ± 27 mmHg to 27 ± 14 mmHg. Perforation of the right ventricular outflow tract was the major complication in 3 patients with 1 fatal event. Infusion of prostaglandin E1 could be discontinued 1–5 days after the procedure. On follow-up, 3 children required a second balloon dilatation with good results. Seven patients monitored for > 9 months with a mean follow-up time of 34.4 ± 16 months had a residual gradient of 11.6 ± 6.7 mmHg. In spite of a hypoplastic pulmonary valve annulus in 7 of the patients, results were good and surgery could be avoided. We have studied the ventricular and valvular morphologic changes, hemodynamic consequences and clinical outcomes of pulmonary balloon valvotomy performed in the neonatal period.[22] We reviewed the outcome of 37 consecutive neonates undergoing attempted balloon dilation. Dilation was accomplished in 35 (94%) of 37 attempts. Immediately after dilation, the transvalvular peak-to-peak systolic gradient decreased from 60 ± 22 mmHg (mean ± SD, range 20–100) to 11 ± 10 mmHg (range 0–45) ($P < 0.0001$), and the right ventricular/aortic systolic pressure ratio decreased from 1.25 ± 0.43 (range 0.5–2.6) to 0.66 ± 0.22 (range 0.2–1.0) ($P < 0.0001$). Oxygen saturation measured by percutaneous oximetry increased from 80 ± 7% to 92 ± 4% ($P < 0.0001$). Three patients died (8%), and 2 required repeat balloon dilation. At the follow-up visit (median 31 months, range 6 months to 8 years), the estimated peak instantaneous Doppler gradient was 15 ± 9 mmHg (range 6–36). Thickening of valve leaflets, initially present in 93% of patients, was found in only 4%, and leaflet mobility improved in all. Hypoplasia of the right ventricle, initially present in 31%, was found in only 4% at the latest evaluation. Pulmonary annulus diameter Z score increased from –3 ± 1.0 to 0 ± 0.1 ($P < 0.0001$). Freedom from reintervention was 90%, 84% and 84% at 1, 2 and 8 years, respectively. Our data support the application of balloon valvotomy as the initial intervention in the treatment algorithm for neonates with critical pulmonary valve stenosis. Medium-term follow-up observations demonstrate sustained hemodynamic relief and support maturation of the right ventricle and pulmonary valve annulus, with the expectation of a good long-term outcome.[22] Others have also shown growth of the right ventricle after successful valvuloplasty. Whether the perceived changes reflect growth or remodeling, or some combination, is uncertain. Gildein and his colleagues have demonstrated growth of the pulmonary valve annulus after balloon dilatation of neonatal critical pulmonary valve stenosis.[25] Ten consecutive neonates with critical pulmonary valve stenosis who underwent balloon valvuloplasty were studied by serial echocardiography to assess growth of right ventricular structures at follow-up. The mean diameter of the pulmonary valve annulus increased from 6.1 ± 1.4 mm to 12.6 ± 3.5 mm (Z scores from –2.9 ± 1.0 SD to –1.3 ± 1.2 SD, $P < 0.0001$) after a mean follow-up period of 2.7 ± 2.0 years. The mean diameter of the tricuspid valve annulus increased from 12.9 ± 3.8 mm to 19.0 ± 3.1 mm; however, the respective Z score did not change significantly (from 0.5 ± 2.4 SD to –0.5 ± 1.0 SD). Right ventricular cavity size was hypoplastic in four patients initially and normal in all patients at latest follow-up. These findings indicate that balloon dilatation of critical pulmonary valve stenosis encourages catch-up growth of the pulmonary valve, and in this experience surgery can be avoided even in those with a hypoplastic pulmonary valve annulus. There is now a substantial literature describing techniques to cross the extremely stenotic valve of the neonate or young infant and the outcomes of valvuloplasty for critical aortic stenosis. For some years in the mid-to-late 1980s surgical valvotomy "competed" with balloon valvuloplasty as therapeutic strategies, but by 1990 most centers had adapted balloon valvuloplasty as the procedure of choice for patients with pulmonary stenosis at any age. In this regard, Castaneda and colleagues did not discuss the management of pulmonary stenosis in their book devoted to cardiac surgery of the neonate and infant, the inference that this problem was in the domain of the interventional pediatric cardiologist.[174A] Gournay and associates have reviewed the outcomes in 97 newborns (82 with critical pulmonary valve stenosis, 15 with atresia) who underwent balloon valvotomy, provided that they had a well-developed right ventricle, including an infundibulum close to the pulmonary artery.[175] In patients with atresia, the outflow tract membrane had to be perforated with a wire needle or a radiofrequency probe. Balloon valvotomy could be performed in 81 patients and was effective in 77. It caused 3 fatal and 16 nonfatal complications. Ten patients with persistent poor right ventricular compliance despite an effective valvotomy required a surgical shunt. Among the 81 patients in whom the procedure could be performed, right ventricular surgery was avoided in 5 (55%) of the 9 patients with atresia (95% confidence interval [CI], 28% to 80%) and 55 (76%) of the 72 patients with stenosis (95% CI, 66% to 86%) at the end of the follow-up period (9.7 years). This group found that balloon pulmonary valvotomy was not always feasible in newborns, but it was relatively safe and effective. Colli and her colleagues reviewed their experience between 1985 and 1992 with 36 consecutive neonates, aged 1–29 days, weighing 2.4–5.0 kg, with critical valvar pulmonary stenosis who underwent attempted balloon dilation.[21] At catheterization, 30 were on prostaglandin (PGE_1) therapy and 20 were intubated. The valve was successfully crossed and dilated in 34/36 (94%), including three with an echocardiographic diagnosis of valvar pulmonary atresia and a right ventricle of adequate size. The valve was first dilated with a 2- to 5-mm balloon and then with serially larger ones (up to 12 mm) to a final balloon/annulus value of 126%. The RV/systemic pressure value fell from 150 ± 32 to 83 ± 30%, oxygen saturation rose from 91 ± 6% to 96 ± 4%, and PGE_1 was discontinued at the end of the procedure. There were 11 complications (31%) including 1 early death from sepsis and necrotizing enterocolitis, endocarditis in another, 2 myocardial perforations, 1 femoral-iliac vein tear, and 1 transient pulse loss. A repeat balloon dilatation was carried out in 5 patients, 2 of whom subsequently had surgery. At follow-up (33 ± 23 months), the 31 patients managed by balloon dilatation alone were well and had echocardiographic gradients of < 30 mmHg in 90% and pulmonary regurgitation, considered mild in most, in 52%.

Table 13A-1 Hemodynamics before and after balloon valvuloplasty

	Before dilation	After dilation
RVP	88 ± 22 (range 37–40)	46 ± 14 (range 19–122)
PAP	40 ± 16 (range 14–85)	39 ± 13 (range 18 -86)
SAP	63 ± 10 (range 38–100)	66 ± 14 (range 30–113)

RVP, right ventricular pressure; PAP, mean pulmonary artery pressure; SAP, mean systemic arterial pressure.

We have reviewed our balloon valvuloplasty experience with 111 neonates 28 days of age or younger seen from September 1985 to October 2002. There were 47 females and 64 males. The mean age at procedure 6.6 ± 6.6 days of age, with mean weight of 3.43 ± 0.86 kg. Table 13A-1 shows the immediate hemodynamic response. Figure 13A-6 depicts the acute change in right ventricular pressure before and immediately after balloon valvuloplasty. The change in systolic pressure gradient before and after balloon valvuloplasty is shown in Fig. 13A-7. The pulmonary valve diameters ranged from 3 to 11 mm, with a mean valve diameter of 7 ± 1 mm. The valve morphologies were as follows: 1 unicuspid, 2 bicuspid, 17 dysplastic, 79 tricuspid, and 12 unknown. For the entire cohort, there was 1 death, 2 procedures were abandoned, and 1 non-life-threatening ventricular perforation occurred. Follow-up information was available for 66 patients the average echo RV to PA gradient was 16 ± 9 mmHg with follow-up from 6 months to 10 years. No patient with typical PVS needed surgery. Three patients (of 7) with a dysplastic valve required later a surgical valvotomy, and 2 patients (one with subvalve stenosis, and one with supravalve stenosis) also required surgery. In 1 neonate a so-called congenital aneurysm of the membranous septum spontaneously ruptured after successful balloon dilatation. This was attributed to chronic mechanical trauma with phasic protrusion and collapse of the aneurysm during the cardiac cycle.[174B]

There is relatively little information on the fate of tricuspid regurgitation in the neonate with critical pulmonary stenosis. The tricuspid valve may be dysplastic, displaced, or in an occasional patient a true cleft may be present. Structural abnormalities of the tricuspid valve are less common and usually less severe than in the patient with pulmonary atresia and intact ventricular septum. In both conditions, however, ischemic damage to the right ventricular papillary muscles may contribute to functional disturbances in tricuspid valve function. Usually, subsequent to a successful balloon pulmonary valvuloplasty and relief of the severely after-loaded ventricle, tricuspid regurgitation will improve, often resolving completely, or nearly so. Some patients will continue to have tricuspid regurgitation, occasionally severe, after successful valvuloplasty. Even with maturation of the pulmonary vascular bed, in some patients little improvement will be observed. In these patients, post-valvuloplasty pulmonary regurgitation by virtue of right ventricular volume loading and annular dilatation can further aggravate the severity of the tricuspid regurgitation. These patients may be very difficult to treat, especially if they remain prostin-dependent. We have seen a few patients who will benefit from surgical tricuspid valvuloplasty, combined with positioning of a homograft valve in the pulmonary position to maintain pulmonary valve competency. Sometimes these patients when several months of age or more will benefit from a bidirectional cavopulmonary shunt to reduce the right ventricular volume.

Longstanding and severe valvar pulmonary stenosis by virtue of promoting severe right ventricular hypertrophy may result in secondary and important infundibular obstruction.[67–73] Usually with relief of the valvar component of the obstruction, the secondary changes in the infundibulum regress.[67–73] These initial observations about regression of infundibular obstruction were published in 1958 by Engle and her colleagues.[71] Sometimes, however, relief of the valvar component results in very severe dynamic infundibular obstruction. This can usually be managed with beta-blocker therapy, although historically some centers performed both a surgical pulmonary valvotomy and infundibular resection.[29,67–73] Subsequent experience showed that some patients did require an infundibular resection and a ventricular patch.[29]

One consequence of surgical valvotomy/valvectomy or balloon valvuloplasty, especially with oversized balloons, is pulmonary regurgitation.[17,22,25,29,134–139,142,145,149,150,154,155,165,168,176–178] The reported incidence of pulmonary regurgitation after surgical valvotomy or balloon valvuloplasty varies considerably from as low as 10–50% or more according to studies cited by Kirklin and Barratt-Boyes.[29] For many years it was thought that

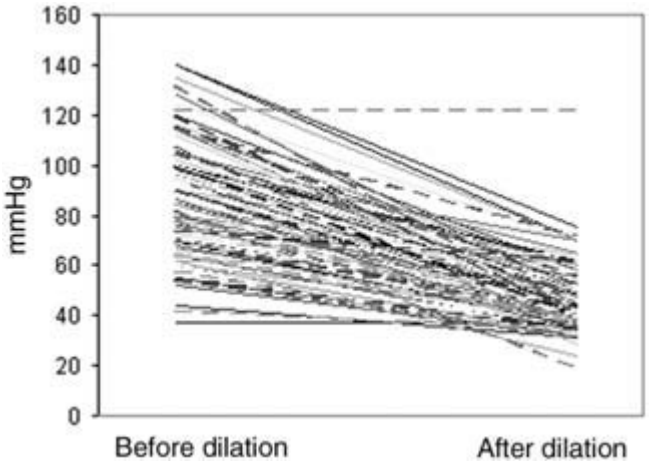


Fig. 13A-6 Right ventricular pressure before and after dilation.

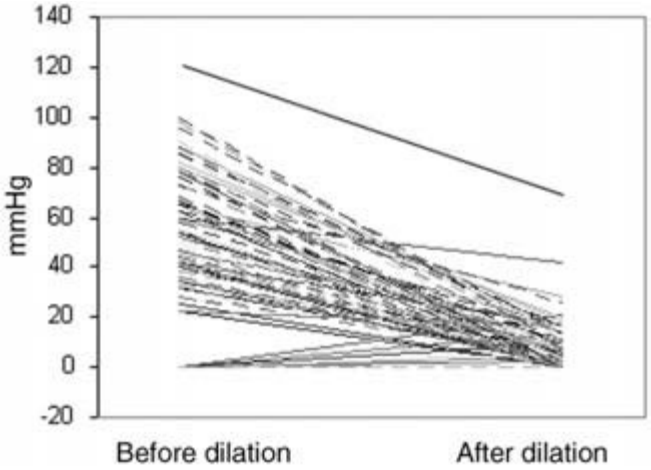


Fig. 13A-7 Pressure gradient across the pulmonary valve before and after dilation.

such pulmonary regurgitation would be well tolerated. This is likely not so. The effect of longstanding pulmonary regurgitation in isolation was shown by Shimazaki and his colleagues some years ago.[179] They searched the literature for case reports of patients with isolated congenital pulmonary valve incompetence and produced an actuarial analysis for freedom from symptoms in the 72 patients identified. The actuarial freedom from symptoms was 77% at 37 years, 50% at 49 years, and 24% at 64 years. Clearly there are problems with this methodology, but the data still convey appropriate concerns about the effect of longstanding pulmonary regurgitation on right heart form and function. While some adults with isolated congenital pulmonary valve incompetence may be asymptomatic, others demonstrating progressive right ventricular dilatation may experience a wide range of clinical symptomatology and may be candidates for pulmonary valve replacement or repair. In the long-term follow-up of surgical pulmonary valvotomy from the Mayo Clinic, pulmonary insufficiency was not associated with late death.[172] For the majority of patients with pulmonary stenosis, mild and untreated or those who have undergone surgical valvotomy/balloon valvuloplasty, the quality of life is excellent.[180] Exercise tolerance is well preserved, but in the majority of patients remained subnormal.[181,182]

Thus, there are data to support progression of mild to severe pulmonary stenosis in infancy, and careful surveillance of even the asymptomatic infant with mild stenosis is warranted. While progression is much less likely in the older infant or child with mild stenosis at initial evaluation, more concerning progression has been infrequently noted. For those babies undergoing valvuloplasty for critical pulmonary stenosis, some will require an additional procedure, perhaps as many as 20–30%.[164] Fortunately in the majority of older infants, children and adolescents requiring a balloon intervention, the effect is prompt in reducing the gradient and long-lasting. A few patients with longstanding and particularly severe obstruction may require a surgical infundibulectomy. Pulmonary regurgitation is common after successful balloon valvuloplasty, especially when oversized balloons have been used. There is sparse clinical information on the impact of chronic and important pulmonary regurgitation on the fate of the right ventricle of these patients (unlike the situation in the postoperative tetralogy patient – see Chapter 16). However the data provided by Shimazaki and colleagues are worrisome in this regard.[179]

In long-term follow-up, whether operated, ballooned, or followed without intervention, there is always the potential for progression in severity, especially those presenting in infancy or childhood with moderate disease. Infective endocarditis is rare no matter what the severity. Longstanding acquired pulmonary regurgitation, especially if moderate to severe, is unlikely to be well tolerated over many years, and certainly some patients may require pulmonary valve replacement. The ability to percutaneously insert a pulmonary valve as performed by Bonhoeffer and colleagues may prove extremely beneficial to these and other patients, perhaps facilitating earlier intervention.[182A] These patients require lifelong surveillance with particular attention placed on heart size, right ventricular and tricuspid valve function, serial exercise tests, and periodic screening with ambulatory recordings for atrial or ventricular tachydysrhythmias.

In summary:

- Beyond infancy, mild congenital pulmonary stenosis tends not to progress in severity.
- Clinical findings in concert with Doppler studies permit excellent serial non-invasive assessment of severity.
- Intervention for congenital pulmonary valvular stenosis has evolved from surgery to catheter-based intervention.
- Balloon valvuloplasty for patients ≥ 2.0 years provides excellent outcomes.
- Most consider systolic pressure gradients between 40 and 50 mmHg indication for intervention.
- Balloon valvuloplasty with oversized balloons especially in neonates tends to induce important pulmonary insufficiency.
- Longstanding pulmonary insufficiency may not be well tolerated.[179]
- Congenital pulmonary valvular stenosis secondary to a dysplastic pulmonary valve may require surgery with valvectomy ± a transannular patch in those with a small annulus.
- Balloon valvuloplasty is the procedure of choice for critical pulmonary stenosis in the neonate.
- The neonate may require a prolonged course of prostin therapy until the right ventricle becomes more compliant. Some babies may require a Blalock–Taussig shunt or ductal stenting to augment pulmonary blood flow.
- Most neonates will eventuate in a biventricular repair. Those with the smallest right ventricle and a small tricuspid valve may be candidates for a one-and-a-half ventricle repair.

Congenital pulmonary insufficiency

Isolated congenital insufficiency of the pulmonary valve is a rare condition. The basis for the valvular deficiency may reflect complete absence of pulmonary valve leaflets, rudimentary vestigial leaflets that do not coapt or isolated deficiency of one of the pulmonary valve leaflets. When there is congenital absence or near absence of the pulmonary valve, the clinical manifestations of this anomaly are diverse.[18,183–185] At one end of the continuum, congenital absence of the pulmonary valve in isolation has the potential for producing fetal heart failure, hydrops and death.[186–189] Yet the functional disturbance may be well tolerated into the seventh or eighth decades of life.[190,191] There

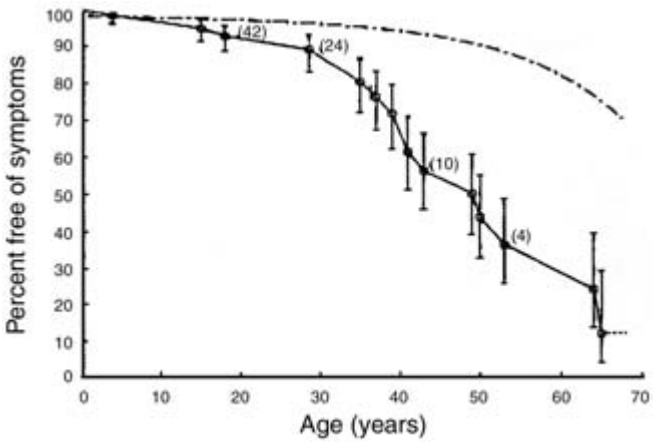


Fig. 13A-8 Actuarial freedom from symptoms in patients with congenital pulmonary valve incompetence ($n = 72$, 17 events). The vertical bars enclose the 70% confidence limits. The numbers in parentheses indicate the number of patients traced beyond the indicated age. The dash-dot-dash line is the actuarial survival of the US general population, starting at birth. (Reprinted from Shimazaki *et al*.[179] with permission from Georg Thieme Verlag.)

are ample data showing that pulmonary regurgitation is not benign, and its impact on the functionality of the right ventricle must be anticipated. The effect of longstanding pulmonary regurgitation in isolation was shown by Shimazaki and his colleagues some years ago.[179] They searched the literature for case reports of patients with isolated congenital pulmonary valve incompetence and produced an actuarial analysis for freedom from symptoms in the 72 patients identified. The actuarial freedom from symptoms was 77% at 37 years, 50% at 49 years, and 24% at 64 years (Fig. 13A-8). Clearly there are problems with this methodology, but the data still convey appropriate concerns about the effect of longstanding pulmonary regurgitation on right heart form and function. While some adults with isolated congenital pulmonary valve incompetence may be asymptomatic, others demonstrating progressive right ventricular dilatation may experience a wide range of clinical symptomatology and may be candidates for pulmonary valve replacement or repair.[192] Finally one should remember that some fetuses may have congenital absence of both semilunar valves, a situation usually associated with fatal fetal hydrops.[188,193] We are not aware of a successful outcome for such a patient.

All references can be found at the end of the book. See pp. 652–7 for Chapter 13A.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

13B

Kalyani R. Trivedi and Lee N. Benson

Peripheral Pulmonary Artery Stenosis

Introduction

Peripheral pulmonary artery stenosis may occur in isolation, as a component of a somatic syndrome, within the constellation of a congenital heart lesion or be acquired. It is the Achilles' heel of numerous therapeutic algorithms for management of a variety of congenital heart malformations. The impact of pulmonary artery stenosis on clinical outcomes depends on its severity and the milieu in which it presents. A number of treatment modalities are available to address these lesions, each with its own impact on care.

Morphology and classification

The spectrum of peripheral pulmonary artery stenosis was classified by Gay *et al.*,[1] dividing the lesion into four forms of stenosis (Fig. 13B-1). In type I, the lesion is a single constriction of varying length, confined to the main, right or left pulmonary arteries. The constriction can vary from a membranous diaphragm within the vessel, to an elongated obstructive lesion. Type II lesions occur at the pulmonary artery bifurcation, with involvement of the distal end of the main pulmonary artery and the origins of right and left pulmonary arteries. The extent of the lesion can vary from a short localized stenosis to long segment obstruction. A type III lesion is a stenosis of multiple segmental pulmonary arteries at their ostium, with prominent poststenotic dilation. The main and the proximal branch pulmonary arteries are normal. A type IV lesion consists of multiple stenoses involving the peripheral segments as well as the central pulmonary arteries.

Incidence

Peripheral arterial stenosis occurs in 2% to 3% of patients with congenital heart disease. It may occur in isolation (40%), in association with other congenital heart lesions, be a component of a syndrome, or may be acquired (Table 13B-1).[1] Associated congenital heart lesions include valvar pulmonary stenosis, atrial or ventricular septal defects, the patent arterial duct or Fallot's tetralogy (20%). Indeed, nearly every type of congenital cardiac defect has been reported with peripheral pulmonary artery lesion.[2]

Acquired lesions occur commonly following palliative or reparative surgical interventions although the precise incidence is not apparent. It has been reported with systemic to pulmonary artery shunts,[3,4] pulmonary artery banding,[5] pulmonary artery unifocalization in the setting of pulmonary atresia with ventricular septal defect,[6] the arterial switch operation for transposition of the great arteries or for double outlet right ventricle with a subpulmonary ventricular septal defect[7–11] and surgical staging for univentricular palliation.[12,13] It has also been seen in rare instances of fibrosing mediastinitis or mediastinal tumors that cause stenosis by external compression.[2,14–17,18]

Palliation by a modified Blalock–Taussig shunt with polytetrafluoroethylene can result in pulmonary artery hypoplasia, discrete stenosis or vessel distortion (tenting) (Fig. 13B-2).[3] Gladman *et al.* identified that a third of patients with Fallot's tetralogy had significantly smaller distal right pulmonary arteries when palliated with a Blalock–Taussig shunt before total repair from an angiographic review of 65 palliated vs. 68 nonpalliated patients. Neonatal palliation was associated with significantly smaller right pulmonary arteries before repair, which necessitated additional transcatheter or surgical intervention.[4]

The size and growth of the pulmonary arteries after the neonatal arterial switch operation for simple transposition of the great arteries was studied in 67 patients by cardiac catheterization, an average of 14 months after surgery, by Massin and colleagues.[10] The diameter of the main pulmonary artery and that of its proximal right and left branches were measured and compared to those of normal children matched for body surface area as well as with the measurements on preoperative angiograms available in 34 patients. The cross-section of the main pulmonary artery after arterial switch operation using the LeCompte maneuver was found to be oval in shape with the branch pulmonary arteries underdeveloped. The LeCompte maneuver flattens the main pulmonary artery with a reduction in its cross-sectional area and due to stretching, the branch vessels become obstructive, with accompanying growth retardation (Fig. 13B-3).[10] Double outlet right ventricle with a subpulmonary ventricular septal defect managed with an arterial switch operation was also found to be associated with pulmonary artery stenosis in 7 of the 27 patients reported by Masuda from Japan.[11]

Pulmonary arterial stenosis occurs with enough frequency, in a number of syndromes (Table 13B-2), such that it has become an expected component within their constellation of findings. The most notable examples include the Williams–Beuren syndrome and Alagille syndrome (Fig. 13B-4).

Genetics

The genetic basis of several somatic syndromes associated with pulmonary arterial stenosis has been characterized (Table 13B-2). The Williams–Beuren syndrome is a neurodevelopmental

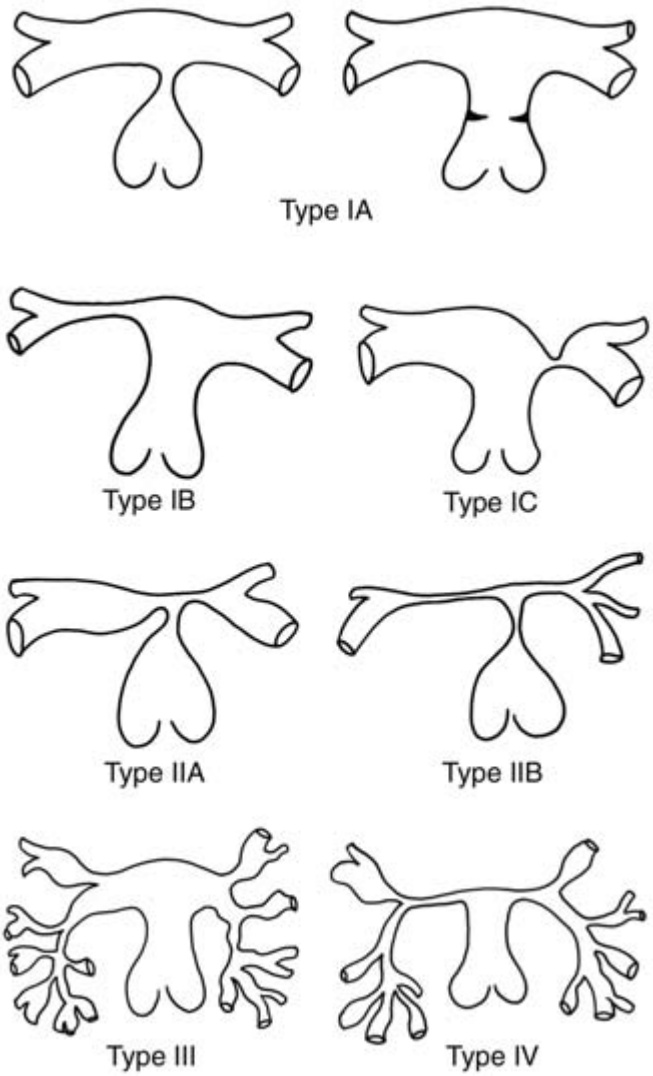


Fig. 13B-1 Classification of peripheral pulmonary artery stenosis by Gay *et al.* Type I: single central stenosis of varying length confined to the main pulmonary artery trunk (A), the right main pulmonary artery (B) or left main pulmonary artery (C). Type II: bifurcation stenosis involving short, localized segments (A) or rather long segments (B). Type III: multiple peripheral stenosis. Type IV: central and peripheral stenosis (Reprinted from Gay *et al.*[1] with permission from the American Journal of Roentgenology.)

disorder first described by JCP Williams[19] and AJ Beuren[20] as an association of supravalvar aortic stenosis and pulmonary artery stenosis, a distinctive facial appearance and growth and developmental delay. Most cases are sporadic, and result from a contiguous gene deletion on chromosome 7q11.23 that results in hemizygosity of the elastin gene.[21,22] The insufficiency of elastin gene results in an abnormality in the gene product tropelastin, which participates in vascular elastic fiber architecture. The vascular abnormalities of the syndrome, most common being supravalvar aortic stenosis followed by the pulmonary lesion, result from these elastin architectural abnormalities.[23,24] Stenosis of the more peripheral pulmonary arteries may also occur.

Alagille syndrome is a genetic disorder that is inherited in an autosomal dominant trait with variable expression.[22] It has been

Table 13B-1 Peripheral pulmonary artery stenosis (% with pulmonary artery stenosis)

Isolated lesion
Syndromes
Williams–Beuren syndrome (39–83%)
Alagille syndrome (70–85%)
Congenital heart defects
Valvar pulmonary stenosis (30%)
Atrial septal defect (15%)
Ventricular septal defect (15%)
Tetralogy of Fallot (15%)
Acquired
Post surgery
Traumatic/associated systemic illness

mapped to chromosome 20p12 with a point mutation of JAGGED1 gene, which is linked to the phenotype.[25–28] The phenotype consists of five major features including a paucity of interlobular bile ducts, pulmonary artery lesions, an eye anomaly (called posterior embryotoxon), hemivertebrae and peculiar facies.[29] The pulmonary artery stenosis can occur in up to 70% to 85% of the patients.[29–31] In a recent report from Emerick *et al.*, of the 73 patients examined, pulmonary artery stenosis was found in 55% and intracardiac lesions in 71%.[32] The pulmonary arterial lesions in Alagille syndrome are usually bilateral and extend distally into the interlobular branches and may be diffuse or focal in distribution.

Right heart obstructive lesions are also commonly associated with syndromes such as the DiGeorge syndrome, the velocardiofacial syndrome and the conotruncal face anomaly syndrome.[33] The combination of dysmorphic features, palatal

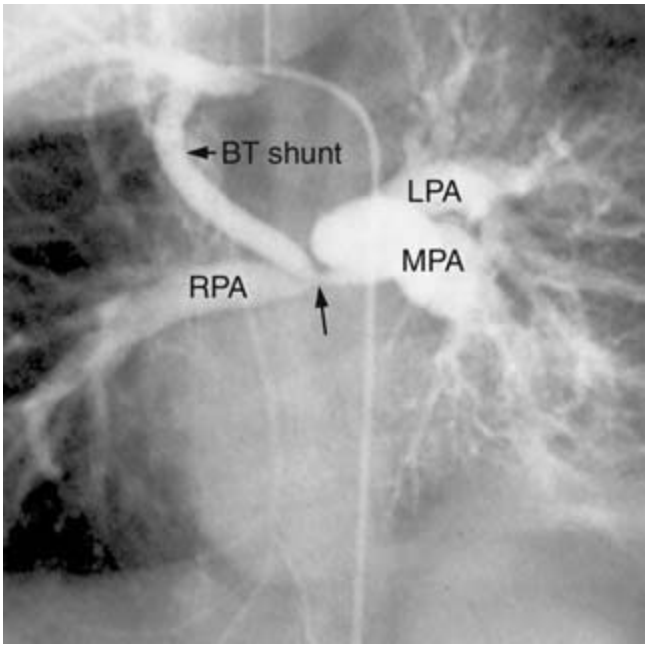


Fig. 13B-2 Angiogram showing distortion of the pulmonary artery due to a right modified Blalock–Taussig (BT) shunt. LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

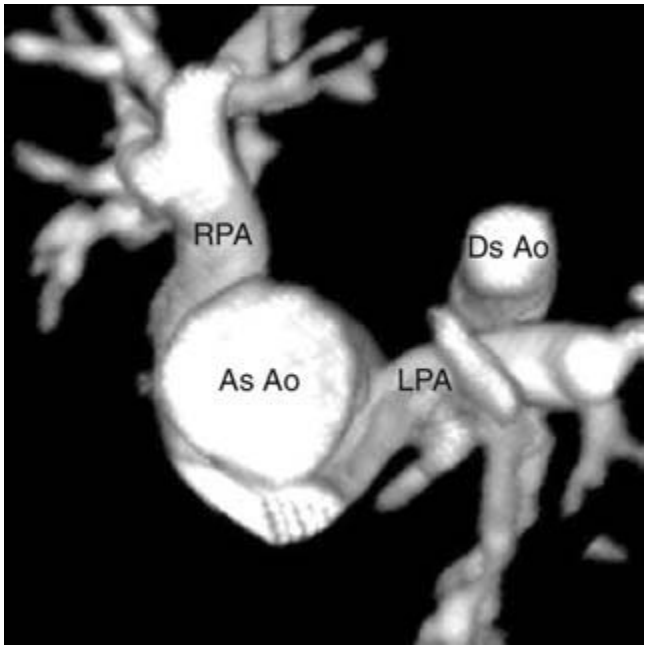


Fig 13B-3 Three-dimensional MR reconstruction showing the LeCompte maneuver, bringing the main pulmonary artery anteriorly to complete the arterial switch procedure. Note how the pulmonary artery bifurcation and branches can be tethered and become taut. As Ao, ascending aorta; Ds Ao, descending aorta; LPA, left pulmonary artery; RPA, right pulmonary artery.

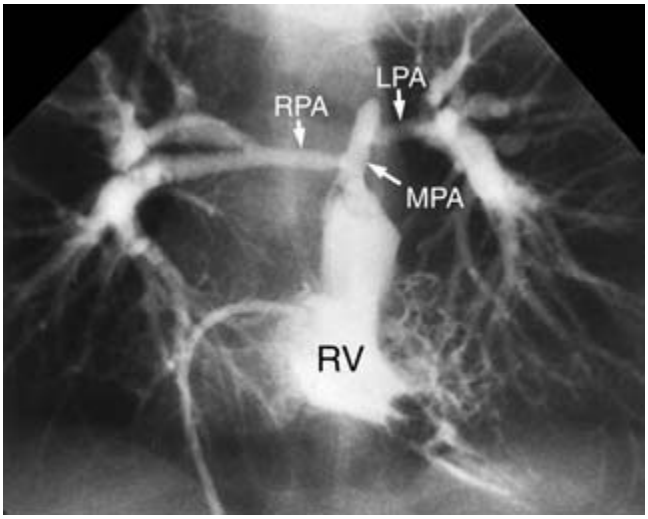


Fig. 13B-4 Angiogram of a patient with peripheral pulmonary arterial stenosis. Note the diffuse nature of the lesion. LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery; RV, right ventricle.

abnormalities, thymic hypoplasia, parathyroid hypoplasia, and cardiac defects has been termed DiGeorge syndrome. The thymic, parathyroid, and cardiac defects result from developmental abnormalities of the third and fourth branchial arches and neural crest. The velocardiofacial syndrome and the conotruncal face anomaly syndrome have similar findings and are clinically grouped with DiGeorge syndrome as the CATCH 22 disorders. The two types of defects associated with these syndromes are conotruncal defects and branchial arch mesenchymal tissue defects. Among conotruncal defects, common arterial trunk is the most common type. Among the branchial arch mesenchymal tissue defects, interrupted aortic arch type b and right aortic arch are the most common. Other lesions include tetralogy of Fallot, double outlet right ventricle, transposition of the great arteries and absent pulmonary valve syndrome. Pulmonary artery stenosis may be found as an associated lesion in any of these cardiac disorders.

Multiple etiologies for DiGeorge syndrome have been found, including chromosome abnormalities, single gene defects, and teratogenic exposures. Approximately 15% of infants with DiGeorge syndrome can be found to have obvious chromosome abnormalities, of which about two-thirds involve a monosomy 22q11. This usually results from an unbalanced translocation involving chromosome 22 and another chromosome. FISH analysis with probes from the critical region has shown that a total of 85% of DiGeorge syndrome patients carry deletions in 22q11. It is likely that haploinsufficiency of one or more of the genes in this locus contribute to the etiology of this disease.

Outcomes in peripheral pulmonary arterial stenosis

The newborn

Pulmonary artery stenosis frequently seen in the newborn is a physiologic stenosis due to relative hypoplasia of the branch

Table 13B-2 Somatic syndromes associated with peripheral pulmonary artery stenosis

Syndrome	Etiology
CATCH -22 syndromes [33]	
DiGeorge syndrome	Monosomy 22q11
Velocardiofacial syndrome	
Williams–Beuren syndrome[21,22]	Insufficiency of elastin gene (7q11.23)
Alagille syndrome[25–28]	Mutation of JAGGED1 gene (20p12)
Keutel syndrome[112,113]	Mutations in the gene encoding for human matrix Gla protein (12p12.3–13.1)
Noonan syndrome[114]	Mutation of the PTPN11 gene (12q24)
Cutis laxa[115,116]	Mutation of the elastin gene (7q11.23)
Congenital total lipodystrophy[117]	
Congenital rubella syndrome[2,20,29,117,113]	Intrauterine viral infection

pulmonary arteries. It resolves rapidly with growth, by 6 months of age in most instances.[34–39]

Chatelain and colleagues[35] studied 21 neonates to determine the etiology of transient systolic murmurs that are frequently heard in the group. They compared the group to 10 controls by echocardiography and found that the diameters of the main, right and left pulmonary arteries were smaller in patients with murmurs. Color Doppler study showed turbulent flow in both branch pulmonary arteries in 20 (95%) of the babies with heart murmurs and flow velocities of both pulmonary branches were significantly higher than in controls. The follow-up study at 3 months in 14 (67%) of the 21 study patients revealed an absent or decreased murmur in 9 (64%). Echographically, absolute and relative diameters of the left and the right pulmonary arteries had increased with a significant decrease in flow velocities. They also reported that the ratio of main pulmonary artery to aorta did not change, suggesting accelerated growth or dilatation of the pulmonary artery branches. They concluded that transient systolic murmurs in neonates are associated with relative hypoplasia of the pulmonary branches, which demonstrate an increased growth leading to disappearance of the murmur in most cases, within 3 months of life.

Miyake and colleagues[38] studied 4 term infants with transient murmurs with characteristics of pulmonary artery stenosis (grade 3/6 systolic ejection murmur transmitted clearly to the precordium and the back). The murmur was detected 7 days after birth in 1 infant and at a 1-month medical check up in the other 3. The murmur continued for 7 to 22 weeks, with an average of 12 weeks with gradual localization in the region of the left sternal border followed by eventual disappearance. A peak velocity of over 2 m/s in the left or right pulmonary artery was detected from the pulsed Doppler examination at presentation. The diameter of the right pulmonary artery was a mean of 58 ± 8% (range 46–64%) of predicted normal. At follow-up examination, when the heart murmur had disappeared, the diameter of the right pulmonary artery was a mean of 97 ± 28% (range 70–126%) of the predicted normal and the peak velocity in the right pulmonary artery had also decreased significantly to under 1.5 m/s.

So and colleagues,[39] assessed the hemodynamics at the bifurcation of the main pulmonary artery using Doppler echocardiography. Peak velocities within the main and the right pulmonary arteries and the ratio of the velocity across the right to the main pulmonary artery were studied in 25 low birth weight infants who presented with a systolic murmur. A compatible control group of 25 healthy low birth weight infants without a murmur were also examined. The initial main pulmonary artery velocity was 80 ± 21 (range 51–152) cm/s in the heart murmur group and 81 ± 14 (range 60–111) cm/s in the control group ($P > 0.05$). The initial right pulmonary artery velocity was 193 ± 60 (range 118 to 388) cm/s in the group with the heart murmur and 100 ± 16 (range 76 to 132) cm/s in the control group ($P < 0.0001$) The initial ratio of the right to the main pulmonary artery velocity was 2.5 ± 0.6 (range 1.6 to 3.9) and 1.3 ± 0.1 (range 0.9 to1.5) in the heart murmur group and in the control group, respectively ($P < 0.0001$). When the murmur disappeared after a period of 2–5 months, there was no significant difference in the right pulmonary artery velocity or the ratio of right to the main pulmonary artery velocity between the two groups. The right pulmonary artery velocity in the heart murmur group reduced significantly to 119 ± 17 cm/s, and as did the ratio to 1.2 ± 0.1 ($P < 0.0001$). Thus, healthy premature infants have physiological stenosis at the pulmonary artery bifurcation at about 1 month of age. The velocity in the right pulmonary artery is higher than the velocity in the main pulmonary artery and the ratio of the right to the main pulmonary artery velocity is usually over 1.5 but eventually both fall to normal levels, with disappearance of the heart murmur.

The main and the branch pulmonary arteries were examined by an echocardiogram in 114 term consecutive healthy neonates aged 1–6 days by Du and colleagues[36] with Doppler flow estimates of pressure gradients across the vessels. In the 30 neonates with pressure gradients above 2.5 mmHg, the peak velocities in the right and the left pulmonary artery (1.2 ± 0.2 and 1.0 ± 0.2 m/s) were significantly higher than that in the main pulmonary artery (0.84 ± 0.13 m/s; both $P < 0.001$). The gradient in the right was slightly higher than in the left pulmonary artery ($P < 0.001$). There was an estimated pressure gradient of 2.5–8.3 mmHg between the main and the right pulmonary arteries in 43% and of 2.5–6.6 mmHg between the main and the left pulmonary arteries in 17% of all neonates. The gradients disappeared within 3–6 months in 12 (40%) of the 30 neonates with an initial gradient above 2.5 mmHg. The authors concluded that the differences in blood flow velocities or pressure gradients could be considered a physiological characteristic in neonates.

Arlettaz and colleagues,[34] studied 50 healthy term newborn infants with a clinical diagnosis of an innocent murmur and 50 babies without a murmur who served as controls with a complete two-dimensional and pulsed Doppler echocardiogram. Branch pulmonary artery stenosis was found in 25 (50%) babies of the group with a heart murmur and 6 (12%) babies of the control group. At 6 weeks the murmur had disappeared in 64% of babies. Branch pulmonary artery stenosis was still present in 8 of 22 (36%) babies at 6 weeks, in 12% at 3 months, but in none at 6 months. At 6 weeks, 7 of the 8 with branch pulmonary artery stenosis still had a murmur compared with 2 of 14 (14%) babies in which the stenosis had resolved ($P < 0.005$). They found that an innocent heart murmur in a term baby is often related to branch pulmonary artery stenosis, particularly if the murmur is still present after 24 h of age. At 6 weeks the murmur disappears and the branch stenosis resolves in up to 64% of the babies while complete resolution occurred in all babies by 6 months.

Kiyomatsu *et al.*,[37] studying 50 neonates with heart murmurs first noticed at 6 to 60 days after birth (mean 33 ± 14) and 50 controls without heart murmurs also concluded that transient heart murmurs in the late neonatal period are caused by branch pulmonary arteries stenosis that was transient. They examined serially the morphology of and the blood flow in the main, the right and the left pulmonary arteries using two-dimensional and Doppler echocardiography. The diameters of the right and the left pulmonary artery in the heart murmur group were significantly smaller and the blood flow velocity significantly greater in the right and the left pulmonary artery as compared to the control group. At the time of disappearance of the heart murmur, the diameters and the flow velocities of the right and the left pulmonary artery were not different, compared with the control group. The two cases that had persistent heart murmurs were diagnosed as having intrinsic congenital peripheral pulmonary artery stenosis.

Peripheral pulmonary artery stenosis and the arterial duct

Pulmonary arterial stenosis may develop in the left pulmonary artery in relation to closure of the arterial duct with or without the presence of congenital cardiac defects (Fig. 13B-5).[37–43] The incidence of a pulmonary arterial lesion can be as high as 36% in patients with right heart obstructive lesions such as pulmonary atresia or stenosis while the prevalence in autopsy cases is about 30%.[43] It may also occur with other complex intracardiac defects. An etiologic similarity between coarctation of the aorta and this type of branch pulmonary artery stenosis has been suggested: both caused by invasion of ductal tissue. It has therefore been suggested that the term "coarctation" of the pulmonary artery would be appropriate.

The morphology of the central pulmonary artery was studied by selective angiography in 21 previously unoperated patients a median of 4 years (range 11 days to 21 years) of age with pulmonary atresia in association with various types of congenital heart disease by Momma and colleagues.[40] Angiographic findings were confirmed at operation in 10 patients. There was juxtaductal stenosis of the left pulmonary artery in two-thirds of the patients with complete atresia of the pulmonary trunk but 6 of the 7 patients without juxtaductal branch artery stenosis had valvar pulmonary atresia. These authors did not find evidence of stenosis of the right pulmonary artery.

Elzenga and colleagues[41] examined 41 post-mortem specimens with pulmonary atresia, 12 of valvar atresia and 29 cases of muscular atresia of the pulmonary orifice to establish the frequency and the nature of lesions of the branch pulmonary arteries and their relation to the arterial duct. Pulmonary artery stenosis occurred exclusively in those specimens where the arterial duct connected to a pulmonary artery and were located in the segment of pulmonary artery between the pulmonary trunk and the duct. Histological examination revealed ductal tissue in the wall of a pulmonary artery in more than half of the cases with muscular atresia of the pulmonary valve and pulmonary artery stenosis frequently coexisted. A clinical study[42] was performed subsequently to establish the prevalence of juxtaductal pulmonary artery stenosis. Of the 15 patients with pulmonary atresia studied, 10 were identified to have pulmonary artery stenosis on angiograms while 5 of the 50 patients with valvar pulmonary stenosis had similar lesions. In 14 out of the 15 patients with the lesion, the location of stenosis was in the branch pulmonary artery ipsilateral to the arterial duct. The majority of the lesions of pulmonary artery stenosis identified angiographically were subsequently confirmed at operation or at autopsy.

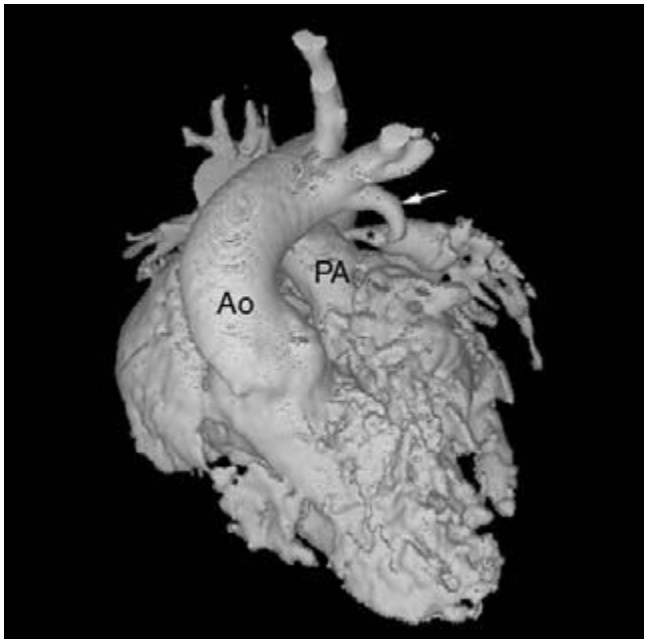


Fig. 13B-5 Three-dimensional CT angiogram shows discrete left pulmonary artery stenosis (asterisk) from contraction of a patent arterial duct (arrow) in a patient with tetralogy of Fallot. There is a right aortic arch and patent arterial duct arises from the left innominate artery. Ao, aorta; PA, main pulmonary artery. (Courtesy of Dr Yang Min Kim, The Sejong Heart Institute, Korea).

Luhmer and colleagues,[43] examined angiograms in 25 consecutive neonates with severe arterial hypoxemia caused by right ventricular outflow tract obstruction and found the prevalence of "coarctation" of the pulmonary artery to be 36%. Interestingly there was no evidence of branch pulmonary artery stenosis in the 8 cases with no evidence of an arterial duct. Conversely, in 9 of 17 neonates with a patent arterial duct, "coarctation" of the pulmonary artery was demonstrated, even during prostaglandin E1 infusion in 7 neonates. They therefore recommended complete excision of ductal tissue in the pulmonary arterial wall to avoid unilateral hypoplasia of the pulmonary arterial tree.

McElhinney and colleagues[44] reported a case of bilateral branch pulmonary artery stenosis from kinking at the site of insertion of bilateral arterial ducts. The patient had a right aortic arch, bilateral ligamental duct and isolation of the left subclavian artery with a complete atrioventricular septal defect.

In a study of 50 preterm infants with pulmonary artery and ductal color Doppler flow velocity assessments before and after closure of the duct, Maroto *et al.*,[45] found that after closure, 15 infants had signs of transient left pulmonary artery stenosis in association with a significant decrease in the diameter at its origin. No significant gradients were noted in the right pulmonary artery. The lesion has also been associated with persistent asymmetric flow and asymmetry of the transitional change from fetal to mature pattern between the right and left pulmonary arterial tree as reported by Zevallos-Giampietri and colleagues in 2 infants.[46]

Peripheral pulmonary artery stenosis and repair in the univentricular circulation (Fontan principle)

Adequately sized and unobstructed pulmonary arteries are critical for a physiologically successful Fontan operation, with pulmonary artery size affecting total pulmonary vascular compliance.[47,48] As such pulmonary artery distortion, hypoplasia and/or stenosis complicate management algorithms and affect outcomes in patients destined for univentricular palliation. Such lesions result in perioperative central venous hypertension and a low cardiac output state. Pulmonary artery stenosis and hypoplasia in such patients may be congenital (e.g. left pulmonary artery stenosis due to contracting duct tissue) or acquired from a prior surgical intervention (e.g. systemic to pulmonary shunts, caval connections, pulmonary artery banding) or anterior compression from the aorta

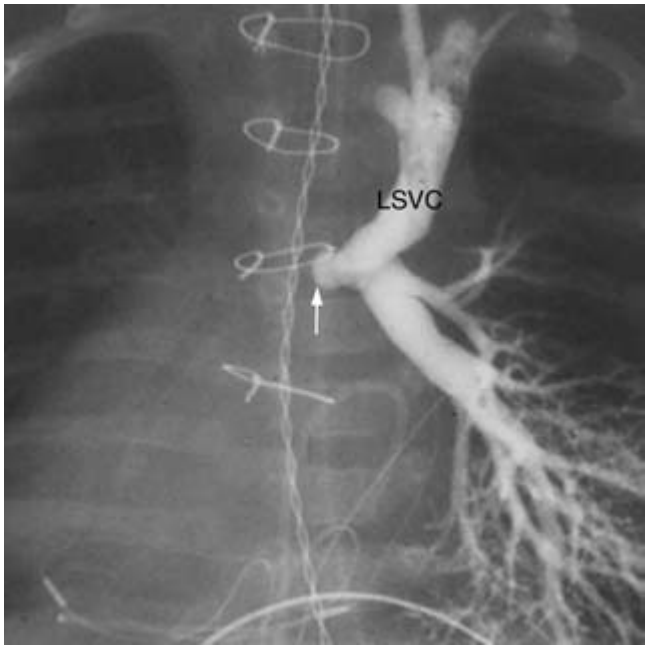


Fig. 13B-6 Anteroposterior projection with caudal angulation of a stenotic left cavopulmonary anastomosis. The central left pulmonary artery ending blindly is due to extrinsic compression by the ascending aorta. LSVC, left superior vena cava.

(Fig. 13B-6).[3,49,50] These lesions can be generally addressed surgically or by use of transcatheter balloon dilation and/or stent placement.[12,51,52] The outcomes of these interventional strategies are described below.

Quantitative indices used for assessment of the adequacy of the pulmonary arteries are the McGoon ratio and the Nakata pulmonary artery index.[53,54] The Nakata pulmonary artery index was established from a study that included 40 normal subjects, 46 patients with tetralogy of Fallot, 26 patients after a Rastelli operation and 15 patients after a Fontan operation. It was obtained by measuring the pulmonary arteries from a pulmonary artery angiogram. An index of 330 ± 30 mm^2/body surface area (BSA) was derived from the normal group and was found to be constant over a wide range of body surface areas, from infancy through adolescence. The incidence of a low cardiac output syndrome after surgery was greater in patients with a smaller index, especially when < 150 mm^2/BSA. The operative mortality was similarly significantly affected by the index, in the Fontan group where 2 patients with an index of < 250 mm^2/BSA died while 12 of 13 patients with an index of > 250 survived ($P < 0.01$). They recommended that those with a Nakata index > 250 mm^2/BSA could be considered good candidates for the Fontan procedure.

Peripheral pulmonary artery stenosis in pulmonary atresia with ventricular septal defect

The variable morphology of the peripheral pulmonary arteries in pulmonary atresia with ventricular septal defect complicates management and is an important determinant of overall therapeutic success. Tchervenkov and Roy[55] have classified such patients into three anatomical subtypes according to the morphology of the peripheral pulmonary arteries. Each of the three types follows a pattern for surgical repair. Type A has native pulmonary arteries supplied by a patent arterial duct, with no major aortopulmonary collateral vessels. Type B has native small pulmonary arteries and major aortopulmonary collaterals. In type C there are no native pulmonary arteries, with the pulmonary circulation supplied solely by major aortopulmonary collateral arteries. In the latter, the central pulmonary arteries are surgically created by direct tissue to tissue anastomosis from the major aortopulmonary collateral vessels (Fig. 13B-7).[56,57] A single or a multistage approach with unifocalization has been used to create adequately sized peripheral pulmonary arteries in patients with type B pulmonary atresia and ventricular septal defect [56,58–66] (see Chapter 18). In all three subtypes, while surgical intervention creates the scaffolding, further rehabilitation of the peripheral pulmonary arteries may be required and can be accomplished by transcatheter interventions (see below).[6,13] The goal of the treatment algorithm is to achieve a normal right ventricular pressure, with closure of all septal defects, and create well-formed central pulmonary arteries, as the single source of blood flow to all the lung segments. Postoperative stenosis is common, especially in the patient without central pulmonary arteries (requiring unifocalization of collateral arteries), as these vessels may not develop sufficiently to accommodate the increasing cardiac output with growth.

Reddy and colleagues[63] reviewed the data on 85 patients with pulmonary atresia with ventricular septal defect who underwent unifocalization (median age, 7 months). Complete one-stage unifocalization and intracardiac repair were performed through a midline approach in 56 patients, whereas 23 underwent unifocalization in a single stage with the ventricular septal defect left open, and 6 underwent staged unifocalization through sequential thoracotomies. There were 9 early deaths. During follow-up (1–69 months) there were 7 late deaths. Actuarial survival was 80% at 3 years. Among early survivors, actuarial survival with complete repair was 88% at 2 years. Reintervention on the neopulmonary arteries was performed in 24 patients. These authors found that early one-stage complete unifocalization can be performed in > 90% of patients, even those with absent true pulmonary arteries, and can yield excellent functional results. Complete repair during the same operation can be achieved in two-thirds of patients. However they felt that there remains room for improvement as actuarial survival 3 years after surgery was only 80%, and there was a significant rate of reintervention.

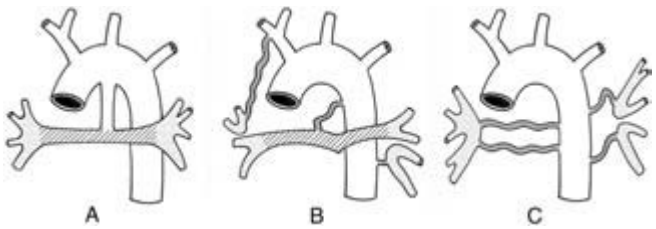


Fig. 13B-7 Three types of pulmonary atresia with ventricular septal defect. Type A has native pulmonary arteries supplied by a patent arterial duct, with no major aortopulmonary collateral vessels. Type B has native small pulmonary arteries and major aortopulmonary collaterals and in type C, there are no native pulmonary arteries, with the pulmonary circulation supplied solely by major aortopulmonary collateral arteries. (Reprinted from Tchervenkov & Roy,[55] Copyright (2000), with permission from The Society of Thoracic Surgeons.)

Amin *et al.*,[6] from the University of California, San Francisco reviewing 74 patients who underwent a single stage unifocalization procedure between 1992 and 1997, found that central and distal pulmonary arteries were prone to stenosis in areas of surgical manipulation. Of the 36 patients who underwent cardiac catheterization after surgery, 24 patients required 1 or more interventions on the pulmonary arteries, with a total of 45 balloon dilation procedures. Of these lesions, 23 were proximal and 22 were distal stenoses. All distal stenoses were at the unifocalization anastomotic site. Balloon dilation was successful in 21 patients and 3 patients required reoperation for stenoses.

Finally, to extend palliation and promote growth of the peripheral pulmonary arteries, an endovascular stent within a stenotic shunt can be considered.[67,68] El Said *et al.*[67] reported on their experience of three cases of pulmonary atresia with ventricular septal defect and hypoplastic pulmonary arteries, who underwent stent placement in either collateral arteries or systemic to pulmonary shunts. All three patients had clinical improvement with stable systemic saturation at follow-up. They concluded that stent placement for maintaining vessel patency was feasible and safe.

Peripheral pulmonary artery stenosis in the Williams–Beuren syndrome

Peripheral pulmonary artery stenosis occurs in 39–83% of patients with the Williams–Beuren Syndrome.[69,70] The lesion may be focal or diffuse, may involve central and/or peripheral branches including multiple and bilateral lobar or segmental arteries at their origin (Fig. 13B-8).[71] Natural history studies indicate that in most instances, there is improvement in the vessel caliber over time with resolution of right ventricular hypertension, even when the stenoses are severe and the right ventricular pressure in the near systemic range.[69,70,72,73]

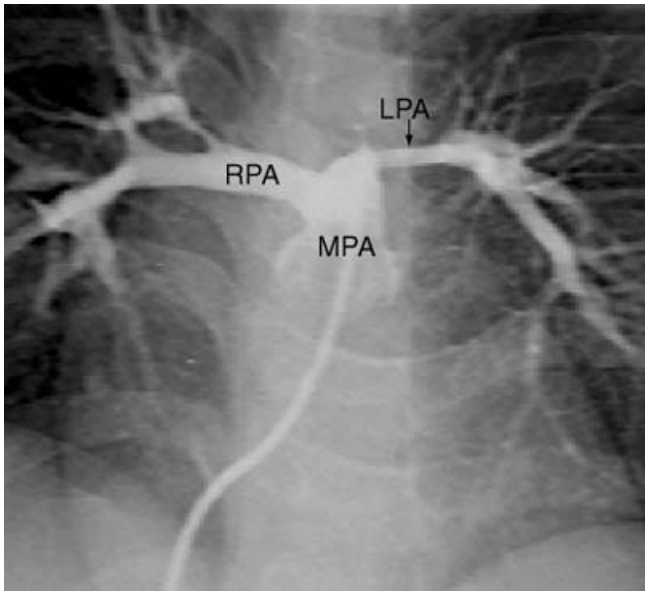


Fig. 13B-8 An angiogram, in the anteroposterior projection with cranial angulation of severe bilateral peripheral pulmonary artery stenosis. LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

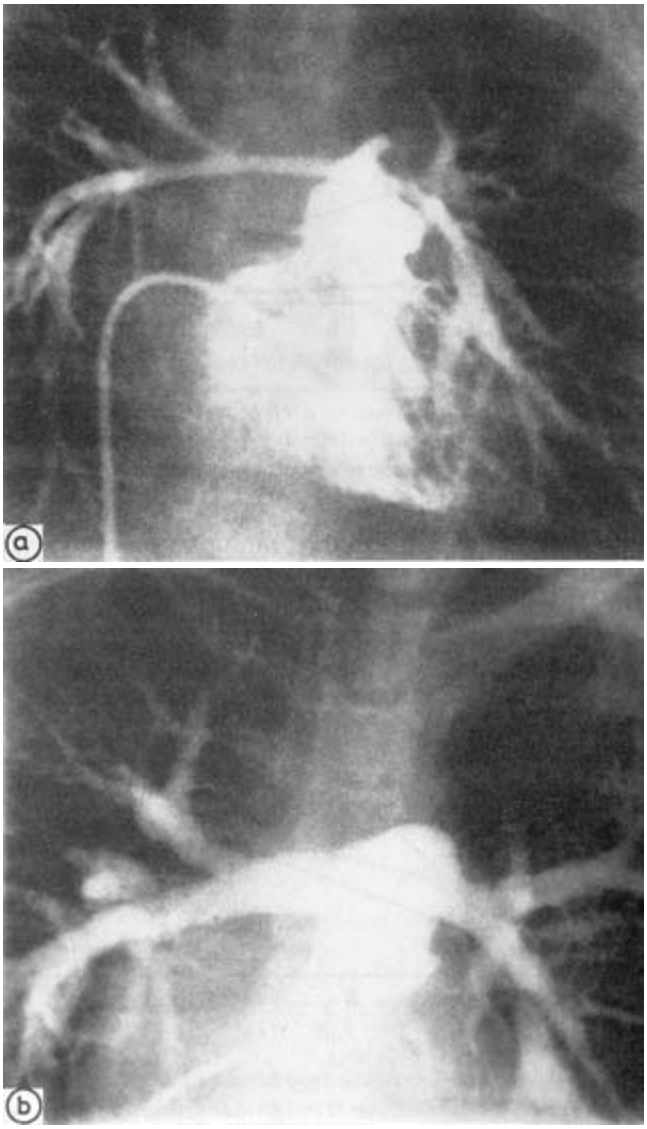


Fig. 13B-9 Posterioanterior view of a right ventricular angiogram showing (**A**) diffuse bilateral peripheral pulmonary artery stenosis with near systemic right ventricular pressure in a patient with the Williams–Beuren syndrome at 9 months of age. The same patient at 9 years of age with normal appearing pulmonary arteries and normal right ventricular pressure (**B**). (Reprinted from Giddens *et al.*,[72] *Br Heart J* 1989; **62**: 315–9, with permission from BMJ Publishing Group.)

Giddens *et al.*[72] reported the hemodynamic findings obtained from two serial cardiac catheterization studies in 8 of 10 patients with Williams–Beuren syndrome in 1989. The right ventricular peak systolic pressure dropped from a mean of 52 (range 16–96) mmHg to 28 (range 20–38) mmHg ($P < 0.05$). The most impressive changes were noted in those with the highest initial right ventricular pressure. The decrease in right ventricular pressure was associated with a striking improvement in the angiographic appearance of the pulmonary arteries (Fig. 13B-9).

Wren *et al.*[73] reported data from 35 patients studying the natural history of supravalvar aortic stenosis and pulmonary artery stenosis. The group was heterogeneous in etiology with

17 patients having the Williams–Beuren syndrome. Pulmonary lesions were present in 19 patients. Right ventricular or pulmonary artery angiography in patients with elevated right ventricular pressure showed less than normal diameters of the pulmonary artery in both systole and diastole, with minimal systolic expansion. On follow-up study, there was an increase in systolic diameter, which paralleled body growth while the diastolic diameter lagged behind body growth. The increase in systolic diameter appeared to correlate with the reduction of right ventricular pressure. They concluded that the decrease in right ventricular pressure was related to an increase is systolic distensibility rather than true luminal growth.

Zalzstein *et al.*[70] studied 49 patients with the syndrome, 19 of whom had pulmonary arterial lesions, 3 patients requiring surgical intervention. The combined follow-up period for the group with pulmonary arterial lesions in isolation ($n = 8$) and the group with right and left sided obstruction ($n = 11$) was 60 months (range 2 months to 18 years). There was a tendency for spontaneous improvement or no change over time in the pulmonary arterial lesions.

Wessel *et al.*[69] further confirmed the outcomes in patients with the Williams–Beuren syndrome. Of the 59 patients studied, 49 had pulmonary artery stenosis. In 23 patients, with serial right heart catheterization, the gradients from the pulmonary arteries to the right ventricle decreased from 23 to 9 mmHg over a mean follow-up of 14 (range 2–24) years (Fig. 13B-10). High-pressure gradients dropped markedly in all but 1 patient. By adolescence through 33 years of age, the gradients were < 20 mmHg in 96% of patients.

Kim *et al.*[74] reviewed cardiac catheterization and angiographic data from 26 patients with Williams–Beuren syndrome. The severity of the pulmonary artery lesions was correlated with age and body surface area in terms of the pulmonary arterial index and right ventricular systolic pressure. In patients with pulmonary arterial stenosis ($n = 20$), right ventricular systolic pressure tended to decrease, and pulmonary arterial index increase, with increase in age and body surface area. Between the groups with and without pulmonary artery stenosis, there was significant difference in age (mean 5 vs. 10, $P = 0.019$), body surface area (0.62 vs. 1.16, $P = 0.002$), pulmonary arterial index (152 vs. 317, $P = 0.002$) and right ventricular systolic pressure (74 vs. 33, $P = 0.006$). Their result also supports those studies, which noted that, with time, pulmonary artery stenosis tends to improve.

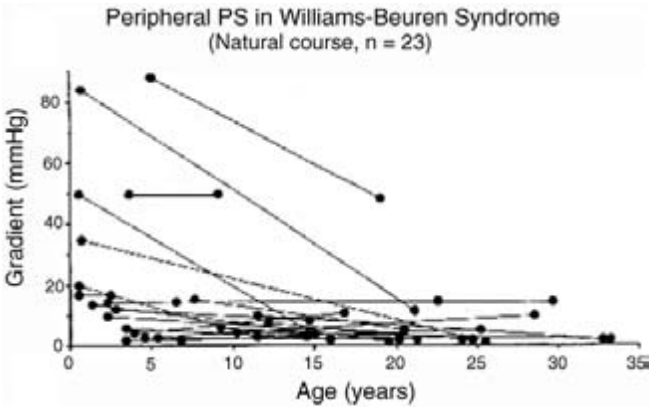


Fig. 13B-10 Natural history of peripheral pulmonary artery stenosis (PS) in 23 patients with the Williams–Beuren syndrome. Systolic pressure gradients on *y*-axis as derived from catheterization data. Age in years on *x*-axis. (Reprinted from Wessel *et al.*,[69] Copyright (1994), with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

It is evident that most pulmonary artery lesions in Williams–Beuren syndrome improve with age (Figs 13B-9, 13B-10) even with severe stenoses and systemic right ventricular pressures. The self resolving pattern of the Williams–Beuren pulmonary arteriopathy requires a critical appraisal of precise indications for surgical or catheter intervention for peripheral pulmonary arterial lesions. Currently, intervention is indicated for those with near systemic or greater right ventricular pressure, significant biventricular obstruction or in those who are symptomatic with lesser degrees of obstruction. When associated supravalvar aortic stenosis requires surgical intervention, a case may be made to intervene for patients with subsystemic or lower right ventricular hypertension.

For patients with severe biventricular hypertension, a manifestation of a severe generalized arteriopathy, it has been suggested that management for the distal pulmonary arterial lesions be performed by catheter intervention initially with subsequent surgical intervention upon the proximal pulmonary arteries and left sided lesions.[71,75] It appears that the central pulmonary arterial stenoses are resistant to dilation (very elastic) and the distal arterial lesions more responsive to balloon dilation. Patients with severe biventricular pressure overload are at risk for developing myocardial ischemia during cardiopulmonary bypass,[76] and right ventricular failure often occurs after surgical repair of supravalvar aortic stenosis in patients with severe generalized arteriopathy.[71,73] Addressing the distal pulmonary artery lesions preoperatively, and relieving the central pulmonary artery lesions at the time of surgery could avoid the deleterious effects of right ventricular hypertension. Using such a strategy, Stamm *et al.*[71] reported the outcomes in 33 patients who underwent operations for supravalvular aortic stenosis while having significant stenoses of the pulmonary arteries. These authors found an 81% (70% CI, 78% to 92%) overall Kaplan–Meier estimate of survival at 5 years and 76% (70% CI, 68% to 84%) at 10 and 20 years. There was, however, no correlation between right ventricular pressure load and survival (Fig. 13B-11). Right ventricular pressure load did, on the other hand, prove to be a risk factor for reoperation or intervention. Only 18% of the patients were free of reoperation or intervention by 10 years in those with systemic right ventricular pressure load at presentation, as compared to 84% ($P = 0.017$) in those with subsystemic right ventricular pressure load. Patients who required reoperation or intervention did not differ significantly in survival from those who did not need intervention ($P = 0.96$).

There are few reports specifically addressing outcomes of transcatheter intervention with balloon dilation for pulmonary artery stenosis in patients with the Williams–Beuren syndrome.[75,77,78] Geggel *et al.*[75] reported successful balloon dilations of the pulmonary arteries (defined by an increase of > 50% in the pulmonary artery diameter) in 51% of patients in a review of 134 dilations during 39 procedures in 25 patients. There was a 112 ± 65% gain in vessel diameter in those with a successful procedure. Successful dilation was more likely with intraparenchymal than mediastinal arteries, as noted above. It was also likely to be more successful in arteries with smaller initial diameters, with balloon/stenosis ratios of ≥ 3, with elimination of stenosis waist and with the occurrence of an aneurysm after dilation. However, right ventricular pressure remained

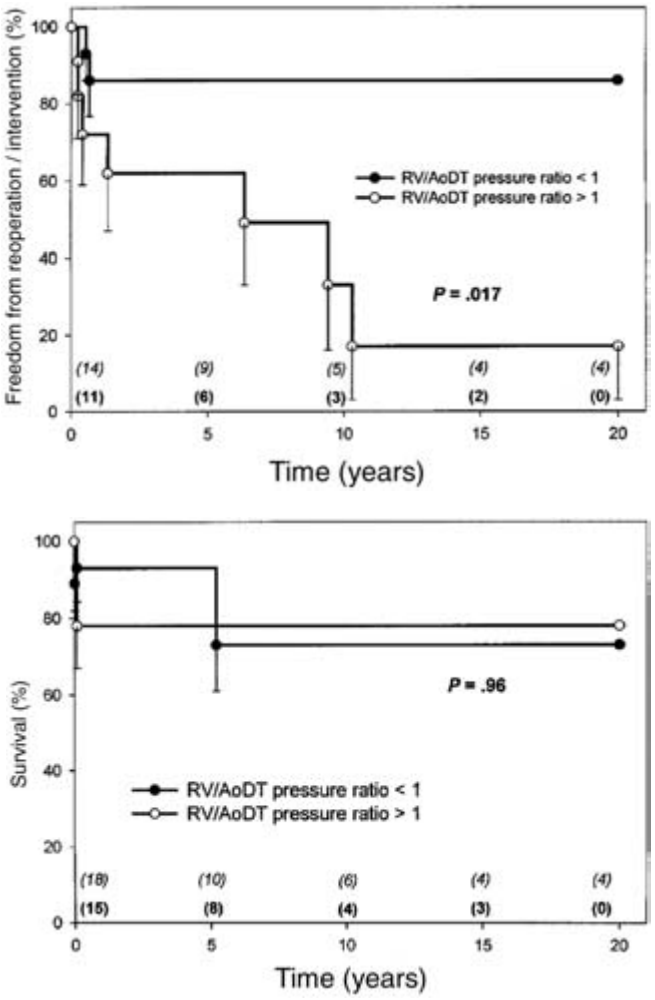


Fig. 13B-11 Kaplan–Meier estimated 20-year freedom from reoperation or catheter intervention (**A**) and survival (**B**) for patients with peripheral pulmonary artery stenosis in conjunction with supravalvar aortic stenosis. The group with a right ventricular to descending thoracic aorta pressure ratio (RV/AoDT) of > 1 indicating suprasystemic right ventricular pressures and the group with the ratio < 1 indicating subsystemic right ventricular pressure. Error bars indicate the lower 70% CI. Numbers of patients at risk are shown in parentheses; the group with a pressure ratio of < 1 is shown in italics, the group with a pressure ratio > 1 is shown in bold. (Reprinted from Stamm *et al.*,[71] Copyright (2000) Mosby Inc., with permission from Elsevier.)

unchanged (96 ± 30 predilation vs. 97 ± 31 mmHg postdilation, $P = 0.72$). This lack of hemodynamic improvement was attributed to lower success rate of balloon angioplasty in the proximal vessels. These authors recommended a serial approach, with dilation of distal pulmonary artery stenoses, followed by surgical repair of the proximal lesions. They also recommended creation of an atrial septal defect in the presence of near systemic right ventricular pressure or a left heart gradient of > 30 mmHg before balloon angioplasty. Overall mortality was 12% before 1993, with no mortality in the last 14 patients after 1993. Improved outcomes may have resulted from the greater use of general anesthesia and the creation of an atrial communication in high-risk patients.

Pulmonary arterial stenosis in Alagille syndrome

Emerick *et al.*[32] reported the outcomes in 92 patients with Alagille syndrome and found that the only feature that was statistically associated with increased mortality ($P < 0.001$) was the presence of congenital heart disease, with an estimated survival of 40% at 20 years, compared to 80% at 20 years in its absence (Fig. 13B-12). Survival of Alagille patients with tetralogy of Fallot or pulmonary atresia with ventricular septal defect was 66% and 25%, respectively, considerably poorer than the reported survival at 10 years of 89% and 58%, respectively, in patients without Alagille syndrome.[32,79] Although, in general, survival in those with cardiac lesions was worse, the study did not quantify right ventricular hypertension nor addressed the impact of right ventricular hypertension on survival. There are no reports addressing specifically the impact on survival of right ventricular pressure the natural history of pulmonary artery lesions and the impact of surgical or catheter based intervention on survival.

Ovaert *et al.*[80] recently reported on 17 patients with Alagille syndrome who underwent liver transplantation at a mean age of 3.5 (range 1.2–13) years. All patients had confirmed pulmonary artery stenosis and none was symptomatic from the cardiac lesions. At the time of liver transplantation, 10 patients had evidence of > 50% systemic right ventricular pressures, 6 confirmed by cardiac catheterization. None of 5 deaths after liver transplantation was of cardiac origin. At a mean follow-up of 6 (range 0.6–15) years for the 12 survivors, there was no evidence of progression of the cardiac lesions. In 2 of the 4 who had more than half systemic pressure before liver transplantation, there was evidence of persistent elevation of right ventricular pressure, which appeared well tolerated. Follow-up liver biopsies did not show signs of hepatic congestion and all patients had significant improvement of quality of life and growth.

Png *et al.*[81] reported a mean reduction of 15 ± 9 mmHg in systolic blood pressure, 5 ± 3 mmHg in the mean pulmonary

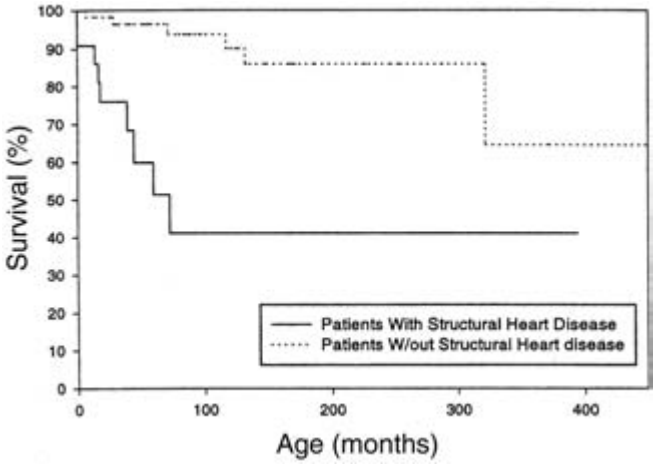


Fig. 13B-12 Kaplan–Meier survival plot comparing survival of patients with Alagille syndrome and associated cardiac lesions (n = 22, dashed lines) to those with no cardiac lesions (n = 70, solid line). The predicted probability of attaining 20 years of age for the group with cardiac lesion is 40% as compared to 80% for those without cardiac lesions. (From Emerick *et al.*[32] with permission.) (Reprinted from Emerick *et al.*,[32] Copyright (1999), with permission from American Association for the Study of Liver Diseases.)

artery pressure and 4 ± 3 mmHg in the central venous pressure with application of the inferior vena caval clamp at the time of liver transplantation in the same group of patients as studied by Ovaert *et al.*[80] No correlation was found between the severity of pulmonary artery stenoses and hemodynamic changes at the time of the transplantation. Use of a venovenous bypass resulted in smaller hemodynamic changes during the transplant procedure. Based on these findings, liver transplantation should be offered even in the presence of right ventricular hypertension.[80,81]. In the presence of severe pulmonary artery stenosis the use of venovenous bypass was recommended to minimize the hemodynamic changes.[81] Ovaert *et al.*[80] further notes that as such, there is no proven uniformly successful treatment option for the peripheral pulmonary arterial lesions in Alagille syndrome. Surgical enlargement of the pulmonary arteries is not feasible due to the diffuse and distal pulmonary arterial involvement and the results of transcatheter balloon dilation are disappointing.[80,82,83] Endovascular stent implantation has been tried but the experience is small.[84]

The mortality (44%) and morbidity of patients with Alagille syndrome who undergo liver transplantation is worse than that of patients undergoing liver transplantation for all causes (36%).[85] Of the 23 children with Alagille's syndrome and end-stage liver disease who underwent liver transplantation, 2 to 9 years (mean 4 years) after surgery, only 13 (57%) children were still alive, with normal liver function and 3 of the 10 deaths were due to cardiovascular failure secondary to associated cardiopulmonary disease. Mortality was higher among patients who had more severe cardiac disease and patients who had previously undergone a Kasai procedure. These authors emphasized the value of cardiopulmonary evaluation before liver transplantation, as 13% of patients in their series of 23 patients died from cardiac failure.

Razavi *et al.*[86] attempted to predict the outcomes of liver transplantation in patients with Alagille syndrome and pulmonary artery lesions hypothesizing that the fixed degree of right ventricular pressure load would impair the sustained increase in cardiac index following transplantation, required to maintain perfusion of the graft. These authors attempted to simulate an increased cardiac index before liver transplantation in 15 children with Alagille syndrome and pulmonary artery stenosis, by administration of intravenous dobutamine. Cardiac index, as measured by thermodilution, increased from 4.4 to 6.4 L/min/m^2 ($P < 0.001$) but the correlation between right ventricular pressure load and the rise in cardiac index was poor, with a correlation coefficient of 0.11. They, however, recommended that with a dobutamine stimulation test, if there is failure to increase the cardiac index by 40% and/or if the right ventricular pressure is more than half systemic, then associated pulmonary arterial stenosis should be addressed by transcatheter stent implantation, as these patients may be at a higher risk of graft failure.

Transcatheter therapeutic strategies

Outcomes of balloon angioplasty

Pulmonary artery lesions remain a challenging problem in the care of patients with congenital and acquired cardiopulmonary disease. Surgical approaches have been met with difficulty over the years and may lead to further distortion of the treated vessels. Balloon dilation first came into use in the 1980s with extension of its use to proximal pulmonary artery stenosis in order to improve distal flow and artery growth and has proved moderately effective.

In most series, balloon angioplasty has been moderately successful, reporting an anatomic success in 50% of patients with a 5% complication rate.[87] The mechanism of action was first observed in lambs, where it was shown that the increase in the luminal diameter was by creation of intimal tears (Fig. 13B-13). In a study by Lock *et al.*,[88] in 1981, pulmonary arterial stenosis was surgically created in a lamb model. Dilation was associated with a decrease in the systolic gradient in all ($n = 13$ from 35 to 8 mmHg) and an increase in the diameter of the stenotic area (from 5 to 8 mm) as evaluated by angiography. The fraction of total flow to the dilated lung rose (19–45%), as did the total flow (30–69 mL/kg/min) to the dilated lung. The average gradient remained below 10 mmHg despite considerable growth (from 10 to 26 kg) an average of 16 weeks after dilation. Gross pathologic examination showed an intact vascular adventitia with multiple linear tears of the intima up to 7 days after dilation (Fig. 13B-13). Complete intimal healing was seen by 2 months after dilation. No significant morbidity could be attributed to the dilation procedure. Based upon these findings, clinical trials followed.

Studies of changes in the appearance of the pulmonary arteries treated by balloon dilation were subsequently obtained in four patients by Edwards and colleagues.[89] Successful dilation in 7 of the 9 vessels was accompanied by intimal disruption and tearing of the media. When 6 successfully dilated vessels were restudied 4–14 months after dilation, the gain in the luminal diameter had been maintained. Histological examination demonstrated that the tears in the intima and media were filled in by scar tissue (Fig. 13B-14). In one artery a dilated segment distal to a residual obstruction showed marked intimal proliferation. Histological examination of the vessel that failed to dilate showed it to be encased by reactive fibrous tissue in association with a previous surgical operation.

Outcomes of balloon dilation therapy

Lock and colleagues[90] further reported in 1983 on the outcomes of balloon angioplasty for PPAS in 7 children with stenosis or

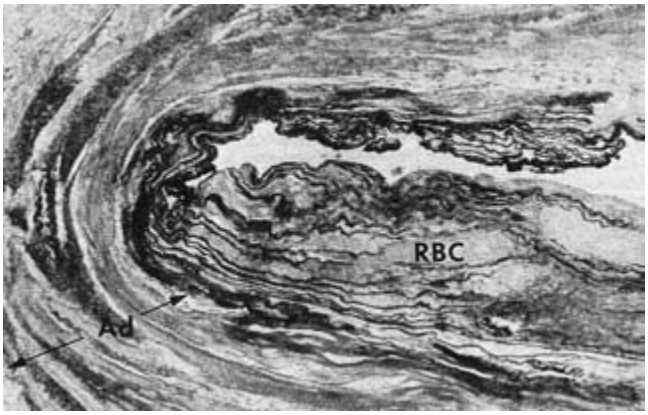


Fig. 13B-13 Photomicrograph of a transverse section through a recently dilated pulmonary artery segment demonstrating an intimal break with separation of media with hemorrhaged red blood cells (RBC) into the media. The adventitia (Ad) is markedly thickened. (Reprinted from Lock *et al.*,[88] copyright (1981), with permission from Lippincott Williams & Wilkins.)

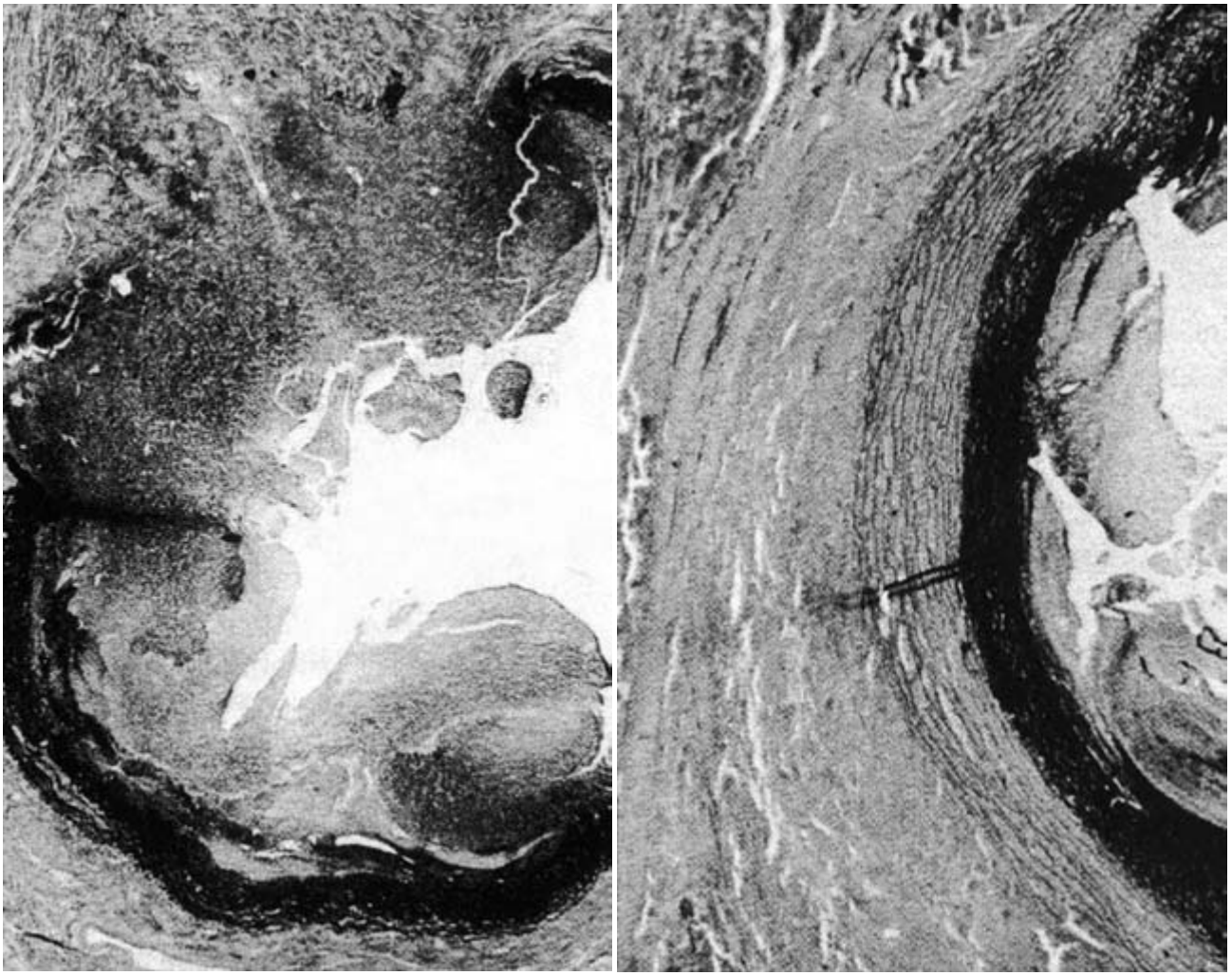


Fig. 13B-14 Photomicrographs of right pulmonary arterial segments dilated 12 months previously. **A**. Cross section of the intermediate branch of the right pulmonary artery. The media between 6 and 9 o'clock is near normal. Between 9 and 12 o'clock recognizable media has disappeared. This seems to represent an intima–medial rupture and separation with healing of the separation by dense collagen fibers intermixed with elastic fibers. **B**. The vessel shows intimal proliferation that was more prominent here than that in undilated arteries. Cross-section through the site of an unsuccessful dilation 14 months previously. The media appears normal. The thickened intima has been fragmented in several places. There is dense scarring of the adventitia and the periadventitia (elastic tissue stain, original magnification ×25 (Reproduced from Edwards *et al*.,[89] copyright (1985), with permission from Lippincott Williams & Wilkins.)

hypoplasia of right and left pulmonary arteries who were treated with balloon angioplasty. Successful in 5 children, a fall in right ventricular pressure (104 ± 42 to 80 ± 30 mmHg, $P < 0.05$), fall in the gradient across the obstruction (61 ± 51 to 32 ± 22 mmHg, $P < 0.05$), increase in the diameter of the pulmonary artery (4 ± 1 to 7 ± 1 mm, $P = 0.02$) and an increase in lung perfusion (41 ± 16% to 52 ± 22%, $P < 0.05$) were noted. There was no procedure related complication and follow-up angiograms in 3 of the 5 patients between 2 and 12 months later indicated persistence of anatomic improvement. They concluded that balloon angioplasty of the pulmonary arteries provided significant hemodynamic relief in patients, where traditional operative management had been unsuccessful.

A more guarded report on the outcomes of balloon angioplasty was presented by Rocchini *et al.*,[91] who found that while balloon angioplasty was not effective in all patients, it did provide significant improvement in some in whom traditional operative management is usually unsuccessful. Of the 13 patients in whom balloon angioplasty was attempted, 5 patients had successful angioplasty as judged by an increase in pulmonary artery size of > 75%, and a > 50% reduction in the peak systolic pressure gradient across the site of stenosis. All patients remained well on follow-up from 6 to 30 months and follow-up angiograms in 2 patients (at 10 and 12 months) showed persistence of the anatomic and hemodynamic changes. In 8 (60%) patients, however, balloons angioplasty was not successful: stenosis at the site of a previous systemic to pulmonary artery shunt could not be dilated in 4, and technical difficulties limited the procedure in the remainder. The authors also reported a significant procedure related complication with perforation of a distal branch pulmonary artery in 1 patient.

Larger experiences were reported subsequently. Ring *et al.*[92] found balloon dilation to be beneficial in the short term, especially when performed early in life, in some patients with hypoplastic or stenotic branch pulmonary arteries. Balloon angioplasty (n = 52 dilations) was undertaken in 24 children

with tetralogy of Fallot with or with pulmonary atresia or isolated peripheral pulmonary arterial stenosis. The age ranged from 4 months to 16 years, with 9 patients being ″ 2 years of age. Procedures were performed in the catheterization laboratory ($n = 44$) as well as in the operating room ($n = 8$). Of these, 26 (50%) were judged successful with an increase (76%) in the average vessel diameter from 4 ± 0 to 7 ± 0 mm, reduction (40%) of the gradient across the narrowed segment from 60 ± 10 to 36 ± 5 mmHg, a reduction (20%) in the main pulmonary artery or right ventricle pressure proximal to the obstruction from 83 ± 10 to 66 ± 6 mmHg and an increase (28%) in the lung perfusion of 40 ± 4 to 51 ± 4% as judged by radionuclide pulmonary perfusion scan to the lung ipsilateral to the dilated pulmonary artery. All changes were statistically significant ($P < 0.005$). Reasons for failure included inadequate technique (balloon too small, inability to position balloon or wire) in 14, and the refractory nature of the lesion itself in 11. Technical failures were age independent. Nondilatable lesions were more common in children > 2 years old (10/25 vs. 1/10) or with isolated lesions (5/7). Five of 7 stenoses near previous shunts were also nondilatable. There was 1 death following rupture of the pulmonary artery during dilation, but few other complications were found. On an average follow-up of 6 months after dilation there was angiographic persistence of improvement, and 2 lesions were successfully redilated to a larger size.

Bass[93] reported similar outcomes as the study by Ring and colleagues.[92] These authors found that balloon dilation was beneficial in some patients with half the attempted dilations being successful, with an increased diameter of the narrowed areas, decreased pressure gradients, and improved pulmonary blood flow to the involved lung. Failure was due to technical limitations (28%) or lesions that were not dilatable with contemporary equipment (22%). Undilatable lesions are more common in children > 2 years of age, in isolated lesions, and when in association with surgical shunts.

Hosking *et al.*,[52] reviewing data on 74 patients with native or postoperative pulmonary artery stenosis with 110 balloon angioplasty procedures, confirmed the observations of other authors, that due to the potential for a beneficial result, with low complication risk, angioplasty should be offered as initial therapy. However, they could not define any predictive factors for success, and often the clinical impact was found to be transient. Balloon dilation was acutely successful in 53% of patients, 17% had recurrent stenosis, and 5% had procedural complications. The mean age at balloon dilation was 7 ± 5 years (range 2 months to 18 years) with 17 patients < 1 year of age. The mean follow-up was 38 ± 23 months (range 16–96 months) with follow-up angiography in 34 patients (44%). The impact on subsequent care was favorably influenced in 26 of 74 patients (35%) with either complete resolution of stenosis ($n = 7$), optimization of future surgical conditions ($n = 14$), reduction in right ventricular pressure by > 20% ($n = 3$) or improvement of ipsilateral lung perfusion ($n = 2$). However, no patient, previously considered inoperable, was subsequently considered suitable for surgical repair, owing to the intervention. No correlation was found between success and cardiac diagnosis ($P = 0.48$), site of stenosis ($P = 0.78$), balloon to vessel ratio ($P = 0.42$), or whether the stenotic area consisted of native or synthetic material ($P = 0.22$).

The Valvuloplasty and Angioplasty of Congenital Anomalies Registry,[94] reported the outcome data from 182 balloon angioplasty procedures performed on 156 patients (age 2 months to 46 years; mean 8 years) from 27 institutions. While they found that long-term outcomes and complications were uncertain, the procedure increased vessel dimensions at the site of the stenoses, reduced systolic pressure gradients and to a minor degree reduced proximal pressures. Vessel dimensions at the site of stenoses increased from 5 ± 2 to 7 ± 3 mm ($P < 0.001$). The mean peak systolic pressure gradients were reduced from 49 ± 25 to 37 ± 26 mmHg ($P < 0.001$) and pressure proximal to the stenoses decreased from 69 ± 25 to 63 ± 24 mmHg ($P < 0.001$). The increase in luminal diameter was greater if the balloon diameter was > 3 times the stenoses. They found no significant benefit related to age or prior surgical intervention, contrary to the findings of other authors. Complications occurred in 13% and included vessel rupture in 5 patients with 2 deaths, and death from cardiac arrest, paradoxical embolism and low cardiac output, in 1 each.

The use of high-pressure balloons with inflation pressures of 17–20 atm has improved the anatomic success rate of balloon dilation from 50% to 81%. Gentles *et al.*[82] reported hemodynamic and angiographic data from 52 patients (age: 3 months to 35 years) who underwent high pressure balloon dilation and compared them with data from previous low pressure dilations in the same patient population. Diagnoses included tetralogy of Fallot and pulmonary atresia with ventricular septal defect in 32 patients, univentricular heart in 8 patients and isolated congenital pulmonary artery stenosis in 7 patients. High inflation pressure angioplasty was performed upon 72 vessels in 52 patients. Of 36 vessels with previously unsuccessful low-pressure dilation, 23 (63%) were successfully dilated with high-pressure balloons. Of the 36 remaining vessels, 29 (81%) underwent successful dilation with high-pressure balloon as the initial procedure. Success was defined as ≥ 50% increase in vessel diameter or > 20% decrease in right ventricular to aortic pressure ratios. Factors associated with success were stenoses at a surgical anastomosis and disappearance of the balloon waist during dilation. Aneurysms developed in 3 vessels. Complications occurred in 13% of patients and included distal pulmonary artery perforations in 2, 1 of which resulted in death.

Restenosis has been described after balloon dilation but little is known as to its frequency, nature of occurrence and time course. Bush *et al.* [95] reviewed the clinical data and measured pulmonary artery diameters from angiograms of 134 dilations on 75 patients (median age 2 years, range 3 months to 32 years). Following a successful dilation (defined as ≥ 50% increase in luminal diameter) restenosis was said to occur if there was ≥ 50% loss in initial diameter gain. The initial success rate was 64% (95% CI, 56% to 73%). Restenosis occurred in 35% (95% CI, 22% to 49%) of the successfully dilated vessels. Only weight at follow-up ($P = 0.02$) was associated with an increased likelihood of restenosis. Predilation parameters, technical aspects of dilation, or immediate results of balloon dilation were not predictive of restenosis. Thus, their findings suggested that restenosis was unpredictable and commoner after balloon dilation than previously appreciated.

The experience with transcatheter balloon dilation has in general been associated with low rate of complication. Balloon dilation of the pulmonary arteries is important in the management strategy of pulmonary artery stenosis; however, success requires a controlled tear of the vessel. Excessive tearing can produce complications ranging from pseudoaneurysm to rupture and death. Baker *et al.*[96] reported on the management and outcomes of patients experiencing pulmonary artery

trauma during balloon dilation. These authors found that pulmonary artery trauma occurs often distal to the site of narrowing, is associated with underlying pulmonary hypertension and is frequently (42%) fatal, in those with unconfined tears. They suggest that intensive management strategies, as well as attention to distal balloon position may reduce the incidence and mortality. Coil occlusion of the traumatized pulmonary artery appeared to be a valuable strategy in preventing fatal hemorrhage. Of 1286 catheterization procedure in 782 patients, pulmonary artery trauma was identified (excluding isolated pulmonary edema and pulmonary artery aneurysms) in 29 procedures (2.2%) in 26 patients (3.2%). The tears occurred distal to the area of stenosis in most cases (62%). The damaged pulmonary artery was successfully coil occluded in 5 patients, with survival in 4. Temporary balloon occlusion did not succeed in preventing death in 2 patients, with 6 deaths from pulmonary hemorrhage. A case–control analysis demonstrated that pulmonary artery trauma was significantly associated with pulmonary hypertension.

Outcomes of stent therapy for pulmonary artery stenosis

The application of stent implantation has proved to be an improved management alternative for pulmonary artery stenosis.[97] In patients unresponsive to balloon dilation, transcatheter stent placement has been applied to provide a framework to maintain vessel diameter and decrease systolic pressure gradients with better success in maintaining luminal integrity in stenotic segments[87].

Several authors have reported on the outcomes of stent treatment for pulmonary artery stenosis. Mendelsohn *et al.*[98] reviewed the initial results of stent implantation for vascular stenosis in 16 children at a median age of 3 years, the median weight being 13 kg. Balloon expandable Palmaz stents (Johnson & Johnson Interventional Systems, Warren, NJ) were implanted intraoperatively ($n = 15$) if the patient was < 1 year of age or < 10 kg in weight, in cases with limited vascular access precluded percutaneous implantation, or as an adjunct to other intracardiac surgical procedures. In the remainder ($n = 5$) percutaneous stenting was performed. In the 13 patients with stent implantation of the pulmonary artery, the mean diameters increased from 6 to 12 mm ($P = 0.001$), with a decrease in mean systolic pressure gradients from 43 to 8 mmHg ($P = 0.005$). Follow-up cardiac catheterization (mean 9 months) in 3 patients revealed no evidence of restenosis, thrombosis, or aneurysm formation.

O'Laughlin *et al.*[99] provided data on intermediate term outcome of stent treatment in a variety of congenital heart lesions. Of the 85 patients who underwent placement of 121 stents, 58 patients had stents implanted within the pulmonary arteries for peripheral stenosis. The procedure resulted in gradient reduction from 55 ± 33 to 14 ± 14 mmHg and the diameter increased from 5 ± 2 to 11 ± 3 mm. Follow-up studies showed stent fracture, restenosis and sudden death in 1 patient each. Of the 85 patients in the entire cohort with vascular stenoses, including the Fontan anastomoses, pulmonary vein lesions and right ventricle to pulmonary artery conduits, 38 patients were reevaluated an average of 9 months after implantation. Compared with immediate postimplant observations, there were no significant changes in luminal diameters or pressure gradients. Redilation was performed in 14 patients, 1 week to 24 months after implantation (mean 10 months) with a small but a significant increase in stenosis diameters. Thus, the efficacy of stent treatment for peripheral pulmonary arterial lesions and other forms of vascular stenoses at medium term was excellent.

The efficacy of balloon expandable stents in the treatment of peripheral pulmonary arterial lesions was further confirmed by Nakanishi *et al.*[100] These authors reported data on 8 stent implants in 7 patients, 3 with tetralogy of Fallot following surgical repair, 2 after a Fontan operation and 2 patients with right ventricle to pulmonary artery conduit stenosis, at a mean age of 13 ± 3 years and the mean weight 37 ± 12 kg. Their findings supported the use of stents in the treatment of these obstructive lesions. The diameter of stenotic segment of the pulmonary artery increased from 6 ± 2 mm to 11 ± 2 mm ($n = 7$). The systolic pressure gradient decreased from 56 ± 26 mmHg to 22 ± 16 mmHg ($n = 5$). At follow-up over between 0.3 to 2 years, no embolization or thrombotic event occurred. The intracardiac conduit stent ($n = 1$) was noted to have fractured at follow-up from compression. There are no data to suggest that stents in pulmonary artery lesions are liable to fracture.

As mentioned earlier, pulmonary artery distortion is a risk factor among candidates for the Fontan procedure. Moore *et al.*[12] demonstrated the efficacy and safety of percutaneous stent implantation in young children after cavopulmonary anastomosis. In 57 such patients, evaluated by catheterization, 8 had proximal left pulmonary artery stenosis. The mean diameter of the pulmonary artery at the site of stenosis was 5 ± 0 mm. Proximal right pulmonary artery diameter was 10 ± 1 mm. Pulmonary artery angioplasty and stent placement were performed through the internal jugular or subclavian veins with enlargement of the lesions using 10 stents, dilated to 10 (7 patients) or 12 mm (3 patients). The narrowest dimensions were significantly enlarged to 10 ± 1 mm ($P < 001$) with no complications. Follow-up studies were performed 4 to 9 months after implantation with no evidence of restenosis and 5 patients had successful completion of the Fontan procedure with the remaining 3 awaiting Fontan completion. The study confirmed the applicability of stent treatment for pulmonary artery lesions in patients awaiting the Fontan operation after a bidirectional cavopulmonary anastomosis.

While stents have a role in the treatment of peripheral pulmonary arterial stenosis and have positively affected clinical care in as many as 27% of implants, the relief may be tempered by the development of intraluminal obstruction as reported by Fogelman *et al.*[51] In-stent stenosis, from intimal proliferation or from relative pulmonary arterial growth has been addressed successfully with redilation of the implant. In a review of 42 patients (38 patients with 49 percutaneous implants, 4 with 6 intraoperative implants) who underwent stent placement in the pulmonary arteries, at a mean age of 6 ± 5 years, there was an increase in the diameter of the stenotic segment of 109 ± 79% ($P < 0.0001$) and a gradient reduction of 74 ± 26% ($P < 0.0001$). Acutely, stent implantation had an important clinical impact. This was confirmed by the finding that of the 38 patients who underwent percutaneous implantation, surgical repair was avoided in 33 and deferred in 4 patients. A patient considered inoperable had important palliative relief following implantation. Symptomatic improvement was reported in 27 patients, and 15 patients remained asymptomatic. At recatheterization (median 15 months) at 1 year after implantation in 29 patients, various degrees and locations of acquired intraluminal narrowing were observed in all cases (Fig. 13B-15). This was noted to

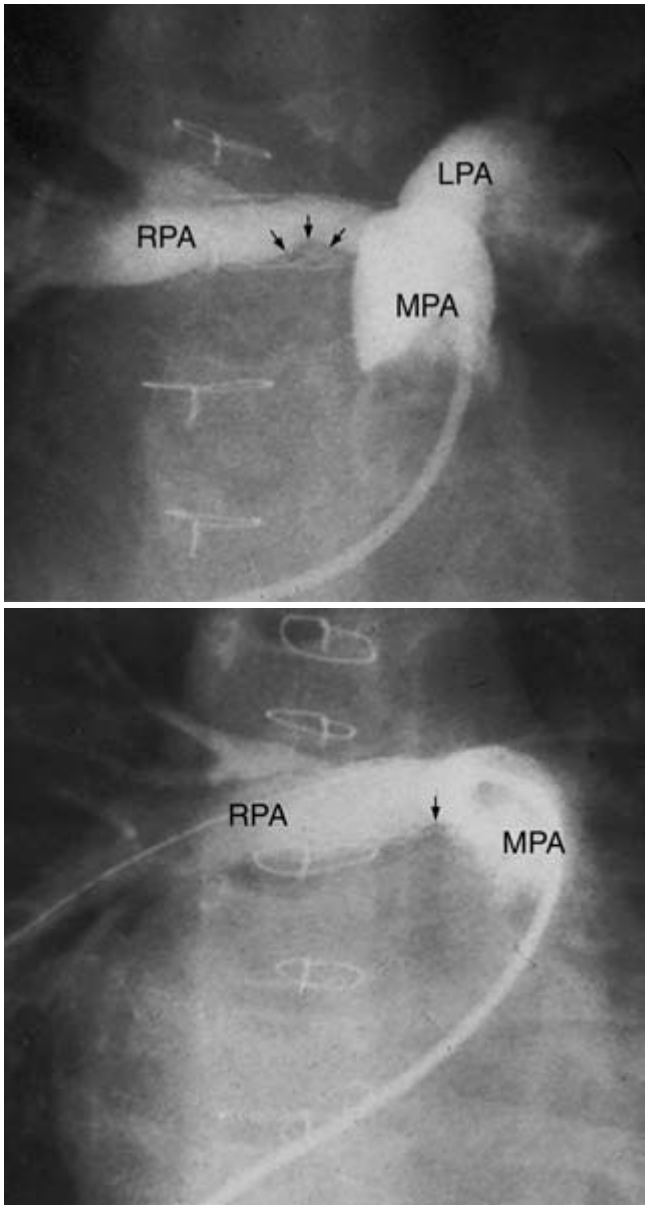


Fig. 13B-15 Restenosis of stented pulmonary artery. **A**. Right pulmonary artery (RPA) stent, placed 2 years before this study. Note proximal intimal in-growth (arrows) creating in-stent stenosis. **B**. Same stent after a balloon dilation, enlarging the length of the stent, and displacing the intimal in-growth (arrow). LPA, left pulmonary artery; MPA, main pulmonary artery.

occur particularly in areas of diameter mismatch, between the stented and nonstented vessel and in 11 patients these were treated with balloon dilation of the stent with a gain in diameter.

The feasibility of reexpansion of stents and the gross and histologic effects of re-expansion on vascular integrity were studied by Morrow *et al.*[101] They implanted stents in the aorta of 10 swine and performed reexpansion in each animal after 11 weeks and 18 weeks. Aortic growth had produced a relative constriction of the aorta of 20 ± 10% at the site of stent implantation, and re-expansion produced a significant increase in mean stent diameter from 10 ± 1 mm to 12 ± 1 mm at 11 weeks and from 11 ± 1 to 14 ± 1 mm at 18 weeks after implantation ($P <$ 0.001) resulting in a relative increase in stent diameter of 21 ± 7% at 11 weeks and 18 ± 4% at 18 weeks. Stent reexpansion was accompanied by plastic deformation of the neointima without neointimal dissection. There was no evidence of medial or adventitial hemorrhage or dissection produced by the re-expansion. Although the study was performed in the systemic circulation, the applicability to the pulmonary artery without significant injury to neointima, media or adventitia appears appropriate.

Ing *et al.*[102] reported a lower incidence of restenosis (3%) and found that repeat dilation of the stent in the pulmonary artery could be performed with safety and efficacy (94% success rate) up to 3 years after implantation. Concurring that the early results of stent treatment for pulmonary arterial lesions were excellent, these authors focused on restenosis and dilation or restenting of the implants. Of the 94 patients with 163 implanted stents in this single center study, 43 patients with 73 stents underwent recatheterization. In 20 patients, 30 stents were re-dilated with only 2 of 73 restudied stents (3%) showing significant restenosis (defined as large discrete waist causing a large pressure gradient). At stent implantation, the mean age of this subgroup was 14 years, the mean intraluminal diameter increased from 5 to 11 mm ($P = 0.0001$), and the systolic gradient (mean) across the stent decreased from 52 to 11 mmHg ($P = 0.0001$). At recatheterization (mean 13 months) all stents were patent. The mean diameter decreased by just over 1 mm ($P = 0.0001$) but the increase in the gradient (mean 3 mmHg) was not significant ($P = 0.11$). After repeat dilation, the diameters increased from 10 to 12 mm ($P = 0.0001$) and the gradient decreased from 14 to 8 mmHg ($P = 0.0003$). The 2 stents with significant restenosis were redilated successfully, and 2 patients underwent a successful second redilation of 3 stents at 18 and 26 months. There were no complications.

The long-term outcomes of stent therapy and the impact of changes in stenting practice were reported by McMahon *et al.*[103] These authors reported data on 664 stents, implanted in 338 patients, 229 of whom were after operative tetralogy of Fallot or pulmonary atresia with ventricular septal defect repair, 61 had congenital pulmonary artery stenosis, 16 following an arterial switch operation and 32 after a Fontan procedure. In all groups, the mean systolic pressure gradients decreased from 41 to 9 mmHg ($P < 0.01$), mean vessel diameters increased from 5 to 11 mm ($P < 0.01$), and the mean right ventricular systemic arterial pressure ratio fell from 0.66 to 0.45 ($P < 0.01$). At a mean follow-up of 5 years, the mean systolic gradient was 20 mmHg, the mean right ventricular pressure ratios 0.5, and the mean luminal diameters were 9 mm. Complications during the early part of the experience included stent migration in 8, and pulmonary edema, hemoptysis and death in 5 each. However, during the last 4 years, no morbidity or mortality associated with stent implantation was noted. Technical changes such as conservative serial dilations in patients with congenital pulmonary arterial stenosis, avoiding overdilation and simultaneous stent treatment of branch pulmonary arteries in those with systemic right-sided pressures, amongst other technical refinements, were contributory to improved outcomes. Technological advances such as availability of shorter stents, improved balloon profiles and strategies to inflate the central part of the stent first were also found to be contributory.

The results of stent implantation for pulmonary artery stenosis have been compared in patients weighing < 20 kg (17 patients, 21 stents) vs. those weighing ≥ 20 kg (11 patients, 13

stents) by Movahhedian *et al.*[104] There were no significant differences in the mean percent increase in diameter or mean percent gradient reduction acutely and at short-term follow-up between the two groups.

Placement of stents for pulmonary arterial lesion has limitations in infants and small children due to stent inflexibility, requirement for large sheaths and concerns about creating fixed obstructions after the placement of small diameter stents in growing patients. Turner *et al.*[105] reported the use of stents designed for deployment through smaller sheaths in 4 high-risk patients with postoperative right ventricular outflow obstruction. Median patient age and weight were 17 months (range 5–32 months) and 8 kg (range 5–11 kg), respectively. In each case, successful stent placement was achieved and cardiopulmonary bypass surgery avoided.

Smaller stents with maximal achievable diameters of 9–10 mm commit the patient to future surgery to enlarge the stented area once it has been dilated to its maximal diameter. However, such implants are life saving in the immediate postoperative period.[13,106] Alternatively, larger stents have been implanted in the operating room, reducing the time for pulmonary arterioplasty and buttressing the vessel from external compression.[98,107] With the patient size permitting, a stent with the potential to be expanded to an adult size has been deployed with success.[102,105,106]

Advances in stent technology with availability of more flexible stents requiring a smaller delivery sheath with equal or increased radial strength and maximal expansion to a greater cross-sectional area should permit the application of this treatment strategy to younger patients.

Outcomes of surgical repair of PPAS

Surgical repair of peripheral pulmonary arterial lesions, in general, has been disappointing with a 50% to 60% restenosis rate at 5 years.[108] Certain lesions however, such as supravalvar pulmonary stenosis or bifurcation stenosis of the branch pulmonary arteries, are best managed by surgical repair.[2] Most patients benefit from a collaborative combined surgical and transcatheter approach, especially those with complex forms of stenosis in the setting of tetralogy of Fallot or one of its variants.[13]

There is limited contemporary experience and outcome data for surgical intervention for bilateral severe branch pulmonary artery stenosis. Fraser and colleagues[109] reported their experience with 1 patient with staged surgical correction involving bilateral branch pulmonary artery reconstruction for severe bilateral branch pulmonary artery stenosis. The technique consisted of initial unilateral reconstruction of the branches by excision of the stenotic segments, augmentation of the stenotic branch points by a cutback angioplasty and restoration of arterial continuity using autologous pericardium followed by a similar repair on the other side at a later operation. Following bilateral repair the pulmonary artery pressure and the right ventricular pressure normalized with a favorable pulmonary artery architecture and normal blood flow distribution to both lungs.

Stamm *et al.*[110] reported on outcomes of discontinuous central pulmonary arteries in 102 patients following establishment of continuity. Among patients with a biventricular repair ($n = 66$), freedom from surgical or transcatheter pulmonary arterioplasty was only 31 ± 11%. Mean branch pulmonary arterial Z scores were –0.5 ± 1.6 and –1.4 ± 1.3 for right and left pulmonary arteries, respectively, at their most recent follow-up. Mean right to left ventricular pressure ratios were 0.61 ± 0.26. Lung perfusion mismatch of > 75:25 was noted in 15 of 51 patients, while in 9 of 58 patients a branch pulmonary artery was occluded. In the 22 patients who underwent primary establishment of antegrade pulmonary artery flow without previous shunt procedures, comparable reintervention rates were noted although the trends indicated higher pulmonary arterial Z scores and lower right to left ventricular pressure ratios. In patients with a single ventricle repair, freedom from pulmonary arterioplasty was 39 ± 9%. Lung perfusion mismatch was present in 10 of the 19 patients. Occlusion of a branch pulmonary artery occurred in 4 of 31 patients, with presence of aortopulmonary collaterals being a risk factor for pulmonary artery occlusion ($P = 0.03$). An initial direct pulmonary artery anastomosis compared to secondary anastomosis after a systemic to pulmonary artery shunt was associated with better survival ($P = 0.006$). Although the reintervention rates have been high as shown in this study, stenosis of the pulmonary arteries can be addressed by surgical repair, with repair of the associated cardiac defects.[13]

It has been recommended that when palliation by a systemic to pulmonary artery shunt is undertaken pulmonary artery stenosis, if present, should be simultaneously addressed. In a review of 12 patients (5 with tetralogy of Fallot, 3 each with double outlet right ventricle and univentricular morphology and 1 with common arterial trunk), Barbero-Marcial and colleagues,[111] performed simultaneous surgical repair of a pulmonary arterial lesion and palliation with a systemic to pulmonary artery shunt. Operative dilation of the stenotic segment was performed in 2, enlargement of the stenotic segment in 3 and resection with end-to-end anastomosis in 4 patients. Nonconfluent pulmonary arteries were corrected in 3 patients with resection anastomosis of the stenotic segment in 1, interposition of right subclavian artery segment between the pulmonary trunk and intrahilar branch pulmonary artery in 1 and disconnection of the right pulmonary artery from the aorta with an interposition tube between the right and left pulmonary artery in 1 patient. There were no intraoperative or late deaths, and the authors found the postoperative angiographic evaluations to be satisfactory.

Cost analysis of treatment modalities

Peripheral pulmonary artery stenosis is a common problem in pediatric cardiology.[112–117] Treatment includes surgery, balloon angioplasty, and balloon expandable stent placement. The cost effectiveness of each of these modes of treatment was assessed by Trant *et al.*[108] by reviewing data on 30 patients admitted for treatment of peripheral pulmonary arterial lesions only. Success of a procedure was defined as an increase in vessel diameter by ≥ 50% or a decrease in right ventricular to left ventricular or aortic systolic pressure ratio by ≥ 20%, or a decrease in peak-to-peak pressure gradients across the stenosis by ≥ 50%. The procedure was also considered a failure if the patient required a second procedure for the same stenosis. The total charges were corrected to 1994 dollars using the Medical Consumer Price Index. There were 46 separate procedures: (12 patients had > 1 procedure and 3 had > 2 procedures), 13 surgical repairs, 13 balloon dilations, and 20 stents. Stents were the most successful (90% acute and 85% at follow-up), but were not statistically superior to surgery (62% acute and at follow-up). Balloon dila-

tion was significantly less successful as compared with stents (31% acute and 23% at follow-up) and was not statistically different from surgery both acutely or at follow-up. The charge data showed balloon dilation was the least expensive followed by stents and then surgical repair. The average total charges (US dollars) per procedure, including outpatient charges, were: surgery $58 068 ± 4372 (standard error), balloon $21 893 ± 5019, stents $33 809 ± 3533($P < 0.001$); excluding outpatient charges: surgery $52,989 ± 3649, balloon $15,653 ± 1691, and stents $29 531 ± 2241 ($P < 0.001$). Average total charges per patient, including all procedure types and grouped by initial procedure were surgery $53 707 ± 6388, balloon $50 040 ± 8412, and stent $34 346 ± 3488 ($P = 0.047$). Stents were at least as effective as surgery and were more effective than balloon angioplasty both acutely and at follow-up. Balloon dilation was least expensive per procedure but was also least effective. The authors concluded that stents are the most cost effective means available in the treatment of peripheral pulmonary artery stenosis.

All references can be found at the end of the book. See pp. 657–60 for Chapter 13B.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

13C

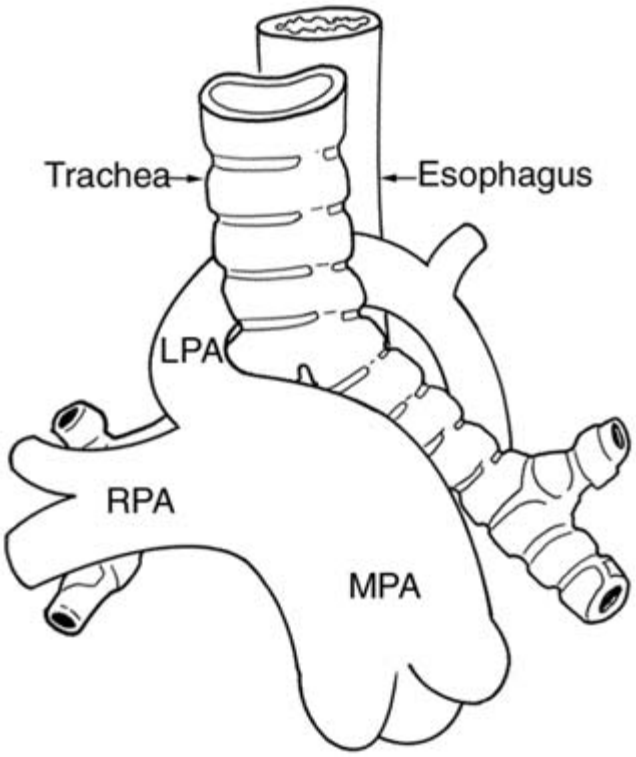
Robert M. Freedom and Shi-Joon Yoo

Pulmonary Artery Sling

The pulmonary artery sling or aberrant left pulmonary artery is an uncommon vascular abnormality that tends to produce severe respiratory symptoms in the young infant or child.[1–10] Occasionally, this anomaly will be detected in an otherwise asymptomatic adult.[11] The aberrant left pulmonary artery (pulmonary sling) is characterized by the left pulmonary artery arising from the proximal right pulmonary artery and coursing between the trachea and oesophagus to reach the left hilum (Fig. 13C-1). The term "pulmonary sling" was introduced in 1951 to differentiate this entity from vascular rings due to aortic arch anomalies.[1] More recently, the term "ring-sling complex" was introduced to emphasise its association with tracheal anomalies.[3] The anomalous left pulmonary artery arises from the distal portion of the main pulmonary artery to the right of the trachea. This branch passes posteriorly over the proximal right bronchus, behind the trachea, and then to the left extrapericardially between the trachea and the esophagus into the left hilum. The sling that is formed may compress the right bronchus and the distal end of the trachea. There may be localized tracheomalacia at the sling level. Associated tracheal anomalies include a tracheal origin of the right upper lobe bronchus, and complete tracheal rings. The anomalous left pulmonary artery may be smaller than the right pulmonary artery. Rarely, the right upper lobe branch may arise from the proximal left pulmonary artery. The anomalous vessel may supply only part of the left lung and may have an unusual course.[5,12]

In this abnormal course, the left pulmonary artery often obstructs either or both of the main bronchi or the trachea. There may be localized tracheomalacia or bronchomalacia at or below the sling level and associated tracheal anomalies such as a tracheal origin of the right upper lobe bronchus, cartilaginous rings and long-segment tracheal stenosis are common to this disorder. The tracheo-bronchial tree is abnormal in most of the cases with pulmonary artery sling, with an abnormal branching pattern in about 80% of the cases. The most common pattern is an unusually long trachea that bifurcates, at the level of the interspace between the sixth and seventh thoracic vertebrae, into the right and left main bronchi with the configuration of an "inverted T" (Fig. 13C-1C). In about one-third of the cases with an inverted T configuration of tracheal bifurcation, there is an errant bronchus arising from the trachea at the level of the interspace between the fourth and fifth thoracic vertebrae and supplying the upper part of the right lung. One may consider the site of origin of the bronchus to the right upper lung as carina, as the T4–5 interspace is the normal carinal level. Then, the vertical airway below the carina should be considered the left main bronchus instead of the distal trachea and the bronchus supplying the right lower lung is considered to arise errantly from the left main bronchus, crossing the midline to enter the right lung. The term "bridging bronchus" has been used to designate the errant bronchus to the right lower lung. Rarely, the trachea bifurcates at its usual T4–5 interspace level, and an errant bronchus to the right upper lung originates from the mid trachea. Regardless of the type of tracheobronchial branching pattern, the left pulmonary artery always passes over the most inferior bronchus to the right lung. The adjacent airway, whether it be lower trachea or left main bronchus, commonly demonstrates intrinsic narrowing and abnormal distribution of cartilage in its wall; the abnormality being either a complete cartilaginous ring or absence of cartilage. Patients with the pulmonary artery sling show hyperinflation of the right lung or both lungs, respiratory distress, and stridor. Clinical manifestations can be observed in the newborn period, and in the particularly severely involved newborn, pneumothorax has been recorded. Initial chest films may show delayed clearing of fetal fluid from the right lung followed rarely by left air-trapping as the result of compression of the proximal left bronchus by the ligamentum arteriosum or fibrosing fasciitis.[13] The symptoms tend to be respiratory in nature and are usually present at or shortly after birth. The stridor tends to be expiratory in contradistinction to inspiratory stridor noted in the aortic vascular rings. Should the obstruction become more severe atelectasis may occur. Atelectasis or emphysema of the left lung may be present due to tracheal compression. On the lateral chest radiograph a posterior indentation on the lower trachea may be apparent. On occasions a mass may be visible between the air-filled trachea and the esophagus. An esophagram often shows an anterior indentation on the esophageal wall at the level of the tracheal bifurcation.[14,15] It should be noted however that the barium study may be normal.[13]

The diagnosis of pulmonary artery sling should be suspected in any infant or child with signs of a compromised airway. An abnormal barium swallow and bronchoscopy may lead to the diagnosis. Historically, pulmonary angiography would be confirmatory of the diagnosis, but most now recommend CT or MRI imaging both to confirm the diagnosis and to image the trachea and major bronchi (Fig. 13C-1).[6,9,10,15–25] The pulmonary artery sling or errant pulmonary artery may be the sole cardiovascular abnormality, but it has been identified in the patient with an arterial duct; total anomalous pulmonary venous connections; tetralogy of Fallot; double-outlet right ventricle; pulmonary atresia and intact ventricular septum; ventricular septal defect; aortopulmonary window with aortic arch interruption; and Williams syndrome.[10,24–32] Some patients have been found



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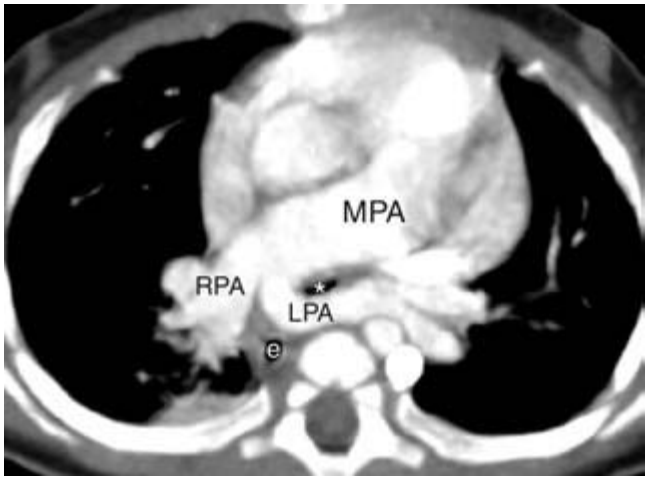

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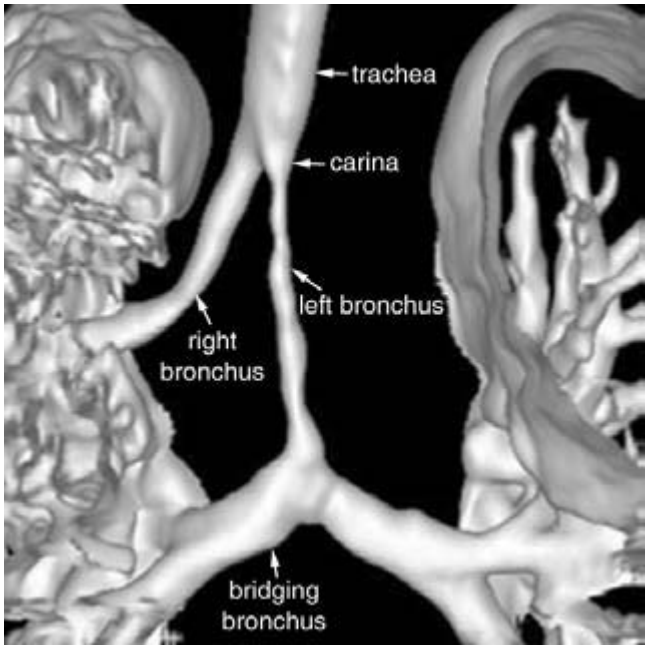

C

Fig. 13C-1 Pulmonary artery sling. A. Schematic drawing showing abnormal origin and course of the left pulmonary artery (LPA). It courses between the trachea and esophagus. B. CT angiogram in axial view showing typical course of the left pulmonary artery between the trachea (asterisk) and esophagus (e). C. Three-dimensional CT image showing a abnormal tracheobronchial branching. It often shows an inverted "T" configuration. The vertical part of the left main bronchus shows diffuse narrowing (arrow) because of complete cartilaginous ring. The bronchus supplying the right lower lobe arises from the left main bronchus and is therefore called a bridging bronchus. MPA, main pulmonary artery; RPA, right pulmonary artery respectively. (Courtesy of Dr Yang Min Kim, The Sejong Heart Institute, Korea.)

to have an absent or hypoplastic right lung.[24–26] Twins have been identified to have pulmonary artery slings,[33] and a patient with trisomy 18 has also been identified with this malformation.[28]

Outcome analysis

The pulmonary artery sling is an unlikely diagnosis to be established in the fetus, and furthermore this condition does not jeopardize the well-being of the fetus. Most centers have only limited experience with this condition.[2,5,6,8,10,34–41] The Pediatric Cardiac Care Consortium operated on 11 infants with pulmonary artery sling, ranging from 3 to 363 days, with 3 deaths.[42] During the same interval, this group operated on 193 patients with a vascular ring.[42] Two operative strategies have been used to repair the pulmonary artery sling.[43–46] The first comprised detachment of the aberrant left pulmonary artery from the right pulmonary artery and its implantation into the main pulmonary artery, and the second, translocation of the left pulmonary artery anterior to the trachea (without implanting it into the main pulmonary artery), resection of tracheal stenosis, and end-to-end reconstruction of the trachea. Both operations can be accomplished with low operative mortality. Yet in most series there is late morbidity and mortality, usually reflecting ongoing respiratory difficulties.[43–46] Backer and his colleagues have had a long interest in the repair and outcome of patients with the left pulmonary artery sling.[44–46] They reported in 1999 their experience with median sternotomy, cardiopulmonary bypass, and re-implantation of the aberrant left pulmonary artery.[46] Their follow-up in 10 patients found that all the re-implanted left pulmonary arteries were patent and blood flow to the left lung by nuclear scan (n = 10) ranges from 24% to 46% (mean 35% ± 9%). Most surgeons today favor this approach of re-implantation. Translocation of the left pulmonary artery anterior to the

trachea without implanting it into the main pulmonary artery is not favored because that could result in anterior compression of the trachea and furthermore there is concern about inadequate growth of the circumferential tracheal anastomosis in neonates and infants.[43–46] We have operated on 11 patients between 1983 and 2000, with 50% dying from respiratory insufficiency, mostly in the first year of life. Some of these patients have been reported elsewhere.[47] In those infants not requiring tracheal reconstruction, there was no mortality. Thus, while some patients may do very well with re-implantation of the aberrant left pulmonary artery, others will continue to experience chronic respiratory difficulties related to the tracheal reconstruction and intrinsic pulmonary pathology.

The pulmonary sling or aberrant left pulmonary artery is but one form of vascular anomaly producing airway compression. We have discussed elsewhere the anatomy and imaging algorithms of the many forms of vascular rings.[48] In the surgical interruption of vascular rings not associated with complex cardiac malformations, there is little mortality, but morbidity may be related to longstanding airway compression.[42,49–53]

All references can be found at the end of the book. See pp. 660–1 for Chapter 13C.

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14A

Henri Justino, Carlos Pedra, Robert M. Freedom, and Lee N. Benson

Congenital Aortic Valve Stenosis or Regurgitation

Aortic valve stenosis is a morphologically diverse condition, which varies in severity from the asymptomatic, to the critically ill and age of presentation from the fetus, to the octogenarian. This chapter will focus on congenital manifestations of the disorder. Other forms of left ventricular outflow tract obstruction, such as sub- or supravalvular stenosis, are detailed in other chapters.

Incidence

A number of studies have documented a male preponderance, with a 2 to 3:1 male to female ratio.[1,2] Congenital aortic stenosis exhibits a variety of morphological subtypes, of which the bicuspid valve is the most prevalent. Indeed, the bicuspid aortic valve represents not only the most common type of aortic valve morphology, but also the most common congenital cardiovascular malformation, with an approximate incidence of 0.4–2.0% in the general population.[1–6] A bicuspid aortic valve is not necessarily stenotic, but represents the mildest form of a spectrum within the constellation of aortic stenosis.[7–9]

Early studies from the 1970s[10–14] established a relatively low incidence of aortic stenosis in the general population, compared to more contemporary investigations. In part, available diagnostic methods are responsible for this difference.[10,13] In Blackpool, England, over a 15-year period from 1957 to 1971, an incidence of 2.5 per 10 000 live births was found,[13] while in the same era, a multicenter US study found an incidence of 2.85 per 10 000.[10] Hoffman *et al.* in the late 1970s found an incidence of 3.07 per 10 000, accounting for 3.7% of cases of congenital heart disease.[14] The New England Regional Infant Cardiac Program, during the years 1969–77, reported only cases of congenital heart disease detected in the first year of life, and found an incidence of aortic stenosis of 0.41 per 10 000 live births.[15]

The late 1970s and 1980s saw the widespread application of echocardiography, and with it, increased rates of detection of congenital heart lesions. Studies performed in this era suggested a higher incidence of aortic stenosis, presumably due to the detection of milder forms of the disease. Kitchiner *et al.* identified 239 patients born between 1960 and 1990. Looking specifically at those born between 1979 and 1989, aortic stenosis was found in 4.7 per 10 000 live births, and constituted 5.7% of cases of congenital heart disease.[16] In a study of 91 823 children born in 1980 in Bohemia, Czech Republic, Samanek and colleagues found aortic stenosis accounted for 7.64% of cases of congenital heart disease, with an incidence of 4.9 per 10 000 live births.[17] In a similar study within the same geographic area, extending from 1980 to 1990, echocardiography was performed in all children with suspected congenital heart disease, and found 391 patients with aortic stenosis, from a cohort of 815 569 children born, for a prevalence of 4.8 per 10 000 live births, accounting for 7.77% of all cardiac malformations.[18] This study, however, did not include normally functioning non-stenotic bicuspid aortic valves. The Baltimore–Washington Infant Study,[19] reporting on 179 697 live births between 1981 and 1982, found a wide disparity in the prevalence of mild forms of congenital heart disease depending on the method of diagnosis. As such, aortic stenosis was detected in the first year of life in 0.8 per 10 000 live births when the diagnosis was made by catheterization, surgery, or autopsy, but the detection rate increased to 1.11 per 10 000 live births when echocardiography was included as a diagnostic tool.

Despite the increased accuracy of echocardiography in detection of aortic stenosis, a bias remained, as only patients with suspected cardiac disease were referred for study, excluding the mildest forms of the disease. In the absence of larger studies addressing the incidence of congenital heart disease using screening of healthy children with echocardiography, the "true" incidence of aortic stenosis remains underestimated. Perhaps the least biased estimate of the frequency of aortic valve abnormalities continues to be necropsy studies, where direct inspection permits detection of all aortic valve abnormalities regardless of severity *in vivo*, with a determined incidence of 0.4% to 2.0% in the general population.[1,2]

Genetics and familial clustering

A number of studies have shown familial clustering of aortic valve disease, particularly bicuspid aortic valves.[20–25] Emanuel reported the incidence of aortic valve disease among 188 living, first-degree relatives of 41 patients with surgically proved aortic stenosis due to an isolated bicuspid aortic valve.[20] Clinical examinations, electrocardiograms, and chest radiographs were performed in all 188 patients, while m-mode echocardiograms were performed in 52 (28%). In total, 8 of the 188 relatives (4%) had evidence of aortic valve disease, involving 7 of the 41 families (14%), a higher incidence than seen in the general population. The second natural history study reported a higher than average incidence of congenital heart disease among offspring of those known to have aortic stenosis,[26] with an occurrence rate of 1.2% (3 of 253) of children of male probands and 1.4% (1 of 72) of children of female probands. Of the 4 affected offspring, 3 had left-sided obstructive lesions (aortic stenosis or coarctation).

Huntington prospectively looked at the incidence of bicuspid aortic valve amongst 210 first-degree relatives of 30 patients with a bicuspid valve, using echocardiography as the screening tool.[27] Of 186 relatives with acceptable echocardiographic studies, 17 (9.1%) were found with a bicuspid aortic valve, with 11 of 30 families (37%) having > 1 member with the diagnosis. The higher rate of involved relatives in this study was likely due to the greater sensitivity of echocardiography over other modalities in detecting bicuspid aortic valves, particularly those forms of the disease with minimal valve dysfunction. For this reason, several investigators have recommended screening echocardiograms be performed in all first-degree relatives of those affected with the disorder.[21,27]

Despite the relatively frequent occurrence of congenital aortic valve disease in the general population, the precise genetic mechanism(s) for this disorder remains elusive. An animal model of bicuspid valve has been developed using knockout mice deficient in ENOS (endothelial nitric oxide synthase),[28] although a more recent study has cast doubt on the involvement of this pathway in the genesis of bicuspid aortic valves in humans.[29]

Aortic stenosis can exist in association with genetic syndromes and inborn errors of metabolism, either as a congenital anomaly, or as an acquired lesion upon a morphologically normal valve. It is estimated that anywhere from 12% to 38% of patients with Turner syndrome have a bicuspid aortic valve, with other common cardiovascular anomalies including coarctation and partial anomalous pulmonary venous connection.[30–39] An average incidence of bicuspid aortic valve in patients with Turner syndrome may be *c.* 18% overall, but varies according to the genetic karyotype (being significantly higher in those with 45 xo compared to those with mosaic monosomy x).[30] Certain systemic disorders, such as the mucopolysaccharidoses[40–45] and progeria[46–48] have a high frequency of development of aortic stenosis upon a (usually) trileaflet aortic valve, due to abnormal thickening and/or fibrosis. Other systemic disorders with propensity to development of aortic stenosis are discussed elsewhere.[49]

Morphological considerations (Fig. 14A-1)

The morphological subtype of valve stenosis is related to the age at presentation, which influences prognosis, both by affecting severity of stenosis, and the frequency of accompanying malformations. Aortic stenosis may be due to annular hypoplasia, abnormalities in leaflet and commissural number, in mobility (related to thickness (dysplasia)) or attachment of the leaflets to each other or to the aortic wall. Each of the factors restricting valve opening may exist alone or in combination, and determines the effective hemodynamic orifice area. In general, the fewer the number of cusps or commissures, the earlier in life the valve will present with significant stenosis.[50]

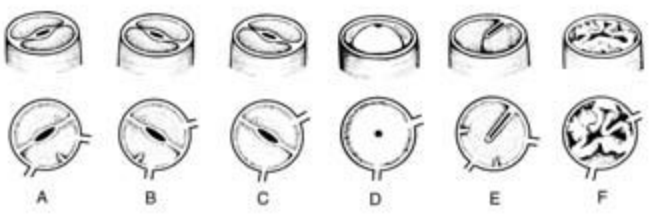


Fig. 14A-1 Line drawings of various forms of valvar aortic stenosis.

By far the most common variant of aortic valve stenosis is the bicuspid aortic valve, and the most common type of valve morphology presenting in childhood and adolescence, accounting for approximately 50% of adult disease, with variable degrees of calcification.[5,51] In most cases, there are, in fact, three sinuses and three visible leaflets, with fusion at one of the commissures (the two fused leaflets, referred to as the "conjoined" leaflets, forming one of the two cusps).[52,53] That two of the three commissures remain open has led other authors to call this a "bicommissural" valve.[54] Most commonly the fusion occurs between the right- and left-coronary leaflets, or between the right- and non-coronary leaflets.[51,53,55] In the former, both coronary arteries arise from the same cusp, whereas in the latter, each coronary arises from a separate cusp. The rate of development of stenosis and sclerosis of the valve leaflets in adults with a bicuspid valve is affected by the morphologic subtype, with the risk being higher when fusion occurs between the right- and left-coronary leaflets.[56] Rare forms of bicuspid aortic valves exist, where only two true leaflets and sinuses are visible.[53] The timing of presentation may be related to the mechanism of stenosis, with children having fusion of the two cusps and variable degrees of thickening of the leaflets, while those presenting in adulthood have superimposed calcification and sclerosis.

While bicuspid leaflets are the most common anomaly involving the aortic valve, the second most common is the unicuspid valve.[2] Two subtypes of unicuspid aortic valves exist: the acommissural (dome-shaped leaflets with no commissural attachments to the aortic wall and a central orifice),[50,57] and the unicommissural valve (effectively a single leaflet with a single commissure that attaches to the lateral aortic wall with an eccentric orifice).[58,59] The most typical form presenting in infancy is the unicuspid unicommissural valve.[52,58,60,61] Despite the single open commissure (usually that between the left- and non-coronary cusps), the presence of two raphes (usually between the right- and left-coronary cusps and between the right- and non-coronary cusps) allows the recognition of a basically three sinus arrangement.[58,61,62] Unicuspid unicommissural valves have a high incidence of associated cardiac anomalies, including mitral valve hypoplasia or atresia, left ventricular hypoplasia, left ventricular endocardial fibroelastosis and others.[58] In contradistinction, the unicuspid acommissural valve represents a rare form of aortic valve disease and the form more commonly seen in pulmonary valve stenosis.[57] Myxoid dysplasia[63,64] is a rarer form of aortic stenosis occurring in valves usually possessing three normally separated leaflets.

Natural history of aortic valve stenosis

The early study of the natural history of aortic valve stenosis was complicated by the observation that few physicians, as Campbell remarked, devoted any interest to congenital heart disease before the era of surgical treatment.[65] Early series, looking at aortic stenosis in the 1940s and 1950s, were plagued by the admixture of other lesions, which could not be differentiated from isolated valve disease. Highlighting these difficulties, Ongley wrote in the 1950s: "the differentiation of aortic valvular stenosis from subvalvular stenosis has not been attempted in this series of patients as we do not know how to make this distinction. There are no reliable clinical tests, which will separate these anatomic variants, and even cardiac catheterization is unreliable for this purpose . . . catheterization of the left side of the heart might seem likely to provide the solution, but it has

been disappointing . . ."[66] Studies performed before routine availability (and safety) of cardiac catheterization lacked hemodynamic information on the severity of the disease, further hampering the understanding of the natural history. The development of improved diagnostic methods paralleled the development of operative techniques, and thus subsequent studies, which included hemodynamic data, were paradoxically hindered by the "loss" of natural history follow-up on patients due to surgical intervention.[65,67–69] More recent studies on survival of patients with aortic stenosis also include a subset of patients undergoing aortic balloon valvotomy.

Aortic stenosis in the fetus

Since the application of fetal echocardiography in the early 1980s,[70,71] prenatal detection of aortic stenosis has been possible.[72,73] With the more recent use of transvaginal ultrasound, cardiac anomalies have become detectable even in the first trimester of pregnancy.[74] The majority of cases of aortic stenosis detected in fetal life reflect those with the severest form of the disease.[75] Milder forms are often overlooked during general fetal obstetrical ultrasounds, as the most common reasons for referral for a fetal echocardiogram originate from abnormalities in the four-chamber echocardiographic view (e.g. left ventricular hypoplasia) or left ventricular dysfunction.[75] Doppler interrogation allows for determination of the severity of stenosis, although in the severest forms (i.e. accompanied by severe left ventricular dysfunction) the cardiac output may be significantly reduced, and Doppler velocities may be normal or only mildly elevated, and therefore not reflect the severity of obstruction.[75] Associated malformations, such as mitral stenosis, mitral regurgitation, endocardial fibroelastosis, and hypoplasia of the left ventricle, ascending aorta and aortic arch, have been detected prenatally. Physiologic changes suggestive of critical obstruction include severe left atrial dilatation, high-velocity reversed (i.e. left to right) flow across the foramen ovale and retrograde flow in the aortic arch or ascending aorta.[76] Fetal hydrops is a particularly ominous finding, and may manifest as fetal skin edema, ascites and pleural or pericardial effusions.[73]

Progression of severity of stenosis and/or failure of normal growth of left-sided structures have been well documented during gestation on serial fetal echocardiograms.[73,76,77] This includes the progression from aortic stenosis to aortic atresia and from normal left ventricular size to the hypoplastic left heart syndrome.[73,77] Premature closure of the oval foramen was initially purported to be a causative factor in the development of the left ventricular hypoplasia.[78] However, others have suggested that it may be a secondary phenomenon caused by elevation in left atrial pressure, given that early fetal echocardiograms have detected a normal foramen in the presence of aortic stenosis with subsequent closure of the foramen as stenosis progresses.[73]

The outcome and growth of left heart structures in 27 fetuses with critical aortic stenosis was retrospectively reviewed by Simpson and Sharland.[79] (cases of mitral or aortic atresia were excluded). Fifteen pregnancies were terminated, with 9 undergoing necropsy: 8 of 9 showing left ventricular endocardial fibroelastosis. Before 25 weeks of gestation, left ventricular end-diastolic volumes were within or above the normal range for fetuses, whereas beyond 25 weeks a wide discrepancy existed between fetuses, ranging from below the fifth to well above the 95th percentile. This illustrates the wide spectrum of left ventricular development in fetal aortic stenosis (from the markedly hypoplastic to severely dilated and poorly functioning ventricle). The aortic root dimension was normal in 12 of 13 fetuses before 28 weeks' gestation, but fell below the fifth percentile in nearly half of the fetuses beyond 28 weeks. Of the 12 pregnancies that continued to term, 2 were offered no postnatal intervention and subsequently died. Two fetuses were offered prenatal balloon aortic valvuloplasty: 1 was successful, but also required a postnatal balloon valvuloplasty, the other was unsuccessful and underwent postnatal surgical valvotomy. The former survived, while the latter did not. Of the remaining 8 infants, 5 underwent postnatal balloon valvotomy, of which 4 were successful, with 3 survivors with a biventricular circulation, and 1 survivor with a Norwood operation. One patient survived a surgical valvotomy, while 2 other infants underwent a Norwood operation and died. Overall, 60% of infants offered intervention (either a single or biventricular circulation) survived. Prognostic indicators of survival with either circulation were not possible due to the small number of patients. Other series also described failure of growth of various left heart structures in fetuses with critical aortic stenosis, but included various types of heart lesions including mitral and aortic atresia.[76]

Detection of critical obstruction in the fetus may ultimately improve results of postnatal management by allowing clinicians to optimize the timing and location of the delivery, as well as allowing infusion of prostaglandin immediately after birth (if deemed necessary) in preparation for surgical or percutaneous interventions.[72,73,79,80] However, data are lacking to suggest that prenatal diagnosis of aortic stenosis significantly impacts the postnatal outcome.[81]

Critical or severe aortic stenosis in the neonate

The term *critical* aortic stenosis has been employed in different contexts, and has been taken to mean severe valve obstruction in the first few months of life,[82–84] or associated with left ventricular dysfunction or a low cardiac output,[85–87] or a duct-dependent systemic blood flow.[86,88] Some authors have employed the term critical to describe severe stenosis in older children.[89,90] We prefer to reserve the term *critical* aortic stenosis for the lesion presenting in the neonatal period with duct-dependent systemic perfusion (i.e. right to left shunting at the ductal level), regardless of valve gradient.

Natural history studies of neonatal critical aortic stenosis predating the era of surgical intervention are lacking, owing to the high mortality and difficulty in establishing the diagnosis. In fact, even publications appearing in the 1960s contain a diverse list of associated malformations that render difficult any meaningful data analysis. In this regard, in Hastreiter's review[91] of 22 symptomatic infants diagnosed clinically in the first year of life (most had been symptomatic from birth), 12 had clinical evidence of coarctation. Of the 22, 16 underwent cardiac catheterization, identifying additional lesions including a ventricular septal defect in 1, and a patent arterial duct in 10 (2 with right to left shunt). Cardiac catheterization in this epoch carried a high mortality, and was usually reserved for the severest cases in which valvotomy was being contemplated. Accordingly, 4 of the 16 died on the same day of the catheterization. Of the original cohort, 16 died, 11 within the first month of life. Necropsy revealed severe aortic stenosis in all, usually with a hypoplastic

aortic annulus and endocardial fibroelastosis, but in addition, 9 had coarctation of the aorta, 7 had mitral stenosis, and a sinus of Valsalva aneurysm was found in 2 (1 with a fistula into the left ventricle). Only 1 patient was found to have an isolated valve lesion at necropsy. Hastreiter introduced the term "congenital aortic stenosis, infantile form" to describe the associated malformations encountered, and suggested that this entity represented an intermediate form between aortic atresia and typical aortic stenosis encountered in older children.

Peckham's study from Toronto in 1963 had similar conclusions: of 300 children and young adults followed with valvular or subvalvular aortic stenosis, only 25 had congestive heart failure. Nineteen of the 25 died, all < 18 months of age. Associated malformations were the rule, with a patent arterial duct in 14, endocardial fibroelastosis in 11, coarctation of the aorta in 5 and a ventricular septal defect in 4 patients. The authors stated that valvular aortic stenosis presenting in the first year of life with congestive heart failure was "invariably fatal unless surgically relieved."[92]

In 1974, Lakier reported 10 infants presenting in the first month of life with isolated severe disease confirmed at cardiac catheterization.[93] The 3 youngest patients had duct-dependent circulation, all of whom died of refractory metabolic acidosis and low cardiac output before surgical intervention, presumably due to duct closure, conferring the highest mortality rate to this subgroup of infants. The remaining 7, without a duct-dependent circulation, lived to undergo attempted surgical valvotomy, 5 of whom died intraoperatively or in the immediate postoperative period. Another patient died 6 months after surgery, for a total of 9 deaths during the follow-up period. Overall, the natural and modified history of neonatal critical or severe aortic stenosis at that time suggested a 90% mortality. All those who died underwent necropsy; 5 had endocardial fibroelastosis, 2 had a small left ventricle, while 7 had normal or dilated left ventricles.

Contemporary studies continue to demonstrate a high mortality for neonatal critical aortic valve stenosis without intervention. In Kitchiner's study of the 239 patients born with aortic valve disease in Liverpool between 1960 and 1990, 22 (9%) had severe or critical obstruction. Of the 22, 12 (54%) died before and 7 (32%) after surgical intervention. Overall, the death rate was 19 out 22 patients (86%) during the follow-up period.[16] A recent multi-institutional study of the management of neonatal critical disease (with variable degrees of hypoplasia of left heart structures) found that 19 of 320 patients (5.9%) died before any procedure to address left ventricular outflow tract obstruction could be performed, suggesting that even today a significant proportion of patients either die before surgical or catheter intervention, or are not offered intervention.[86]

Aortic stenosis in the infant and child

Estimates by Campbell suggested that aortic valve stenosis presenting within the first year of life carried a mortality rate of 23% before the era of surgical treatment.[65] By comparison, the mortality thereafter, for the first two decades of life was 1.2% per year.

Studies reviewing presentation in infancy in the 1950s and 1960s (before routine catheterization) focused primarily on the clinical status of affected patients. In contrast to aortic stenosis presenting at birth or shortly thereafter, it was generally thought that the lesion beyond the neonatal period almost never presented with congestive heart failure.[66,92] In part, this was related to the frequent association of other cardiac lesions in those presenting shortly after birth.[91,92] Moller's study in 1966[60] reviewed the course of patients in the first year of life, and specifically looked at patients with an isolated lesion (only 1 of the 18 patients having a small patent arterial duct). His series suggested that isolated aortic stenosis (without accompanying left ventricular, mitral, or aortic hypoplasia) could indeed present beyond the neonatal period with congestive heart failure. Of the 18 patients, signs of congestive heart failure developed in 12, by 2 months of age, and in 5 infants by 4 months of age. Seven of the 18 infants underwent open surgical valvotomy, with 3 survivors. Overall, 15 of the 18 patients died in infancy. At necropsy, 9 had a unicommissural valve, 1 had a bicuspid valve, 1 an acommissural unicuspid valve, and 8 had evidence of endocardial fibroelastosis. An important observation was the atrophy and infarction of the papillary muscles in 10 of the 11 infants. This formed the basis for a subsequent publication, which suggested that papillary muscle infarction was responsible for the severe mitral regurgitation frequently encountered in infants.[94] It took another decade, however, before a detailed understanding emerged of the precise mechanism accountable for papillary muscle infarction, namely, decreased subendocardial blood flow owing to an elevation in left ventricular end-diastolic pressure, with an accompanying increase in myocardial oxygen demand imposed by the elevated left ventricular systolic pressure.[95,96] In the study by Lakier and colleagues it was also suggested that this subendocardial fibrosis and papillary muscle infarction, a reflection of myocardial systolic and diastolic dysfunction, resulted in the high mortality rate despite surgical intervention.[93] In the study by Hohn *et al*.,[97] there were 18 infants with congestive heart failure and left ventricular outflow tract obstruction. Ten infants were treated medically with 5 deaths (50%), and 8 were operated upon with 5 deaths (63%), highlighting the ominous prognosis of this subgroup of patients at that time, whether operated on or not.

The poor prognosis for aortic stenosis presenting in the young child (< 2 years old) was also confirmed by larger scale natural history studies.[89,98] Between 1958 and 1969, 25 patients with aortic stenosis < 2 years were entered into the first natural history study of congenital heart defects. Sixteen of the 21 were catheterized and had a peak-to-peak systolic gradient of > 50 mmHg. Ten of the 25 were known to have died by the time of the second natural history study in 1993, 8 within 1 week of entry into the first study. The 1-year estimated survival rate was 64 ± 10%, compared to an age and sex matched expected 99% survival for the general population. Thirteen of the 25 patients were managed surgically, 7 of whom died within 2 days of surgery.[98]

Although Campbell suggested that aortic stenosis was a progressive disorder in the adult,[65] Hohn and colleagues were among the first to report progression of stenosis in childhood.[97] This was documented with progressive changes on electrocardiograms from 56 patients over a 5-year period, and by inference, from repeat invasive hemodynamic assessments in 4 patients. Following such follow-up studies, were a series of investigations employing serial invasive pressure determinations to assess progression in older children. The emerging rigorous application of catheterization and angiography allowed the precise diagnosis of valvar disease in all patients. As well, the determination of aortic valve gradients allowed an attempt at

correlations with symptoms and mortality. Friedman *et al.*[67] showed progression of the severity of disease in children with serial cardiac catheterizations in patients during follow-up, and concluded that serial hemodynamic evaluation was necessary. Only 2 patients had an associated lesion, 1 each with a small patent arterial duct and a coarctation of the aorta. In their study of 9 children, with initially asymptomatic stenosis, left ventricular systolic pressures were determined either by retrograde or transseptal catheterization, or by direct left ventricular puncture, at an average age of 7 years (range 4–10 years). At the time of reassessment, at an average age of 13 years (6 to 20 years), they found that the peak systolic gradient across the aortic valve increased from a mean 28 (range 15 to 40) mmHg to 62 (range 20 to 100) mmHg. Only 2 of the original 9 patients developed symptoms, and 3 underwent surgical valvotomy. Cohen and colleagues[99] published a series of 15 children in whom serial catheterizations were also performed. These authors suggested that the mechanism responsible for the progression of stenosis was the constancy of the hemodynamic valve orifice in the setting of an increase in body size. These authors cautioned against over-reliance on clinical, roentgenographic or electrocardiographic parameters, as these were sometimes found to be unchanged over time, despite hemodynamic progression. El Said and colleagues reviewed serial hemodynamic measurements (an average of 4 years apart) in 37 patients with various forms of left ventricular outflow tract obstruction.[100] These authors reached similar conclusions as Cohen *et al.* ascribing progression of valvar stenosis to an increase in flow across a fixed valve orifice as a result of body growth, but also documented an actual decrease in valve area over time in some patients. Again, serial hemodynamic studies were recommended due to the poor reliability of clinical criteria in determining severity of stenosis.

The first natural history of congenital heart defects study [89] reviewed prospectively 473 patients < 21 years of age, with valvar aortic stenosis who underwent serial cardiac catheterizations 4–8 years apart. Enrollment was at the first cardiac catheterization, performed between 1958 and 1969. Of these, 179 patients (38%) were treated surgically, and 294 were treated medically during the follow-up period. A pressure gradient at catheterization of < 25 mmHg was defined as trivial obstruction, while 25–50 mmHg was considered mild, 50–79 mmHg was considered moderate, and > 80 mmHg was considered severe. Progression was found in most, and appeared to be age related, with infants progressing rapidly, children at a moderate rate, and adolescents progressing slowly over time, in the medically managed group. In most patients, a worsening of the clinical status accompanied worsening in the valve obstruction. However, as the authors indicated, the difference in rate of progression was also related to differences in initial severity between the age groups, with younger children generally having more severe stenosis at the time of the initial catheterization. Accordingly, from the entire cohort, surgery was performed upon 68% of the infants, but only upon 33% of the children 2–11 years of age. Furthermore, the group receiving medical treatment had milder disease overall than the surgical group (average gradient at enrollment 30 mmHg vs.75 mmHg, respectively). There were 7 deaths in the 294 medically treated patients (2%), of which 2 were infants; all 7 had at least moderate obstruction. Four of the deaths were sudden. Overall, significant clinical deterioration occurred in 40% of those treated medically, while clinical improvement was rare. Congestive heart failure was seen exclusively in infants. Cardiac enlargement and symptoms were more common in childhood, whereas a strain pattern on the echocardiogram was more commonly encountered in teenagers and young adults. Of the 179 patients who underwent surgical treatment, the majority had severe aortic stenosis. With only 1 exception, all underwent valvotomy by direct vision, and in 96%, a pump oxygenator was used. There were 33 nonfatal complications in 29 patients, including 6 neurologic injuries. Mortality occurred in 12 of 179 (7%), of which 7 were infants, and 2 were late sudden deaths in older children. At follow-up catheterization (mean of 7 years after surgery, range 3–9 years) adequate relief of obstruction (to a gradient of ≤ 50 mmHg) was demonstrated in 66%. Restenosis occurred in 6 patients, confirmed by 2 or more postoperative catheterizations, showing an initial adequate relief of obstruction. The authors noted that patients with severe stenosis fared better with surgical than medical management, as mortality in this surgical subgroup was 4%, and 18% (2 out of 11) for those medically managed.[101] In fact, the results for those with moderate stenosis (gradient 50–79 mmHg) also favored surgical over medical therapy, both in terms of mortality and overall clinical status.

Looking at a total of 432 subjects > 2 years, the Second Natural History Study[98] (Fig. 14A-2) estimated survival to be 90 ± 1% at 20 years, as opposed to an expected age- and sex-matched survival of 98% for the general population. Of those who were medically managed (291 patients) in the First Natural History Study, 87 ultimately required surgery. The freedom from operation at 20 years' follow-up was estimated to be 67 ± 3% for this cohort. For those over age 2 years initially surgically managed (138 patients), 36 required reoperation (78% valve replacement, 22% repeat valvotomy). Freedom from reoperation for this cohort was estimated to be 73 ± 4% at 20 years. The authors of the Second Natural History Study recommended management strategies dependent on the degree of obstruction. For those with peak gradients at catheterization of < 25 mmHg, medical management was advised, although approximately 21% of such patients ultimately required intervention during the subsequent 25 years. Patients with gradients of ≥ 80 mmHg should clearly undergo intervention. Those patients with gradients of 50–80 mmHg should be considered

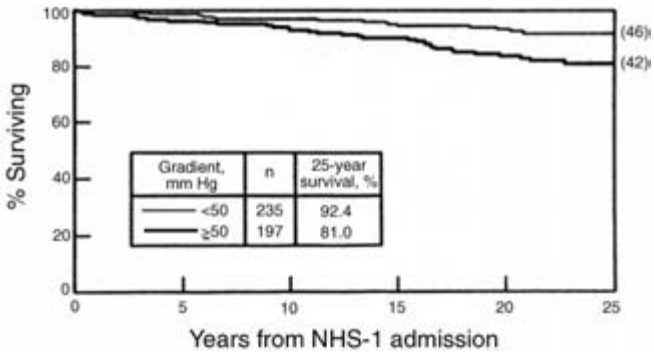


Fig. 14A-2 Kaplan–Meier survival curves for aortic stenosis patients at least 2 years of age at First Natural History Study (NHS-1) admission grouped by gradient at admission (< 50 and ≥50 mmHg). Numbers in parentheses indicate number of patients remaining under observation at 25 years. (Reproduced from Keane *et al.*,[98] copyright (1993), with permission from Lippincott Williams & Wilkins.)

for intervention, and should be monitored closely. This subgroup carried a 71% chance of ultimately requiring intervention in the following 25 years. The recommendations were less clear for those with gradients between 25 and 50 mmHg. These patients appeared to be at increased risk of sudden death and serious arrhythmias, and 41% ultimately required valvotomy. The consensus was that medical evaluation was required yearly given that progression to more severe obstruction was common. These recommendations have, with minor revisions, been incorporated into contemporary guidelines.[4]

Since the First Natural History of Congenital Heart Defects Study, a number of additional studies have addressed the long-term outlook for children with aortic valve disease, using either serial catheterization or echocardiographic examination to assess progression. Hossack and colleagues followed 218 children and young adults over an average of 9 years (range 1–26 years) before routine use of echocardiography[102] (Fig. 14A-3). Of 153 patients who presented with clinical evidence of mild obstruction (mean age at presentation 6 years, range 1–25), 55% remained with mild stenosis at the end of the follow-up period, while 18% had progressed to moderate, and 3% to severe stenosis. Surgery was required in an additional 23% (transventricular or transaortic valvotomy), and 1 died of bacterial endocarditis. Among the 54 patients who presented with clinically moderate obstruction at a mean age of 12 years (range 1–25 years), 42% remained with moderate stenosis after follow-up, while 10% progressed to severe stenosis, 42% surviving surgery. Six percent of patients had died of various causes after initially surviving surgery (mainly endocarditis). It appears that progression of stenosis is a function of age severity of stenosis at presentation, and duration of follow-up. In a study of 187 patients with either mild disease or a normally functioning bicuspid valve, hazard analysis predicted that patients with mild stenosis had < 20% chance of still having mild stenosis after 30 years[103] (Fig. 14A-4). In contrast, those with a normally functioning but bicuspid valve had no progression beyond mild stenosis although the duration of follow-up (mean 10 years) may not have been long enough to detect slow progression, occurring later in adult life.

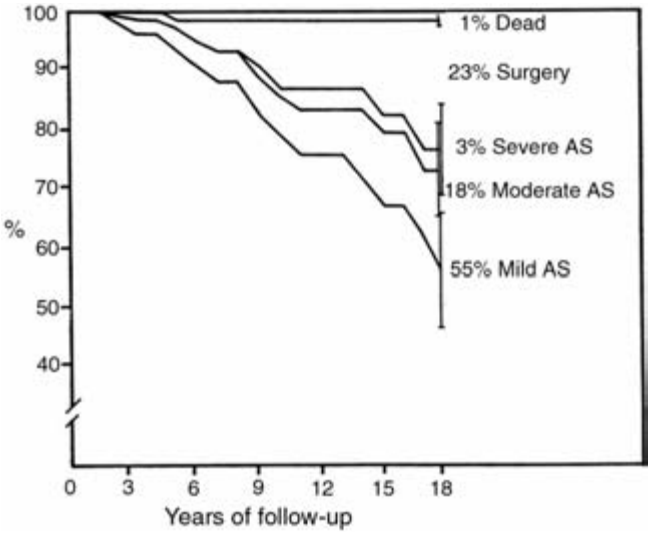


Fig. 14A-3 Cumulative actuarial curves of 153 patients presenting with mild aortic stenosis. The actuarial curves are plotted to the point where the smallest subgroup has 10 members at risk. Bars show ± 1 standard error at this point. Mean age at presentation, 6.5 years (range 1 to 25 years); mean follow-up, 8.8 years (range 1 to 26 years). (Reprinted from Hossack *et al.*,[102] *Br Heart J* 1980; **43**: 561–73, with permission from BMJ Publishing Group.).

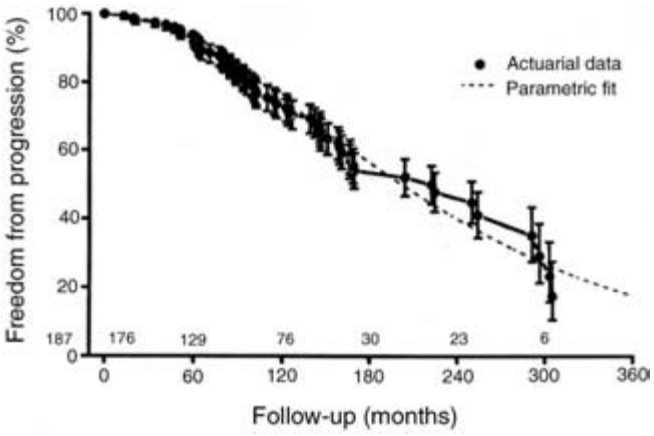


Fig. 14A-4 Actuarial analysis of freedom from progression. Each event is documented as a single dot with associated 70% confidence limits. The patient with the longest follow-up time experienced the event at 319 months and reduced the actuarial estimates to 0%. By convention this event is the parametric model with 70% confidence limits generated from analysis of the progression data in the hazard function domain. Estimates from the model are shown extrapolated to 360 months. (Reprinted from Kitchiner *et al.*,[103] Copyright (1993), with permission from Elsevier.)

As surgical results improved, greater numbers of patients with moderate to severe stenosis underwent valvotomy. In a study by Kitchiner *et al.* Surgery was performed when the peak-to-peak aortic valve gradient at catheterization was > 60 mmHg, the development of symptoms or left ventricular strain on the electrocardiogram.[16] Of the 239 children followed by the authors, 60 (25%) required operation, the severity of stenosis at presentation predictive of the need for surgery. Twenty-eight of the 184 patients (15%) with mild stenosis at presentation required surgery, whereas 22 of 33 (67%) patients with moderate stenosis underwent surgery ($P < 0.0001$). Reoperation rates were high (28%), most of which (70%) were valve replacements. Overall, prognosis was also influenced by the severity of stenosis at presentation, with those having mild disease achieving 5- and 20-year survival rates of 98% and 94%, respectively. In comparison, those with moderate stenosis at presentation had 5- and 20-year survival rates of 72% and 45%, respectively. When all significant events were reviewed (surgical or balloon valvotomy, endocarditis or death), the probability of event free survival for a hypothetical 2-year-old boy with mild stenosis after 20 years was calculated at 69%, whereas for moderate stenosis, it was only 5% (Fig. 14A-5). Progression of the severity of stenosis, as assessed echocardiographically, was found in all patients during the follow-up period, including all those who presented with insignificant or mild disease. However, of those with a normally functioning bicuspid aortic valve (39 patients), progression was only up to the mild range of stenosis.

In a more recent study of 129 children with aortic stenosis[83] (all of whom had serial yearly echocardiograms), Kiraly *et al.* found that progression in severity of stenosis was the rule at all ages, with 89% of children < 2 years old showing progression,

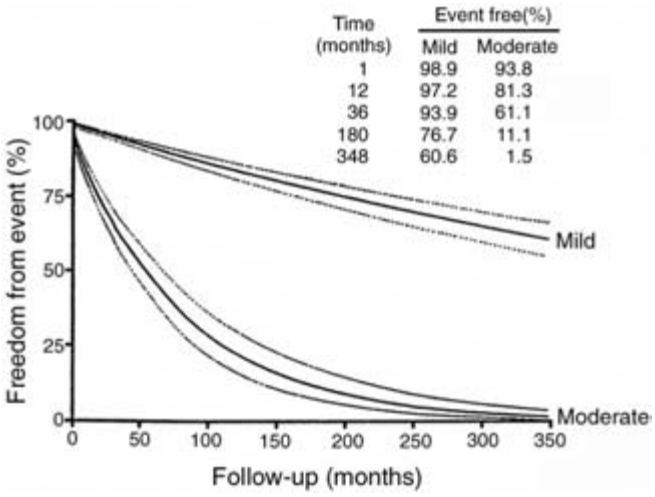


Fig. 14A-5 Predicted freedom from first significant event (aortic valve surgery or balloon dilation, endocarditis, or death) plotted from equations developed in the hazard function domain for a male patient without other cardiac lesions presented at 2 years of age with either mild or moderate aortic stenosis. Broken lines show the 70% confidence interval. (Reprinted from Kitchiner *et al*.,[16] *Br Heart J* 1993; **69**: 71–9, with permission from BMJ Publishing Group.)

as well as 61% of children > 2 years old. Changes in the severity of the stenosis were found to be rapid (often over an interval of 1 to 2 years), and could occur at any age.[90] Progression in severity has been documented in infants, although very rapid progression in the first few weeks of life is a rare, but a reported observation. Anand and Mehta[104] recently described 13 infants with asymptomatic aortic stenosis, 5 of whom showed rapid progression in the first 2 years of life. However, 2 infants progressed unusually rapidly from mild stenosis at birth to severe stenosis requiring intervention within the first 2 months of life.

Using necropsy data from 1952 to 1979, before the introduction of cardiac surgery in Central Bohemia, Samanek *et al.*[105] found of 946 children with congenital heart disease who died < 15 years of age, 26 (2.7%) had aortic stenosis. Of those 26, 43% died within the first month, while 77% died within the first year of life, suggesting that those who succumb to this disease were more likely to do so early in life. Looking at the same data from the perspective of the survivor, it was estimated that the actuarial survival rate among live born children with aortic stenosis was 96% for the first week of life, 95% for the first month, and 91% for the first year.[106] With both surgical and balloon aortic valvotomy available (1980 through 1990), Samanek *et al.*[18] found that the overall survival for the 391 patients with aortic stenosis was 96% after the first week of life (95% CI, 94% to 98%), and 91% (95% CI, 88% to 94%) at 6 months of life. Nine per cent of the cohort died within the first 6 months, representing those with critical obstruction; however, the cause of death (natural vs. postoperative) was not specified. Attrition was gradual thereafter, with a survival of 91% (95% CI, 88% to 93%) at 1 year, and 88% (95% CI, 85% to 92%) at 15 years.[18] The overall survival probability was similar before and after the introduction of cardiac surgery, which reflects the scarcity of severe stenosis amongst the roughly 800 000 children born over one decade in a geographically small area.

Aortic stenosis in the adult

Germane topics in adult congenital aortic stenosis include answering the following questions:[1] *who* is likely to develop significant valvular stenosis and[2] *when* is this likely to occur? Several studies that address the natural history of aortic stenosis in the adults have been published. Mills *et al.*[9] looked at the natural history of a normally functioning bicuspid aortic valve in 41 adult patients followed clinically over a mean period of 11 years (range 5–25 years). Significant morbid events included 3 episodes of endocarditis (with 1 death, and development of significant aortic insufficiency in the other 2), and calcific stenosis in 2 requiring valve replacement. Mild insufficiency developed in 3 patients, and 4 progressed to mild stenosis clinically. Overall, 26 of the patients (63%) continued to have clinical findings compatible with an uncomplicated functionally normal, but bicuspid valve. This study suggested that many patients, who have only an ejection click at the time of presentation, have a good prognosis; particularly true if bacterial endocarditis can be prevented.

A necropsy study by Fenoglio *et al.*[107] found 152 patients aged 20 or older with a bicuspid aortic valve and variable degrees of valvular dysfunction. Overall, 43 (28%) had pathologic evidence of aortic stenosis, the presence of which was age-dependent: 46% in those > 50 years of age, 53% in those > 60, and 73% in those > 70 years of age. While this and other necropsy studies document worsening obstruction in specimens from older subjects, clinical studies also have supported progression of aortic stenosis with advancing age. Pachulski and Chan[108] specifically looked at progression of stenosis in a bicuspid valve by performing serial echocardiograms in 51 adults whose mean age was 36 years (range 21–67). Median follow-up was 21 months (range 6–46 months). Most patients at the beginning of the study (31 of 51, or 61%) had a mean Doppler flow gradient of ≤ 25 mmHg and initially no more than mild insufficiency. Twelve patients had moderate and 3 had severe insufficiency, while 3 had moderate stenosis and 2 had combined stenosis and insufficiency. Of the 31 with initially minimal valve dysfunction, 22 remained in this category at the end of the follow-up period, with the remaining 9 patients progressing to significant stenosis (4 patients), significant insufficiency (2 patients), or required surgery (3 patients). This study suggested that development of significant insufficiency was a more likely phenomenon among young adults, and that development of significant stenosis was more common among those > 50 years of age. Beppu and colleagues[56] followed 75 patients aged 15 to 76 years (mean 44 years) with a bicuspid valve. The rate of progression of stenosis was found to be related to the morphology of the valve. Cusps oriented anteroposteriorly (commissure left to right) with both coronaries arising from the same leaflet were found in 46 patients (61%), and a right-left oriented valve (i.e. coronary arteries arising from separate leaflets) in 29 patients (Fig. 14A-6). Pressure gradients were found to increase by 20 mmHg per decade in the anteroposterior group and by 10 mmHg in the right-left group, with correspondingly faster development of sclerosis in the former. Furthermore, those in the anteroposterior group with eccentric aortic valves (defined as a ratio of the width of the major cusp to the width of the minor cusp ≥ 1.2) had an even greater progression of stenosis, averaging 27 mmHg per decade.

Numerous additional clinical studies assessing the progression of aortic stenosis in adults have been published.[109–114]

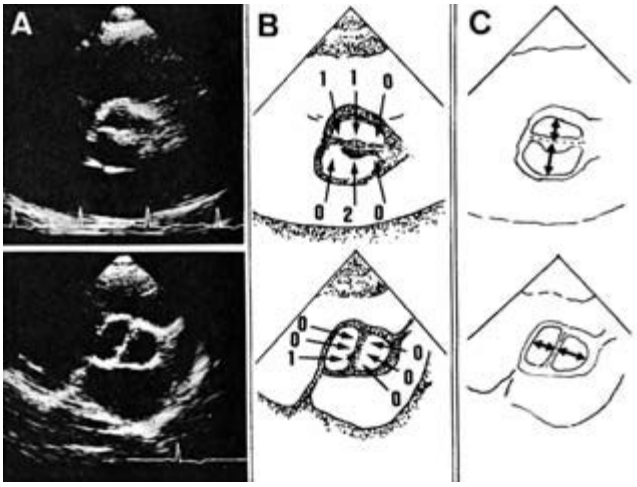


Fig. 14A-6 **A**. Short-axis views of anteroposteriorly located (top) and right-left located (bottom) cusps of bicuspid aortic valves. **B**. Schematic demonstration of scoring of cusp sclerosis. Each cusp is divided into three segments: central and both commissural segments. Sclerotic scores for each segment are summed as sclerotic index, which is 4 at top and 1 at bottom. **C**. Measurement of cusp eccentricity. Cusp is designated as eccentric or symmetric when ratio of width of cusp is ≥ or < 1.2 respectively. (Reprinted from Beppu *et al*.,[56] Copyright (1993), with permission from Excerpta Medica.)

Regrettably, these studies either combined all etiologies of aortic stenosis or disregarded etiology altogether, and thus, many of the conclusions may not be applicable to those patients with congenital stenosis. One recent study of adults with severe asymptomatic stenosis suggested that a less calcified valve was associated with fewer morbid events. The authors contended that the etiology of the stenosis may not be important in the rate of progression. However, the majority (84%) of those with minimally calcified valves, indeed had congenitally bicuspid valves, notwithstanding the fact that among those with severely calcified valves the morphology was often unclear.[115]

There are important differences and similarities between congenital and acquired aortic valve stenosis. While the congenital lesion accounts for approximately 50% of adult severe stenosis[5,51] and for the majority of aortic valve replacements in the modern era in developed countries, these patients tend to be a decade younger than those with an acquired lesion and have a lower incidence of accompanying coronary artery disease.[116] Despite these important demographic differences, similar risk factors for progression may exist. There is growing evidence that degenerative aortic stenosis in adults bears histological similarities to generalized atherosclerosis[117] and both aortic calcification[118] and progression of aortic stenosis[119–122] are associated with many of the same cardiovascular risk factors, such as smoking, hyperlipidemia, and hypertension. While limited information is available about the role of traditional cardiovascular risk factors in the progression of stenosis specifically on congenitally bicuspid valves, it appears that these risk factors may be implicated. A recent study by Chan and colleagues[123] compared 48 patients with bicuspid valves and significant stenosis (mean Doppler flow gradient ≥ 25 mmHg), with 52 patients with normally functioning bicuspid valves. The authors found that total cholesterol levels and systemic hypertension were associated with development of stenosis, despite similar ages between groups.

Clearly not all patients with a bicuspid valve develop stenosis, and more research is needed in this area to elucidate the risk factors associated with deterioration of valve function. It is safe to state that those diagnosed at an early age and more severe stenosis at diagnosis are certainly at higher risk for deterioration of valve function. Echocardiographic assessment of valve morphology plays an important role in determining the likelihood of progressive stenosis, with those having anteroposteriorly oriented cusps being at higher risk. With the elucidation of the emerging role of traditional cardiovascular risk factors in the progression of disease, greater ability to predict those at risk for deterioration of valve function is possible, and with it comes the prospect of possible prevention of such deterioration.

Naturally occurring complications of aortic stenosis

Sudden death

Sudden death is a prevailing cause of death in patients with left ventricular outflow tract obstruction, although the exact frequency of this occurrence varies widely across different studies, from as high as 19% to as low as 1%.[124,125] Campbell,[65] summarizing a number of other studies, suggested that the overall risk of death in aortic stenosis in the first two decades of life was 1.4% per annum, with the risk of sudden death being 0.4–0.9% per annum. The risk was found to increase further in later decades of life. Ominous signs and symptoms in many studies included exertional dyspnea, angina, syncope, and left ventricular strain pattern on an electrocardiogram, although it was noted that not all cases of sudden death are preceded by symptoms or left ventricular strain.[65,124] Doyle and colleagues[126] specifically looked at the incidence of electrocardiographic abnormalities in cases of sudden death with left ventricular outflow tract obstruction. They suggested that 70% of previously reported cases of sudden death had evidence of left ventricular strain pattern, while 9% were completely normal. Symptoms of easy fatigability, chest pain, exertional dyspnea, or syncope were present in almost all reported cases of sudden death. However, the study was tainted by the inclusion of known cases of subaortic stenosis.

While clinical studies performed before the era of surgical intervention would have the highest theoretical potential for accurately determining the frequency of sudden death (since even the severest forms would have gone unoperated), those very same studies are complicated by poor diagnostic accuracy in determining the site of left ventricular outflow tract obstruction. For instance, a relatively high mortality rate of 8.2% among 73 patients < 20 years of age was found in the study by Braverman and Gibson.[127] But as stated by the authors, "no attempt has been made to distinguish clinically between valvular and subvalvular stenosis." Conceivably, a subset of those who died may actually have had hypertrophic cardiomyopathy with subaortic obstruction, a condition that carries a high incidence of sudden death in some families. Such was the case in the study by Thornback and Fowler[128] where the incidence of sudden death was 1% for valvular aortic stenosis, while 17% of those had hypertrophic cardiomyopathy. A multicenter study of sudden death in children with congenital heart disease collected data on 254 cases of sudden death.[129] The largest group of

patients were those with left ventricular outflow tract obstruction, accounting for 33 deaths (18%). However, only 16 of those patients actually had confirmed valvular aortic stenosis, while in the remainder, the site of obstruction was either subvalvular, supravalvular, or unknown. Clearly, meaningful estimates of risk of sudden death need to derive from studies that include only patients with proven valvular disease. Therefore, estimates must be sought from studies in the era of routine cardiac catheterization or echocardiography, accepting that, as surgical results improve during these epochs, more patients are successfully treated, averting a naturally occurring complication.

The risk of sudden unexpected death was addressed in the Second Natural History of Congenital Cardiac Defects Study.[98] Of the original cohort of patients, 12% died and more than half of the deaths were sudden and unexpected, most patients having been asymptomatic, but with significant stenosis or insufficiency. The risk of serious arrhythmias (multiform premature ventricular contractions, ventricular couplets, or ventricular tachycardia) was significantly higher in patients with stenosis than in the general population according to ambulatory electrocardiography.[130] Overall, 45% of those with aortic stenosis had at least one serious arrhythmia, with those surgically managed having a significantly higher rate of arrhythmias compared to the medically managed group. Multivariate analysis suggested that risk factors for serious arrhythmias in the entire cohort included an increased left ventricular end-diastolic pressure (LVEDP) (odds of a serious arrhythmia doubled with a 5 mmHg increase in LVEDP), previous aortic valve replacement (odds fivefold higher), male gender (odds fourfold higher), and significant insufficiency (odds 12-fold higher). Previous aortic valve replacement as a risk factor for arrhythmias was felt to be due to the severity of pre-existing valve disease in this subgroup, rather than due to the nature of the operation itself. The propensity to serious arrhythmias in patients with stenosis or insufficiency appears to be related to development of subendocardial ischemia, which both increasing obstruction and regurgitation aggravate. However, ischemia is not exclusively a subendocardial process linked to a hemodynamic burden. Rare cases of myocardial ischemia in aortic stenosis have been reported due to direct coronary obstruction due to ostial occlusion or entrapment.[131] Imaging of the coronary arteries is therefore mandatory in those with symptoms or signs of ischemia out of proportion to that dictated by the hemodynamic severity of the valve dysfunction.

Dilation, dissection or rupture of the ascending aorta

Fragility of the ascending aorta is known to occur in patients with congenital aortic valve abnormalities, and manifests clinically as dilation (aneurysm) of the ascending aorta, dissection (limited or extensive cleavage of the medial layer of the aorta), or rupture (usually at the site of aneurysm or dissection).[132] Whether the clinical fragility of the ascending aorta is a consequence of the functional abnormality of the aortic valve or a manifestation of a common underlying vascular disorder has been the subject of much debate.

It is clear that Maude Abbott had already recognized the association of a bicuspid aortic valve with aortic rupture in her review of coarctation of the aorta in 1928.[133] She wrote:

> The presence of a bicuspid aortic valve appears to indicate, at least in a portion of the cases in which it occurs, a tendency to spontaneous rupture of the aorta, which hangs always, like a sword of Damocles, above the unsuspecting subjects of this type of coarctation, for this anomaly occurred in quite half the cases so terminating. A causal relation between the three conditions is not clear, but it seems probable that the thinning, which is not infrequently seen in the wall of the ascending aorta in these cases, may also be of congenital origin and due to the same arrest of development that led to an incomplete evolution of the endocardial cushions destined to become the aortic cusps.

Erdheim[134,135] published shortly after Abbott two case reports of patients who died with ruptured aortic aneurysms. He described the histological changes and coined the term "cystic medionecrosis," or cystic medial necrosis. Cystic medial necrosis is, in fact, a misnomer given that the media in the affected aorta is neither truly cystic nor necrotic,[136,137] and a more appropriate term may be "medial degeneration"[138] (Fig. 14A-7). This histological pattern has been found most consistently in the ascending aorta of patients with the Marfan syndrome,[136,139] but it has also been found in patients with ascending aortic dissection in association with aortic valve disease.[138,140–142] However, a similar histological appearance was seen in cases of so-called senile aortic dilatation,[143] in isolated aortic dissecting aneurysms,[143] in coarctation of the aorta,[144] and in even in normal the aorta as an age related phenomenon.[137] A recent study by Niwa *et al.* also found histological evidence of medial degeneration in the great arteries in a number of other congenital heart malformations. Histologically involved were the aortas in patients with bicuspid aortic valves, coarctation of the aorta, tetralogy of Fallot (with pulmonary atresia or stenosis),

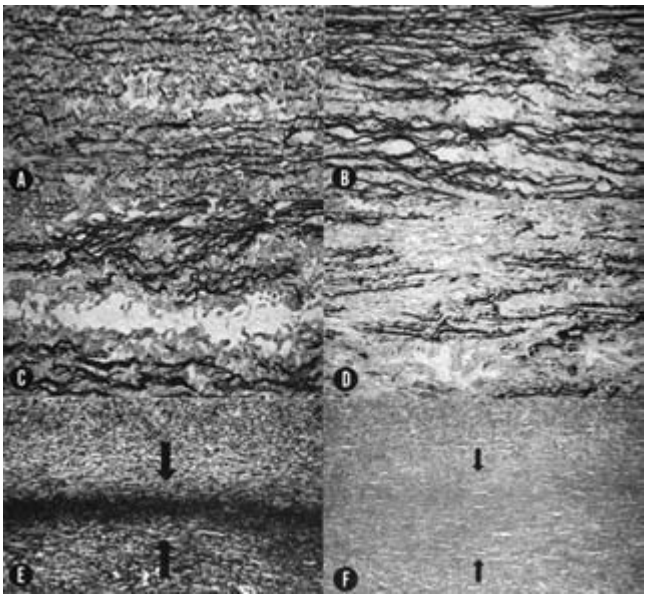


Fig. 14A-7 Histopathological characteristics of aortic medial disease in aortic dissection. A to D, medial degeneration (so-called cystic medial necrosis), with fragmentation and loss of elastic laminae and with bubbly pseudocystic pooling of glycoproteins, resulting in a weakened aortic wall. A to D, correspond to grade 1 to 4 lesions. E, F, central laminar necrosis (between arrows), with band-like loss of smooth muscle cells and resultant close apposition of intervening elastic laminae. A to E, elastic-van Gleson; F, hematoxylin-eosin stain; A to C, magnification X 180; D, F, X 90; E, X 35; all panels reduced by 23%. (Reprinted from Larson and Edwards,[138] Copyright (1984), with permission from Excerpta Medica.)

and truncus arteriosus, among other anomalies; and the pulmonary trunks in pulmonary valve stenosis, tetralogy of Fallot with absent pulmonary valve syndrome, and ventricular septal defect with Eisenmenger syndrome, among others.[145]

It has been suggested that medial degeneration is the result of ongoing injury and repair within the aortic media, as a consequence of the continuous hemodynamic burden to which the aorta is subject.[137,143] However, others have suggested that the medial change may be congenital, having been detected in infants < 24 h old.[144] A more recent study, investigating the role of apoptosis as a mechanism responsible for the smooth muscle cell depletion seen in cystic medial necrosis, found massive focal apoptosis within surgical aortic specimens from subjects with dilated ascending aortas. However, compared with subjects with aortas of normal caliber, those with a bicuspid aortic valve had a significantly higher apoptotic index than those with a tricuspid aortic valve, suggesting a link between the congenital malformation of the aortic valve and the genetically programmed cell death of smooth muscle cells in the aortic media.[146]

A final point of contention revolves around the cause and effect relationship between the histological entity of medial degeneration and the clinical entity of aortic fragility manifested as aortic dilation, dissection or rupture. While some have suggested that medial degeneration may be the underlying cause for aortic fragility,[147,148] attributing the weakness in the aortic wall to the fragmentation of elastic fibers and depletion of smooth muscle, others regard it as a nonspecific histological finding with no direct effect on structural integrity, citing the frequent finding of this histological pattern in aortas with no demonstrable clinical fragility.[136,137,143]

Regardless of the poor specificity and unclear relevance of the histological pattern of medial degeneration, one thing appears certain: patients with certain aortic valve abnormalities do, indeed, manifest clinical features of aortic medial fragility. There is mounting evidence that congenital aortic valve abnormalities, particularly a bicuspid aortic valve, are associated with a primary aortic wall pathology that predisposes to dilation, dissection, and rupture. The term "post-stenotic dilation" has been employed to account for the aneurysmal ascending aorta so commonly seen in association with congenital aortic stenosis (Fig. 14A-8). This term implies that the dilation is produced by a hemodynamic consequence of the stenotic valve itself. In fact, several lines of evidence seem to point away from this rather simplistic explanation.

First, several studies in recent years have confirmed that the degree of aortic root dilation is unrelated to the severity of congenital aortic valve stenosis.[149–152] In the article by Pachulski *et al.*, 101 patients with normally functioning or only mildly stenotic bicuspid aortic valves (Doppler mean resting aortic valve gradients < 25 mmHg) were compared to an age- and sex-matched control group. The aorta was measured at the level of the sinuses, rather than distal to the sinotubular junction, specifically to avoid any potential effect of "post-stenotic dilation" (which would only be expected to occur distal to the sinotubular junction, according to the authors). They found a significant difference in the aortic root diameter at the level of the sinuses, the bicuspid valve group having an average measurement that was *c*. 5 mm larger than the control group.[149] Hahn and colleagues then looked at a cohort of 83 subjects with a bicuspid valve and variable degrees of stenosis or regurgitation.[150] All had significantly larger aortic roots (measured at three levels: the sinuses, the sinotubular junction, and the ascending aorta) than an age- and sex-matched control group, even after correction for body surface area. Furthermore, the aortic root dilation was found to be independent of altered hemodynamics or patient age. Nistri and colleagues[151] studied military recruits, and also found significantly larger aortic roots (at all levels except the annulus) in a cohort of 66 young men with normally functioning bicuspid aortic valves when compared to 70 age-matched controls. When the bicuspid valve group was further subdivided, half of those with a bicuspid valve were actually found to have an aortic root measurement that fell within the normal range, while the other half had abnormally dilated aortic roots according to accepted criteria. The authors suggested that subset of patients with normally functioning bicuspid aortic valves have, in addition, early onset of aortic root dilation. As several studies indicate, aortic root dilation cannot possibly be simply "post-stenotic," since it is frequently found associated with normally functioning bicuspid valves.

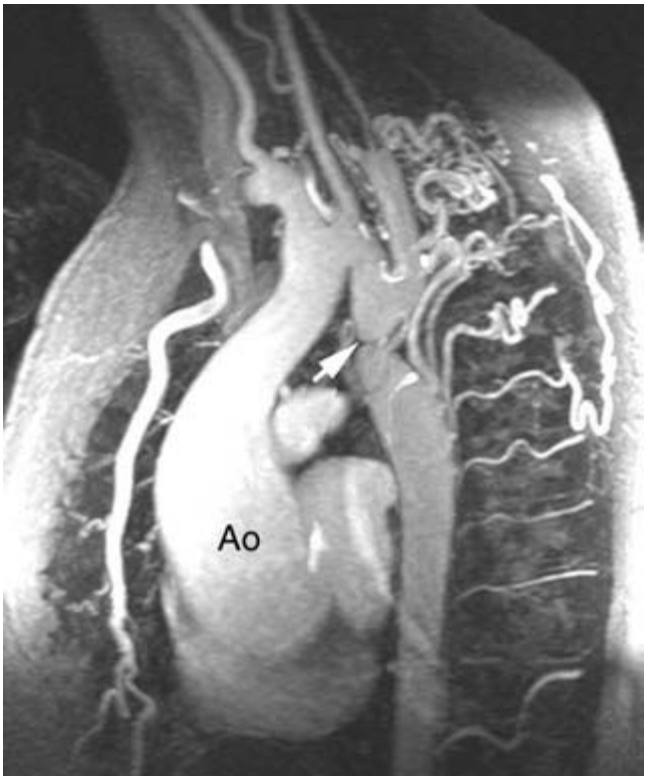


Fig. 14A-8 MR angiogram of a dilated aortic root, in association with a bicuspid aortic valve and coarctation, suggestive of a diffuse vasculopathy.

Keane and colleagues[152] further studied 118 patients with a bicuspid valve compared to a control group consisting of subjects with acquired aortic stenosis upon a tricuspid aortic valve, matched for the degree of stenosis and regurgitation. Paired analysis found significantly more dilated aortic roots in the bicuspid subjects (measured at all levels) compared to those with acquired tricuspid aortic valve disease, this despite the older age of the latter group. This provides the second line of evidence against aortic root dilatation being a simple "post-stenotic" phenomenon: it occurs preferentially in those with congenital rather than acquired aortic valve disease. A third line of evidence against aortic root dilation being purely a "post-stenotic" phenomenon lies in its very early occurrence, includ-

ing the neonatal period.[72,93] In Lakier *et al.*'s study[93] of 10 infants with critical aortic stenosis presenting in the first month of life, 5 (50%) had a dilated ascending aorta at cardiac catheterization. Four of the 5 had necropsies: 2 had tricuspid valves, 1 a bicuspid valve, and 1 a unicuspid valve. This study suggested that aortic root dilation was not exclusive to congenitally bicuspid aortic valves, but may be found in various types of congenital aortic valve abnormalities.

The case for a strong association between aortic medial fragility and congenital aortic valve abnormalities exists not only for aortic root dilation, but also for aortic dissection and rupture originating in the ascending aorta. The frequency of aortic valve anomalies in necropsy series of ascending aortic dissection would presumably be identical to that of the normal population (i.e. 1–2%) if the aortic valve anomaly were purely coincidental. However, almost every study has found a far greater incidence of congenital aortic valve anomalies (particularly bicuspid) than one would surmise by chance alone. In fact, the only large study of aortic dissection (204 subjects spanning 92 years) in which congenital aortic valve anomalies were not found was that of Wilson and Hutchins.[153] This study, however, has been widely criticized due to its reliance on necropsy records rather than detailed examination of necropsy specimens, and it seems likely that a bicuspid valve may have been simply overlooked in the original reports.[138,154] Gore and Seiwert[155] studied 85 aortic dissection specimens from all ages and found 11 (13%) with a bicuspid aortic valve. In a subsequent study of aortic dissection specifically in subjects < 40 years of age, Gore found that 28% (9 out of 32) had a bicuspid valve.[156] Edwards *et al.*[157] found 11 cases of nonstenotic bicuspid valves among 119 cases of dissecting aortic aneurysm (9%), 5 of whom were young (< 29 years of age). In a necropsy study of 161 cases of aortic dissection, Larson and Edwards[138] found 121 subjects with intimal tears involving the ascending aorta. Of those 121, 17 (14%) had a bicuspid valve, and 2 (1.7%) had a unicommissural valve. The incidence of a bicuspid or unicommissural valve in this series, compared to the incidence in the entire necropsy population over a 21-year period (21 417 cases), was 10- and 22-fold greater, respectively. Viewed from the reverse perspective, aortic dissection was found in 6% (18 of 293) of cases of a bicuspid aortic valve, and in 12% (2 of 16) of cases with a unicommissural aortic valve. The authors concluded that compared to aortas with tricuspid aortic valves, aortic dissection occurred 9 times more often with a bicuspid aortic valve and 18 times more often with unicommissural aortic valves. Roberts and Roberts[154] also found a greater incidence of congenital aortic valve anomalies, than chance alone would predict, in necropsy specimens of aortic dissection; 14 out of 186 (8%) had a bicuspid valve, and 2 (1%) had unicommissural valves. The purported association between aortic fragility and a bicuspid aortic valve applies, therefore, as well to unicommissural valves, and potentially to other congenital aortic valve anomalies, with the possible exception of the quadricuspid aortic valve.[138] A familial form of aortic dissection with cervicocephalic arterial extension associated with bav has even been reported, again suggesting a common genetic etiology.[158]

A number of reports in the literature describe aortic dilation, dissection or rupture in patients with the Turner syndrome.[35–38,159–173] It appears that the majority of such patients have risk factors including a bicuspid aortic valve, coarctation, and/or systemic hypertension, thereby accounting for a propensity to develop complications of aortic medial fragility. In fact, it has been suggested that aortic dissection and dilation are entirely related to these risk factors and that these patients do not have a greater risk of aortic complications than others without Turner syndrome who have similar risk factors.[37] However, a small number of patients with Turner syndrome but with no discernible cardiovascular risk factors have also been reported to have complications related to aortic medial fragility, suggesting that the Turner syndrome may indeed represent an independent risk factor.[35]

While the relevance of cystic medial necrosis remains unclear, it appears incontestable that clinical aortic fragility is indeed associated with congenital aortic valve anomalies, a subject that has so far received insufficient attention. Thorough monitoring of the patient born with a congenital aortic valve abnormality consequently includes not only constant vigilance of valvular function but also increased alertness of the possible disastrous consequences of weakened aortic wall integrity.

Non-iatrogenic aortic insufficiency and endocarditis

Endocarditis was previously considered one of the most frequent causes of morbidity and mortality among patients with aortic stenosis. It was the cause of death in 55% of subjects > 30 years of age and 13% of those > 70 years of age, according to Grant in 1928.[174] It has been suggested that between 10% and 30% of bicuspid aortic valves develop endocarditis, and that 25% of endocarditis occurs on a bicuspid valve.[5] The exact rate of occurrence of endocarditis is difficult to estimate, and depends on whether clinical or necropsy studies are used. Of the 152 patients > 20 years of age with a bicuspid aortic valve in Fenoglio *et al.*'s study,[107] active or healed endocarditis was found in 9 (21%) of the 43 patients who had some degree of stenosis, but only in 4 of the 48 who had normally functioning bicuspid valve, suggesting that the likelihood of endocarditis was in part related to the degree of stenosis. In contrast, 77% of the subgroup with aortic insufficiency had evidence of active or healed endocarditis, which was felt to be the cause of the aortic valve incompetence. Looking at the entire cohort of 152 patients, endocarditis was the most common cause of mortality in the series, accounting for 40% of deaths. In Hossack *et al.*'s study of 218 patients < 25 years of age with stenosis, there were 3 non-surgical patients who developed bacterial endocarditis, with 1 death, for an incidence of 2.7 episodes per 1000 patient-years.[102] In Kitchiner *et al.*'s study the incidence of endocarditis was 1.3 episodes per 1000 patient-years.[16] In Campbell's study, the endocarditis rate was 0.9% per annum.[65] The First Natural History of Congenital Heart Defects Study suggested an incidence of 1.8 cases per 1000 patient-years.[175] The Second Natural History Study found an overall incidence of endocarditis of 2.7 per 1000 patient-years in aortic stenosis, but subgroup analysis determined that the incidence among those medically managed was only 1.6 per 1000 patient years, whereas it was 4.1 per 1000 patient-years for those patients surgically managed.[176] The discrepancy in incidence appears at first glance to be related to the management algorithm, but a constant bias exists, in that the majority of those surgically managed had severe stenosis. When management strategy, age, severity of insufficiency, and stenosis were analyzed independently, the degree of stenosis was by far the most important determinant of the incidence of endocarditis.

Naturally occurring (non-iatrogenic) aortic insufficiency may complicate isolated aortic stenosis as a result of various mechanisms, such as previous inflammatory conditions (e.g. rheu-

matic fever), endocarditis, aortic root dilation, aortic dissection, aortic valve prolapse, and spontaneous valve rupture. In a review of the surgical pathology of 225 cases of pure insufficiency, Olson and colleagues[177] found 54 examples of congenitally bicuspid valve. Endocarditis was responsible for insufficiency in 9 (17%) patients, 5 of whom had leaflet perforations, 3 had focal deficiencies in the cusps creating poor coaptation, and 1 patient had both lesions. The remaining 45 subjects developed insufficiency as a result of mechanisms related to the morphology of the valve itself and its associated pathologies. Insufficiency was associated with aortic root dilation in 14 of the 45 patients (31%), and dissection of the ascending aorta in 3 patients (7%). Cusp prolapse appeared responsible for the insufficiency in the majority of cases (28 of 45, or 62%), while intrinsically regurgitant valves were seen in 10 cases (due to a fenestrated raphe). One case was notable for the presence of a raphal cord that ruptured, producing acute insufficiency. Overall, calcification was felt not to play a significant role in the genesis of aortic insufficiency. In addition to a bicuspid valve, the only other congenital aortic valve anomaly found to be associated with insufficiency was a quadricuspid valve, occurring in two instances.

Aortic root dilation in association with congenital aortic valve anomalies has been discussed in detail in the previous section. The mechanism whereby root dilation may produce aortic insufficiency is intuitive. The aortic leaflets are attached to the aorta peripherally at the sinotubular junction,[178] which, when pulled away from the center of the aorta by dilation of the root, leads to failure of leaflet coaptation with resulting leaking.[150] It is of no surprise, then, that the most regurgitant bicuspid valves had the greatest degree of root dilation in Keane *et al*.'s[152] and Hahn *et al*.'s[150] studies. Curiously, Keane suggested that insufficiency "may play a role in facilitating the dilation of the bicuspid root,"[152] whereas the reverse explanation (that root dilation facilitates insufficiency) was proposed by Hahn *et al*.[150] The latter seems more logical.

Edwards suggested that aortic valve prolapse may be a mechanism responsible for insufficiency in patients with a bicuspid valve.[7] Aortic valve prolapse (without associated ventricular septal defect) is a frequent finding in bicuspid aortic valve, and is defined as an abnormal degree of inferior diastolic displacement of the aortic leaflet below its level of insertion.[179] A small degree of displacement is common in normal valves. When assessed by two dimensional echocardiography, Stewart and colleagues[179] found significantly more prolapse in bicuspid valves with vertically rather than horizontally oriented commissures. The degree of insufficiency was found to correlate with the aortic valve prolapse volume (a mathematical estimate of the volume occupied by the prolapsed cusp), but a correlation between cusp orientation and insufficiency could not be established. Sadee and colleagues[124A] studied 148 surgically excised bicuspid aortic valves, 23% were truly bicuspid, 34% were bicuspid with a raphe, and 43% were bicuspid with a raphe and an indentation in the free edge of the conjoined cusp. The presence of aortic root dilation carried a relative risk of pure valve insufficiency of 3.99, while the relative risk for a valve with a raphe and an indentation in the conjoined leaflet was 4.95. Interestingly, no valves with prolapse were identified.

Spontaneous (unrelated to endocarditis) rupture of a bicuspid valve causing acute severe insufficiency has rarely been described. Becker and Duren described such a case in 1977.[180] The surgically excised valve showed a strand of tissue inserting in the free upper rim of the conjoined cusp, with the other end of the strand free-floating, presumably having ruptured from its attachment on the ascending aorta. Of 189 patients with a bicuspid valve, Roberts *et al.*[181] identified 13 patients with pure aortic insufficiency (7%) none of whom had pathologic evidence of active endocarditis or rheumatic fever. Three cases had coarctation of the aorta, and hypertension may have played a role in exacerbating the insufficiency. One of the 13 cases had a similar strand of tissue still attached to the ascending aortic wall. In the study by Olson *et al.*,[177] 1 similar case of ruptured strand inserting into the conjoined leaflet was found from 225 specimens, as discussed above. Walley and colleagues[182] described a series of such valves, from 291 surgically excised bicuspid aortic valves, 17 (6%) were notable for the presence of (sometimes multiple) raphal cords attaching the conjoined cusp to the aortic wall. The authors found that the valves with raphal cords also had a fenestrated raphe, although not all were necessarily regurgitant. Rupture of the cord, however, was considered a plausible explanation for sudden development of aortic insufficiency.

Apart from the above entities responsible for pure insufficiency, the common condition of progression of leaking in a stenotic valve (mixed aortic valve disease) merits mention. In the study by Subramanian *et al.*[183] of 213 specimens with mixed stenosis and insufficiency, calcification was found superimposed on a bicuspid valve in 19% and on a unicommissural valve in 6%. Calcification and sclerosis undoubtedly play a role in progression in congenitally malformed aortic valves, likely by fixation of the leaflets edges preventing coaptation.[183] This mechanism appears to be found particularly in valves with mixed disease, as calcification is seldom encountered in purely regurgitant valves.[177]

Modified history: surgical valvotomy

Perhaps the earliest attempt at surgical relief of aortic valve stenosis dates to the turn of the twentieth century, when Tuffier reportedly attempted to dilate an aortic valve by invagination of the wall of the aorta.[184] Successful aortic valve surgery was pioneered by Bailey in 1951, reporting the technique of closed transventricular aortic valve commissurotomy for rheumatic aortic stenosis.[185] Application to treat congenital aortic stenosis soon followed, and Marquis and Logan reported a pilot study of transventricular valvotomy in 1955.[186] In 28 patients, ranging in age from birth to 25 years, 6 were deemed clinically to have sufficiently severe stenosis to undergo attempted valvotomy, their ages ranging between 13 and 24 years. The authors described the surgical technique as follows: ". . . the approach was through the left ventricular wall, and an expanding dilator introduced into the aortic orifice was opened to its full extent (4 cm) in 2 or more directions, without prior incision of the valve."[186] A "tearing sensation" as the dilator opened was described in 4 of the 6. All survived the procedure, and all but 1 developed an increase in heart size postoperatively, suggestive of significant insufficiency. The authors were pessimistic about the general applicability of this technique in congenital aortic stenosis, and concluded: "It is clear that the results of valvotomy in congenital aortic stenosis are not always wholly beneficial and that they are to some extent unpredictable . . . in the meantime, aortic valvotomy is not, in our opinion, justified in congenital stenosis except when there is danger of sudden death or deterioration of a degree that might prejudice the outcome of postponed surgery."[186] Interestingly, they predicted the next

milestone in aortic valve surgery when they stated: "even in young patients without calcification of the aortic valve, it would be over-optimistic to expect normal valve function even if the valve were divided under direct vision."[186]

Indeed, direct vision aortic valvotomy was the next logical step. Swan and Kortz first applied this technique in a patient with rheumatic aortic stenosis in 1956,[187] with others publishing a similar technique the same year.[188] Two important advances in the field of cardiovascular surgery allowed for this successful endeavor: first, was the application of circulatory arrest by caval inflow occlusion, and second, the use of hypothermia to slow metabolism. Their patient was surface-cooled to a rectal temperature of 28.6°C and exposed to 6 min 15 s of circulatory arrest with no reported sequelae. Although hypothermic circulatory arrest continued to be used, the development of cardiopulmonary bypass, reported in 1954 by John Gibbon Jr,[189] provided other advantages, including more rapid and efficient cooling and rewarming, and a greatly extended duration of exposure of the aortic valve. The two techniques evolved in parallel, with some centers advocating circulatory arrest, others cardiopulmonary bypass, with closed transventricular valvotomy eventually falling into disfavor, particularly beyond infancy.

Surgical valvotomy in children and young adults

In 1963, Morrow and colleagues reported on 44 patients who underwent surgery using cardiopulmonary bypass with continuous myocardial perfusion.[190] Of these, 30 had valvular aortic stenosis; in 18 patients the valve was bicuspid, in 11 it was tricuspid, and in 1 patient it was unicommissural. The authors described 3 patients with a bicuspid aortic valve who required replacement of one or more of the aortic valve leaflets using individual Teflon® leaflet prostheses. Results were good, with 39 survivors of the 44 who were operated. Unfortunately, results were not stratified by valve morphology, and thus specific outcomes cannot be clearly discerned.

In the 1970s, as minor refinements in surgical technique and greater operator experience accrued, mortality for valvotomy decreased, and attention was increasingly paid to avoidance of reoperation. Because reoperation was invariably related to either significant aortic insufficiency or residual or recurrent stenosis, avoidance of these conditions became paramount. The latter was the lesser of the two evils, given that repeat valvotomy for significant stenosis was feasible, whereas surgery for significant aortic insufficiency entailed valve replacement, which was a difficult undertaking in young children, with the inevitability of repeated valve replacements in order to accompany somatic growth. Lawson *et al*.'s study[191] of 32 patients who underwent valvotomy for valvular aortic stenosis suggested that no child survived longer than 16 years without reoperation, which was a particularly sobering finding, and somewhat out of keeping with other contemporary studies. The authors describe converting 11 of 21 bicuspid valves into a tricuspid pattern by incision of the fused commissure. Accordingly, 65% of patients who underwent postoperative cardiac catheterization were found to have moderate to severe insufficiency. An editorial comment suggested that the investigators had been too radical in their approach to relieving the stenosis.[191] The decision to incise the fused commissure (raphe) in the setting of a bicuspid aortic valve requires careful attention to the resulting support of the newly divided leaflets in order to avoid severe aortic insufficiency. In cases where adequate support was unlikely, a policy of deliberately performing a limited incision of the fused commissure rather than a radical correction existed in some institutions, with residual stenosis being considered preferable to significant insufficiency.[192] Illustrating the widely disparate and polarized views on this matter, other investigators described never incising the raphe.[193] In Presbitero *et al*.'s study,[193] 52 children and young adults underwent open valvotomy between 1961 and 1978 with cardiopulmonary bypass and normothermia or moderate hypothermia. In 42, the valve was bicuspid, and in 26 a raphe was visible, although not incised. This policy, not unexpectedly, resulted in higher reoperation rates for residual stenosis, with relatively rare cases of severe iatrogenic insufficiency. The overall reoperation rate was 35% within 2–14 years after the original valvotomy (most reoperations occurred within 8 years). Furthermore, the risk with reoperation was considerably higher (17%) than that associated with a routine first valvotomy (4%) or first aortic valve replacement (6%). Actuarial survival was 98% at 7 years and 80% at 18 years after surgery. Freedom from reoperation at 20 years was only 14%. The authors described, as well, a particularly ominous form of stenosis in older children consisting of a "lumpy" (dysplastic) valve with an element of subvalvular and supravalvular stenosis, with annular and root hypoplasia. Since 7 of these patients with complex left ventricular outflow tract obstruction were included in their published results, one would anticipate that actuarial survival and reoperation rates would actually be more favorable for those with isolated valvular stenosis.

The long-term outcome of aortic surgical valvotomy performed before 1968 in Boston was the subject of a retrospective analysis.[194] Of 74 early survivors of valvotomy performed beyond infancy, 15 were lost to follow-up, and actuarial survival curves were constructed for the remaining 59 patients. Median age of initial operation was 11 years, and all were performed with cardiopulmonary bypass and moderate hypothermia. All fused commissures were incised. Total follow-up represented 1044 patient-years (range 0.3 to 26, mean 18 years). Actuarial analysis (Fig. 14A-9) predicted the probability of survival to be 94% at 5 years, 87% at 10 and 15 years, 82% at 20 years, and 77% at 22 years. Of the 13 deaths, 7 were sudden (representing 12% of the entire cohort, but 54% of all causes of death). Three more deaths were related to reoperation. Overall, there were 25 reoperations in 21 patients, of which 20 were valve replacements, 3 were repeat valvotomies, and 2 were left ventricular to descending aorta conduits. Actuarial analysis predicted the probability of reoperation to be 2% at 5 years, and 44% at 22 years.

Jones and colleagues[195] reviewed the data on 41 patients with valvular aortic stenosis who underwent open aortic valvotomy with cardiopulmonary bypass between 1958 and 1974. Surgery was performed at a median age of 13 years (range 2–17 years), and surgical indications were standard (peak gradient at catheterization of 50 mmHg or more, the presence of symptoms, or both). There was no surgical mortality. Seven of 41 (17%) required reoperation, with no early deaths, but 2 late deaths after reoperation. Overall, late deaths occurred in 8, of which 6 were cardiac, and 5 were sudden and unexpected, for a late survival rate of 80% at 15 years after initial surgery. Kaplan–Meier curves predicted a survival of 93 ± 4% at 10 years, 86 ± 6% at 15 years, and 68 ± 11% at 20 years. In comparison, the anticipated survival rates for the general population matched for age and year of operation are 99.7 ± 0.02% at 5 years, 99.1 ± 0.03% at 10 years, and 98.4 ± 0.04% at 15 years, and 97.7 ± 0.05% at

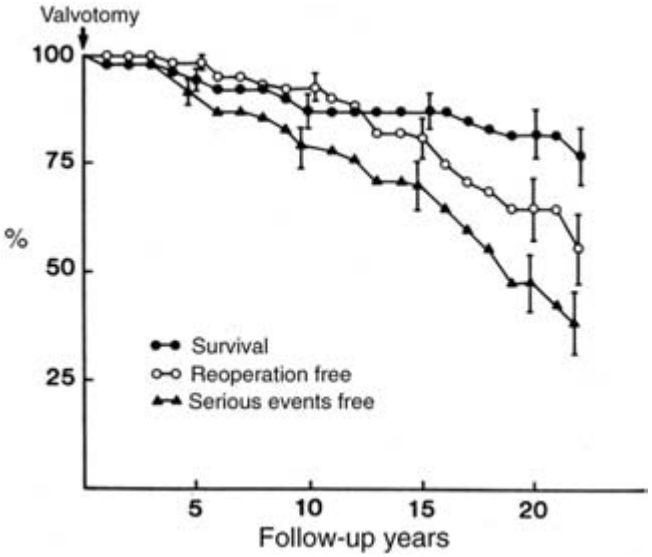


Fig. 14A-9 Three actuarial curves of survival, remaining free of reoperation and serious events, among 59 patients after aortic valvotomy. Serious events include death, reoperation and bacterial endocarditis; each patient is represented only once. Reoperation includes all types of aortic valve surgery. Bars represent ± standard error. (Reprinted from Hsieh *et al*.,[194] Copyright (1986), with permission from Excerpta Medica.)

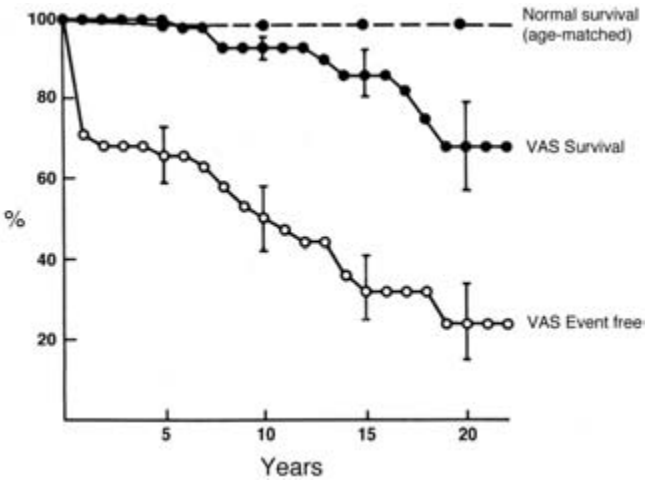


Fig. 14A-10 Postoperative life table analysis for survival and postoperative events for 41 patients having aortic commissurotomy for valvar aortic stenosis (VAS). The survival curve is compared with that of age-matched population at large. (Reprinted from Jones *et al*.,[195] Copyright (1982), with permission from Excerpta Medica.)

20 years (Fig. 14A-10). Ankeney *et al.*[196] reviewed 70 consecutive patients aged 2–20 years undergoing open surgical valvotomy at a single center between 1958 and 1980. Cardiopulmonary bypass and hypothermia (28–30°C) were used in all operations, while cardioplegia was not, and coronary perfusion was required only once. The authors describe incising fused commissures whenever possible (attempting to create tricuspid valves when feasible), with the additional technique of applying everting horizontal mattress sutures near the ring of the newly incised commissure when it appeared that coaptation was inadequate. There were only 2 operative deaths (3%), and 4 late deaths, of which 3 were noncardiac and 1 was due to endocarditis. Eleven patients were reoperated, and interestingly, in only 1 was significant insufficiency the indication. The remainder underwent either valve replacement or repeat valvotomy for significant stenosis; there were 2 operative deaths, and 1 late death. Actuarial survival was estimated to be 91% at 10 years, and 86% at 15 years.

In 1980, a large retrospective series was published from the Hospital For Sick Children, Toronto.[197] A total of 187 children underwent surgical aortic valvotomy between 1956 and 1975. Cases of subvalvular or supravalvular stenosis were excluded from the review. The 25 infants will be examined in a separate section. Of the remaining 161 children > 1 year of age, 70% were male, and 123 (76%) were between the ages of 5 and 15 years. Associated malformations in this group were rare. Surgery was performed by direct vision with the aid of cardiopulmonary bypass in all. There were 3 deaths within the first month, representing a surgical mortality of 2%. Ten patients were lost to follow-up, and the remaining 148 were followed for a mean duration of 7 years (range 0.5–16 years), for a total of 1094 patient-years. Reoperation was required in 20 patients (14%), including 6 valve replacements for mixed stenosis and insufficiency, with 4 intraoperative deaths. There were 5 non-surgical deaths, 2 due to endocarditis, and 2 were sudden. The actuarial survival rates at 5, 10 and 13 years were 97%, 93%, and 81%, respectively, while the freedom from serious incidents (reoperation, endocarditis, or sudden death) at the same time intervals were 92%, 69%, and 58% (Fig. 14A-11). Overall, there appeared to be a slow but gradual increase in the risk of serious events in the first 10 years after operation, with a more marked increase in subsequent risk, suggesting that longer follow-up would disclose a greater number of serious postoperative events.

In more recent published studies, the increased duration of follow-up has allowed insight into the outcome of not only the primary operation, but also that of reoperation. In some cases,

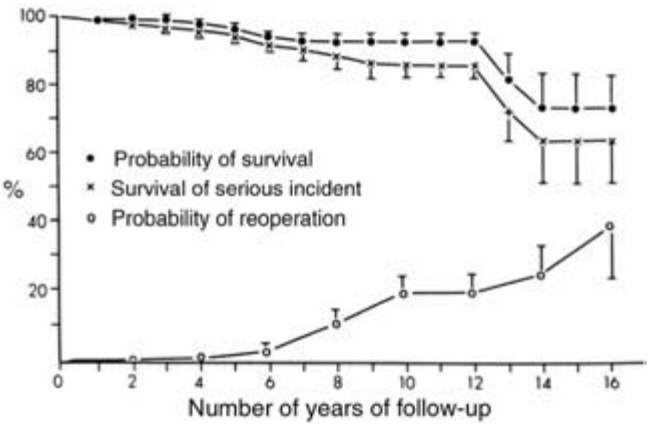


Fig. 14A-11 Actuarial plots of probability of survival, probability of survival free of serious incident, and probability of reoperation. Serious incident includes infective endocarditis, sudden death, or reoperation. Reoperation includes all types of aortic valve operations. Bars represent standard error of the *P* values. The small sample size for patients followed beyond 13 years accounts for slight incompatibility of the final points on the survival of serious incident and probability of reoperation plots. (Reprinted from Sandor *et al.*,[197] Copyright (1980) Mosby Inc., with permission from Elsevier.)

third operations on the valve emerge in the cohort, provided that duration of follow-up is sufficient. DeBoer and colleagues[198] reported 51 children > 1 year of age operated upon between 1956 and 1986 for isolated valvular aortic stenosis. Indications for the most part were standard (peak gradient at catheterization > 50 mmHg, the presence of symptoms, or both), although 1 patient was operated for symptoms alone in the setting of a gradient of approximately 25 mmHg. Seventy-three percent of the valves were bicuspid, and the average age at operation was 11 years (range 1–18 years). All procedures were open valvotomies with cardiopulmonary bypass and either hypothermia or cardioplegia. This study is one of the few that systematically performed cardiac catheterizations before and after valvotomy. Before surgery catheterization was possible in all patients, while after valvotomy, catheterization was performed in 43 of 49 survivors (88%) within 6–12 months. Gradient reduction was significant, from a mean of 91 ± 5 to 27 ± 4 mmHg, representing a 74 ± 3% reduction. Six (14%) patients had gradients > 50 mmHg after surgery, suggesting inadequate relief of obstruction. Only 7 patients (16%) had documented by catheterization aortic insufficiency after surgery, although the severity was not stated. The mean follow-up was 17 years, the longest was 28 years. Forty-nine patients survived the operation, for an operative mortality of 4%, although this reflected deaths occurring in 1956 and 1957 only, with no operative deaths thereafter. Overall, 75% (38 patients) were alive at latest follow-up, therefore amounting to a 22% long-term mortality (14% cardiac related). The reoperation rate was 36% (19 patients), predominantly due to symptomatic restenosis, at a mean of 18 years after the original valvotomy. All reoperations but 1 consisted of valve replacement, which differs from other series that include a significant proportion of repeat valvotomies. Only 1 patient required a third operation (redo valve replacement). When noncardiac deaths were excluded, actuarial survival was 100% at 5 years, 94% at both 10 and 15 years, 82% at 20 and 25 years, and 80% at 28 years. Reoperation-free survival was 98% at 5 and 10 years, 89% at 15 years, 64% at 20 years, 50% at 25 years, and 44% at 28 years (Fig. 14A-12). In other words, the likelihood of repeat operation was 0.2% per year for the first postoperative decade,

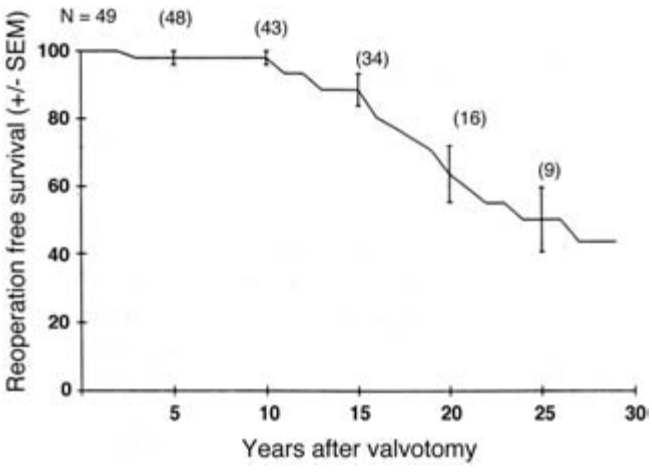


Fig. 14A-12 Actuarial analysis of operation-free survival in percentage of all patients surviving aortic valvotomy for congenital aortic stenosis. (N = number of patients at risk; SEM = standard error of the mean.) (Reprinted from DeBoer *et al.*,[198] Copyright (1990), with permission from The Society of Thoracic Surgeons.)

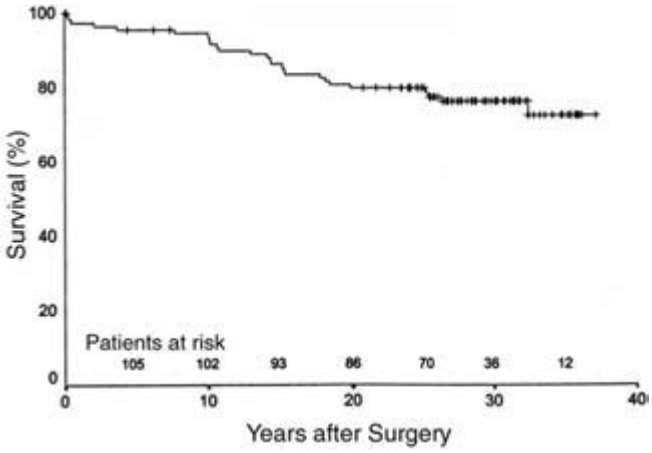


Fig. 14A-13 Actuarial long-term survival of the 113 early survivors after aortic valvotomy. Numbers below the curve indicate the numbers of patients at risk. (Reprinted from Detter *et al.*,[199] Copyright (2001), with permission from The Society of Thoracic Surgeons.)

and increased thereafter (and continued linearly) to 3.3% per year. Assuming continued linearity of the curve, the authors estimated that all would require reoperation within 40 years of the index procedure.

Undoubtedly one of the largest and most thorough series published on the long-term outcome of surgical valvotomy is that of Detter and colleagues, from Munich.[199] The authors reported on 116 patients (85 male) who underwent aortic valvotomy between 1960 and 1977, with a median follow-up of 26 years (range 0.1 to 37 years), with complete follow-up available in 96% of patients, representing an impressive total of 2761 patient-years. The median age at operation was 13 years (range 0.1–30 years). Four children were < 1 year of age, but were not judged to have critical stenosis. All underwent preoperative cardiac catheterization. Surgical indications were a gradient ≥ 50 mmHg, or the presence of symptoms. All valvotomies were performed using cardiopulmonary bypass and moderate hypothermia, without cardioplegia. Fused commissures were incised widely attempting to avoid aortic insufficiency. A bicuspid aortic valve was found in 84 patients (72%), with a tricuspid valve present in the remainder. Calcification of aortic leaflets was found in 15 patients (13%), and debridement of calcium deposits was performed in 12 patients at valvotomy. Preoperative gradients were 78 ± 32 mmHg, with a significant decrease to 20 ± 11 mmHg (postoperatively). Only 1 patient was left with a significant gradient (60 mmHg). There was no significant difference in preoperative or postoperative gradients between bicuspid and tricuspid valves, and calcification had no effect on postoperative gradient or degree of insufficiency. Mild insufficiency developed postoperatively in 21 patients (18%), and none had moderate or severe degrees in the early postoperative period. Surgical mortality was 2.6% (n = 3, none were infants), all due to cardiac failure, possibly related to inadequate myocardial protection. Late deaths occurred in 22% (26 of 113 operative survivors, 19 of cardiac causes), for an estimated mortality rate of 0.94% per patient-year. Actuarial survival rates at 10, 20, 30, and 37 years were 95%, 80%, 76%, and 72%, respectively (Fig. 14A-13). Multivariate analysis found that preoperative New York Heart Association (NYHA) class, leaflet

calcification, date of operation, and postoperative endocarditis were all significant determinants of long-term survival. The authors reported a 32% reintervention rate (37 patients), with a median interval between procedures of 19 years (range 2–34 years). Indications for reintervention were recurrence of stenosis in 25 and severe insufficiency in 12, indicating that progression of both was common in the follow-up period. Aortic valve replacement was performed in 34 patients, while repeat surgical valvotomy was performed in 2 and balloon valvotomy was performed in 1 patient. Freedom from reintervention at 10, 20, 30, and 35 years was 94%, 80%, 57%, and 45%, respectively (Fig. 14A-14). The actuarial freedom from reintervention curve had two distinct phases, with an early low-risk phase that was linear at 0.73% per year for the first 15 years. An inflection point occurred at the 15-year mark, with a steeper phase thereafter, during which the reintervention rate increased significantly to 2.31% per year. Third operations occurred in 6 patients, with 5 occurring after a valve replacement and 1 after a repeat valvotomy. On multivariate analysis, older patient age at valvotomy (> 15 years) and leaflet calcification were found to be independent risk factors for reoperation. Degree of early postoperative stenosis or insufficiency had no significant effect on reoperation risk.

Detter and colleagues[199] reported on a variety of other determinants of well-being, frequently omitted in other series. Of the 50 patients who were alive and had not required reoperation, 92% were in the workforce, 4% were homemakers, 2% were retired, and only 2% were unable to work. The vast majority (94%, 47 patients) were in NYHA functional class I or II, with the 3 patients (6%) in class III, and none in class IV. Symptoms persisted in 28% of patients, with dyspnea, angina, and peripheral edema occurring in 26%, 4%, and 2%, respectively. Ten patients (20%) required cardiac medications. An electrocardiogram revealed atrial fibrillation in only 1 patient, while the remaining were in sinus rhythm. Other rhythm disturbances included ventricular arrhythmias in 1, and a left anterior hemiblock in 2 patients. There were no instances of atrioventricular block or need for pacemaker implantation. Echocardiograms were obtained in 44 (88%) of these 50 survivors. Peak instantaneous pressure gradient was 44 ± 23 mmHg, with a mean pressure gradient of 29 ± 18 mm Hg. Severe stenosis (defined as a peak instantaneous gradient > 80 mmHg or a mean gradient > 50 mmHg) was seen in 3 patients (6.8%) and severe insufficiency was found in 2 (4.5%). Left ventricular systolic function as assessed by fractional shortening was normal in all. Left ventricular hypertrophy (defined as a wall thickness > 12 mm) and dilation (defined as an end-diastolic dimension > 5.6 cm) was seen in 18 (41%) and 12 patients (28%), respectively.

Given these series, aortic valvotomy provides excellent treatment for valvular aortic stenosis, with low mortality, excellent quality of life, and low reoperation rates in the first 15 years after surgery. This allows for somatic growth to occur, and enables an adult-sized valve implant to be used, if necessary, at subsequent procedures. Furthermore, preservation of the native valve allows anticoagulation to be avoided. The risk of reoperation is greater in older children and in those with calcified valves at first valvotomy, and thus earlier operation in children may be able to afford a more durable result. However, subjecting patients to surgery before standard criteria are met would expose them to surgical risk unnecessarily. A corollary is that valve replacement may be a better option in older patients with calcified valves.

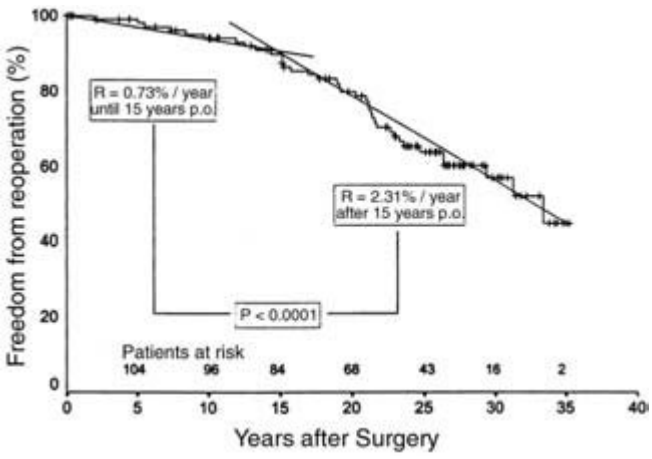


Fig. 14A-14 Actuarial freedom from reoperation after aortic valvotomy. The curve shows two different phases that are distinct. The early, low-risk phase lasts 15 years; thereafter, the risk increases significantly. Risk of reoperation (R) per year, as a linearized number, is calculated for each phase. Numbers below the curves indicate the numbers of patients at risk (*p*.o. = postoperatively). (Reprinted from Detter *et al.*,[199] Copyright (2001), with permission from The Society of Thoracic Surgeons.)

Surgical valvotomy in infants

Coran and Bernhard[200] had one of the earliest series of aortic valvotomy in the first 2 years of life. The authors reported on 21 children between 1958 and 1967; 16 were < 6 months of age, and 5 were between 9 and 24 months of age. Associated anomalies occurred in 10 (48%), and consisted of coarctation of the aorta, patent arterial duct, and mitral valve abnormalities. A variety of surgical techniques were used, and the merits and drawbacks of each were described. Cardiopulmonary bypass was used in 7 infants, with 5 deaths within 24 h, 3 from "postperfusion lung syndrome" (diffuse atelectasis and interstitial hemorrhage) and 2 from aortic insufficiency. Pulmonary complications of cardiopulmonary bypass were frequently seen in those < 6 months of age, and accordingly, the only 2 survivors were 18 and 23 months of age. Hypothermic (32°C) circulatory arrest with inflow occlusion was employed in 2 infants, but ventricular fibrillation occurred in both. The authors speculated that left ventricular failure (so prevalent in infants with severe stenosis) resulted in additional myocardial irritability, and an unsuccessful defibrillation of the cold myocardium. Inflow occlusion using normothermia and a hyperbaric environment was used in the remaining 12 infants. The rationale for hyperbaric oxygenation was derived from the observation that an arterial PO_2 of 1500–1800 mmHg could be achieved using 100% O_2 ventilation, at an environmental pressure of 30 pounds per square inch, thereby allowing for sufficient tissue oxygenation to safely perform valvotomy during circulatory arrest. Of the 12 patients, 8 had ventricular fibrillation during the operation, but defibrillation was possible in all, and 10 survived to hospital discharge, with 2 late deaths. The remaining 8 patients were alive at a follow-up of 1.5 to 4 years, with 1 having undergone aortic valve replacement for aortic insufficiency, and 1 having a repeat valvotomy 1 year later. Overall, there were 10 survivors from the original cohort of 21, and the authors stressed that in infants "the structure of the valve cusps is so embryonic in character that the

operative procedure is undoubtedly palliative rather than corrective in nature."[200]

In Lakier *et al*.'s report of 10 infants presenting in the first month of life with isolated severe aortic stenosis, 3 had a duct-dependent circulation and died before surgery.[93] The remaining 7 underwent open surgical valvotomy, although the details of the surgical technique were not provided. There were 5 deaths intraoperatively or in the immediate postoperative period, with 1 additional death 6 months after surgery. Necropsy findings in the 9 fatalities included a tricuspid aortic valve in 3, a bicuspid valve in 4, and a unicuspid valve in 2 patients, with thickening of the aortic valve leaflets in all cases. Two of the cases also had a hypoplastic mitral valve annulus. The left ventricular cavity was normal or dilated in 7 of the 9 cases. Two of the 3 youngest had mild left ventricular hypoplasia, and included those with a duct-dependent systemic circulation.

The series published in 1980 from the Hospital for Sick Children, Toronto, included 25 infants, all < 6 months of age, who underwent valvotomy with cardiopulmonary bypass.[197] Associated malformations were common, with endocardial fibroelastosis, mitral valve anomalies, a patent arterial duct, and mild left ventricular hypoplasia in most. Mean follow-up duration was 4 years (range 1–15 years, and 16 patients were < 1 month of age. Subgroup analysis according to age disclosed a significantly greater mortality (9 of 16, 68%) in the first month of life compared to later in infancy (2 of 9, 22%). When survival was stratified according to associated lesions, a similar discrepancy was revealed, with the mortality rate being 21% for those with only an additional patent arterial duct compared to 82% for those with other associated malformations. It is probable that the youngest group was also those with a greater number of associated lesions, but this conclusion cannot be reached from the data provided. Two patients underwent reoperation: aortic valve replacement in 1, and repeat valvotomy and subsequent valve replacement in the other. Actuarial survival analysis could not be performed due to insufficient numbers.

A comparison of closed and open aortic valvotomy was also reported from Toronto,[201] where 40 patients with critical stenosis (from 1965 to 1985) were compared. There were 18 patients who underwent closed transventricular valvotomy (access through the left ventricular apex using either a series of hegar dilators or a balloon catheter), and 21 patients who underwent an open valvotomy (using either cardiopulmonary bypass or inflow occlusion). Overall mortality was 57%. Survival in the first 48 hours after surgery appeared to favor a closed approach (36% survival vs. 50%), but the difference was no longer significant by 3 months of age. In fact, early (< 1 year) reoperation rates were greater in those having undergone a closed procedure (8 of 14 vs. 1 of 10 for open valvotomy). Reoperations among those having initially received a closed procedure included open valvotomies, but also Konno procedures, and repair of an iatrogenically created ventricular septal defect. In essence, while a rapid, closed procedure without bypass was found to be safer initially, inadequate relief of obstruction often resulted, with a consequent high reoperation rate. In another study comparing valvotomy techniques, 40 neonates in 3 institutions were identified between 1983 and 1989 with associated lesions included only a patent arterial duct, coarctation of the aorta, or both.[202] Thirty patients underwent open valvotomy, while 10 underwent a transventricular closed valvotomy. The common thread in this series was the use of cardiopulmonary bypass in all patients, even those undergoing closed valvotomy. Overall hospital survival rate was 88% (35 of 40). There was no significant difference in survival rate between those who received a closed procedure (9/10, 90%) vs. an open procedure (26/30, 87%). The authors suggested that, contrary to widespread belief, cardiopulmonary bypass did not have a deleterious effect on survival. In fact, cardiopulmonary bypass was felt to play an important role in stabilizing patients during surgery. This series had an exceptionally high survival rate, but patients were selected specifically excluding associated malformations in order to more closely approximate those considered candidates for percutaneous balloon valvotomy.

Although technical approaches to valvotomy may impact outcome, the underlying anatomical substrate in neonatal and infantile aortic stenosis may be more important. The prejudicial role of leaflet dysplasia in achieving an adequate valvotomy in infantile stenosis was emphasized in Dobell *et al*.'s series.[192] Of 50 children undergoing valvotomy with the aid of cardiopulmonary bypass, 12 were < 1 year of age (all with congestive heart failure). Overall, there were 7 early postoperative deaths, of which 6 occurred in infants < 2 months of age, including the 4 with a duct-dependent circulation. Although no patient died as a result of residual obstruction, the particular challenge posed by the thickened dysplastic leaflets seen in neonates was underscored. In these, simple valvotomy was deemed unsuccessful because (as in the dysplastic pulmonary valve syndromes) the reason for stenosis was not leaflet fusion but rather leaflet immobility, compounded by the bulk and space-occupying effect of the leaflets, in the setting of a frequently marginal annular dimension.

The impact of the underlying pathologic substrate in critical aortic stenosis was further illustrated in a series by Karl and colleagues from Melbourne,[88] in which 26 infants underwent surgical valvotomy in the first month of life, between 1980 and 1989 with a common management algorithm. The mean age and weight at operation were 9 days and 3 kg, respectively. Inotropic support, mechanical ventilation, and administration of prostaglandin E_1 were required preoperatively in 58%, 42%, and 35% of patients, respectively. The surgical technique involved cardiopulmonary bypass, systemic hypothermia (30–32ºC), and cardioplegic arrest in all. Of 26 patients, 22 had a bicuspid valve, 3 had a tricuspid and 1 patient had a unicuspid valve. Identifiable commissures were incised, and dysplastic nodules or excrescences were debrided. Operative mortality for the entire cohort was 31% (8 of 32 patients). Patients whose only additional operative procedure included ligation of a patent arterial duct (concomitant with valvotomy) fared much better, with no operative mortality ($n = 9$), compared to those requiring additional cardiac surgical procedures (either at the same or another operation) who had an overall operative mortality of 47% (8 of 17). Six patients had coarctation of the aorta, of which 1 had repair before valvotomy, 3 had repair as a second procedure after valvotomy, and 2 had repair at the same time as valvotomy, in addition to either closure of an atrial and/or ventricular septal defect. Additional surgeries in the remaining patients with complex lesions included conversion to univentricular palliation, mitral valve replacement or repair, atrial defect closure, and a Konno operation. Independent factors found to impact on early mortality were the presence of an additional cardiac malformation, and operation before the last 2 years of the study period. Follow-up was 1 to 113 months (mean 37 months), during which 4 late deaths occurred. Reoperations at a subsequent hospitalization were limited to a single instance

of subaortic resection 9 years after the primary procedure. Actuarial survival for the entire cohort was 53% at 38 months, with no additional deaths to 113 months. The authors stressed the importance of adequate patient selection in ensuring survival with a biventricular repair, as other authors have underscored. Patients in whom significant hypoplasia of the aortic annulus, ascending aorta, mitral valve, and left ventricular cavity is present represent a subset that may be better served by a Norwood-type operation, or cardiac transplantation. Of course, the challenge lies in determining how small is too small. A number of authors have suggested that a left ventricle that is not apex-forming and dimensions of left-sided structures < 60% of the expected mean for body weight constitute contraindications to valvotomy alone (see below).

Studies of the long-term outcome of infants with severe or critical aortic stenosis are few, in part owing to small numbers and high mortality rates. In a study that retrospectively attempted to address these issues, all survivors of surgery in infancy at a single institution during a 30-year period from 1958 to 1988 were reviewed.[203] In total, 51 patients underwent surgical valvotomy in the first 3 months, of life using a variety of surgical techniques, including a closed valvotomy in 3 patients, and an open valvotomy technique in 45 (3 with inflow occlusion and 42 with cardiopulmonary bypass). Three infants died in the operating room before valvotomy. The specific morphology of the valves and associated malformations were not specified, and the number who were duct-dependent is unclear. Of the entire cohort, 29 were < 1 month of age, and 22 were between 1 and 3 months of age. Heart failure was the surgical indication in all. There were 30 perioperative deaths (i.e. within 30 days of surgery), with an overall mortality of 59%. Deaths were evenly distributed between neonates and infants aged 1–3 months: 20 of 29 neonates (69%), and 10 of 22 infants (46%) ($P = 0.15$). The study focused on the 21 patients who survived beyond 30 days. One patient was lost to follow-up, and 2 late deaths occurred (1 due to endocarditis at age 13 years, the other due to dislodgment at age 14 years of a prosthetic valve). Both late deaths were among those operated between 1 and 3 months of age. Actuarial survival for those who lived beyond the first 30 days after surgery was 100% at 10 years, and 75% at 15 years. Reoperations occurred 7 times in 6 patients, and included 2 valvotomies, resection of an apical aneurysm with creation of a conduit from left ventricle to descending aorta, and 4 aortic valve replacements due to severe aortic insufficiency. Actuarial analysis revealed a freedom from reoperation of 90% at 10 years, and 67% at 15 years. Progressive deterioration in valve competence was also documented among the cohort that survived surgery. Within the first 2 postoperative years, 20 of 21 patients (95%) had mild insufficiency or less, with that number decreasing to 63% within 5 years after surgery. Of the 16 patients who were evaluated between 6 and 10 years after surgery, 56% had progressed to moderate or severe insufficiency. When examined beyond 10 years after surgery, 5 of 8 patients had severe insufficiency, and all were either scheduled for, or had already undergone, aortic valve replacement. Overall, there was no significant difference in survival, reoperation rate, or progression of aortic insufficiency between those who underwent initial valvotomy in the first month of life and those operated on between the first and third month of life. More importantly, this study suggests that despite the high initial mortality rate in infants, the survival rate and freedom from reoperation appears to be relatively good among the initial survivors.

While individual institutions espouse different methods for relieving critical stenosis, including closed transventricular valvotomy using balloons or dilators, open valvotomy using inflow occlusion, cardiopulmonary bypass, or circulatory arrest, or, more recently, percutaneous balloon valvotomy (see below), it appears that long-term outcome is less related to exactly how relief of stenosis is established, and appears to be more intimately related to associated lesions and proper patient selection. Adequacy of left heart structures is a major determinant of outcome of biventricular repair in critical aortic stenosis. A retrospective study in 1986 analyzed the outcome of 24 infants with severe congestive heart failure undergoing surgical valvotomy in the first 6 months of life.[204] Nineteen infants (80%) were operated in the first month of life, and 9 (38%) were < 3 days old. All patients underwent cardiac catheterization in order to determine the gradient across the aortic valve and the end-systolic and diastolic dimensions of the left ventricle. All valvotomies were performed with cardiopulmonary bypass using hypothermia. Perioperative mortality was 21% (5 of 24). The authors found no significant difference in the preoperative gradient across the aortic valve between the survivors and non-survivors. Left ventricular volumes were calculated and indexed to body surface area. The calculated left ventricular end-diastolic volume index (LVEDVI) was no different between survivors and nonsurvivors (37 ± 17 mL/m^2 vs. 36 ± 7 mL/m^2, respectively). In fact, 4 survivors had an LVEDVI of < 26 mL/m^2, and 1 had an LVEDVI of 20 mL/m^2. Left ventricular end-systolic volume index (LVESVI) was similarly not found to correlate with survival. The authors did find, however, that the significant predictors of mortality were diminished left ventricular ejection fraction (EF), elevated left ventricular end-diastolic pressure (LVEPD), and the presence of endocardial fibroelastosis (EFE). Specifically, these values in survivors vs. nonsurvivors, respectively, were: EF 60 ± 17% vs. 36 ± 2%, LVEDP 16 ± 7 mmHg vs. 30 ± 14 mmHg, and EFE present in 25% vs. 100%. The age of survivors and nonsurvivors was not significantly different, although all nonsurvivors were < 3 weeks old at operation.

In another series, also reviewed in an effort to determine factors predictive of mortality,[205] 33 patients who underwent open aortic valvotomy in the first 6 months of life were studied. All were operated using cardiopulmonary bypass, and some with circulatory arrest. There were 19 survivors and 14 nonsurvivors. Significant factors affecting survival were preoperative elevation in pulmonary artery pressure (29 ± 3 mmHg in survivors vs. 54 ± 3 mmHg in nonsurvivors) and left ventricular hypoplasia (LVEDVI of 50 ± 8 mL/m^2 in survivors vs. 20 ± 4 mL/m^2 in nonsurvivors). Valve morphology was found not to be predictive of outcome. It is difficult to interpret the meaning of elevated pulmonary artery pressure as a determinant of mortality. Pulmonary artery pressure in critical aortic stenosis is representative of a number of interrelated factors, such as systolic performance of the left ventricle, left ventricular filling (affected by hypoplasia of the left ventricular cavity or chamber compliance), the presence of EFE, mitral stenosis or regurgitation, an atrial septal defect, and most obviously, the presence of a large patent arterial duct.

Using mainly echocardiographic parameters, other investigators have found different predictors of survival. Parsons and colleagues retrospectively analyzed the size and function of various left sided heart structures in 26 infants aged < 3 months who underwent surgical valvotomy between 1980 and 1990.[206] They found significant differences between survivors and non-

survivors, including, respectively, age at operation (30 ± 28 days vs. 3 ± 1 days), mitral valve annulus diameter as measured in the apical four-chamber view (10 ± 2 vs. 8 ± 2 mm), left ventricular end-diastolic dimension by m-mode (18 ± 6 vs. 11 ± 3 mm), left atrial dimension by m-mode (15 ± 4 vs. 10 ± 2 mm), left ventricular cross-sectional area measured on the parasternal long-axis view (4 ± 2 vs. 2 ± 2 cm^2) and angiographic LVEDVI (43 ± 23 vs. 11 ± 5 mL/m^2). Factors that were found not to affect survival included body weight, surface area, aortic root dimension as measured by m-mode, left ventricular EF, or LVEDP at preoperative catheterization. The authors found that a left ventricular cross-sectional area of < 2 cm^2 as measured echocardiographically predicted an angiographic LVEDVI of < 20 mL/m^2, thereby obviating the need to perform angiographic determination of ventricular volume. Previous investigators[207] have determined that the normal range for left ventricular cross-sectional area in infants aged 5 days and weighing 3 kg is 1.8 to 3.5 cm^2, a mean 2.65 ± 2 cm^2.

Perhaps the most widely quoted study characterizing predictors of survival in critical aortic stenosis is that by Rhodes and colleagues.[208] The authors retrospectively identified 65 patients who were diagnosed within 2 months of life with severe stenosis and left ventricular dysfunction with clinical evidence of congestive heart failure. Three patients died before any form of intervention, while 16 were felt to be poor candidates for biventricular repair (according to the responsible physician, without resorting to any specific anatomic criteria) and therefore underwent a Norwood[209] operation (anastomosis of the main pulmonary artery to the aorta, with creation of a systemic to pulmonary artery shunt). Among these 16 patients, 14 were felt to have satisfactory echocardiograms for measurement of anatomic variables, and comprised the single ventricle repair group. The other 46 patients were felt to have adequate left ventricular size to undergo a biventricular repair, and initial procedures were: no intervention in 1, percutaneous balloon valvotomy in 36, surgical valvotomy in 4, and repair of coarctation of the aorta in 5 patients. Of these 46 patients, 3 were excluded due to unsatisfactory echocardiograms, and the remaining 43 constituted the biventricular repair group. Reintervention was necessary in 15 of the 36 patients who were initially palliated with balloon valvotomy (7 repeat balloon valvotomies, 2 coarctation of the aorta repairs, and 6 Norwood procedures), in 1 of the 4 patients who initially had a surgical valvotomy (balloon dilation of the mitral valve was performed), and in 3 patients who initially underwent coarctation of the aorta repair only (2 required a balloon aortic valvotomy and 1 patient a Norwood procedure). There were 26 deaths in all (3 patients who received no intervention, 9 after single ventricle repair, and 14 after biventricular repair). Comparison was then made between those who survived biventricular repair vs. those who died. There was no significant difference with respect to age, body surface area, EF, or Doppler gradient across the aortic valve between survivors and nonsurvivors of a biventricular repair. In total, 11 specific morphometric variables were found to be significantly associated with death after a biventricular repair. Nonsurvivors of a biventricular repair had significantly smaller indexed diameters of the aortic annulus, root (measured at the sinuses of Valsalva), arch (measured between the brachiocephalic and left common carotid arteries), and isthmus, than their counterparts who survived. In addition, the following parameters were also found to be significantly smaller in nonsurvivors: indexed left ventricular long-axis dimension and ratio of left ventricular long-axis to long-axis of the heart, LVESVI, LVEDVI, left ventricular mass index, indexed mitral valve area, and ratio of the mitral valve area to tricuspid valve area. Using multivariate analysis, the authors devised an equation, which allowed calculation of a discriminating score that would predict death after a biventricular repair: score = $14.0(BSA) + 0.943(ROOT_i) + 4.78(LAR) + 0.157(MVA_i) - 12.03$, where BSA is the body surface area, $ROOT_i$ refers to the indexed aortic root as measured at the sinuses of Valsalva, LAR the ratio of left ventricular long-axis to long-axis of the heart, and MVA_i the indexed mitral valve area. A score of < –0.35 was found to be predictive of death after a biventricular repair. When the authors applied this equation to their own patient group, outcome was correctly predicted in 88–94% of patients.

These authors also simplified the scoring system based upon the four factors that were found to have the greatest independent relation to survival. For these four factors, the critical levels were: LAR < 0.8, $ROOT_i$ < 3.5 cm/m^2, MVA_i < 4.74 cm^2/m^2, and a left ventricular mass index < 35 g/m^2. According to this simplified scoring system, 1 point was counted for each of the 4 factors that fell below the threshold value. When the scoring system was applied to the 43 patients, mortality was 100% in the 12 patients with 2 or more points, while only 8% in the 31 patients with 1 or fewer points. The most arduous of these four factors to calculate is the left ventricular mass index, and exclusion of this factor allowed the scoring system to predict with a 79% accuracy patients who died after biventricular repair.

The so-called Rhodes score provides insight into the relative importance of the left-sided heart structures in determining survival after a biventricular repair. However, several caveats apply. First, the score was designed to predict death following a biventricular repair "based on the assumption that it is preferable to perform an aortic valvotomy if there is any chance of survival because the surgical alternatives are either cardiac transplantation or univentricular repair."[208] however, as early mortality rates improve for single-ventricle repair or transplantation, selection of patients for biventricular repair may have to follow even more stringent criteria. Secondly, long-term survival in marginal cases after a biventricular repair may entail multiple future surgical or percutaneous procedures on the aortic valve, the mitral valve, and the aortic arch, the cumulative risk of which may, in some cases, ultimately amount to greater risk than that of a univentricular treatment algorithm or cardiac transplantation. Furthermore, among the nonsurvivors, the latest death was at 122 days of age. Actual duration of follow-up was not provided, and the occurrence of late deaths in either treatment algorithms was not accounted for. Another important limitation is that although survival was considered, functional capacity was not, and the larger question of which treatment algorithm affords a greater quality of life, remains unanswered. An important corollary from the rhodes study is that patients who initially failed a biventricular repair and were subsequently diverted to univentricular treatment strategy by performing a Norwood operation had a mortality rate of 86% (1 out of 7 survived), suggesting that these patients may have been better served by primary univentricular repair (which carried a 50% mortality in this series). However, the optimal timing for Norwood's operation in failed cases of valvotomy has not been established.

Lastly, it is important to remember that the Rhodes score was described in infants with critical aortic stenosis, and application of these morphometric parameters to other forms of congenital

heart disease with variable degrees of hypoplasia of left-sided cardiac structures is of dubious value.[210–213] None the less, patient survival and growth of left-sided heart structures even in those with critical stenosis in whom the Rhodes score would have predicted nonsurvival has recently been documented.[214] Growth of left-sided structures has even been demonstrated in duct-dependent neonates with variable expression of the hypoplastic left heart syndrome subjected to biventricular repair.[213]

Recently a multi-institutional study of neonatal critical aortic stenosis was conducted by Congenital Heart Surgeons Society.[86] Between 1994 and 2000, 320 neonates with critical aortic stenosis from 24 institutions were enrolled in a prospective study which sought to determine which risk factors would favor survival in a univentricular vs. biventricular repair algorithm. Entrance criteria were the presence of critical stenosis (defined as a duct-dependent circulation or moderate to severe reduction in left ventricular function) and a procedure aimed at relieving left ventricular outflow tract obstruction performed within the first 30 days of life. There were 25 patients who were subsequently excluded, including 19 patients who died before intervention and 6 who underwent primary cardiac transplantation. Of the remaining 295 patients, 179 underwent univentricular repair with a Norwood operation, and 116 underwent a biventricular repair (83 received an initial percutaneous balloon valvotomy, and 33 received an initial surgical valvotomy). There were 64 subsequent deaths in the univentricular repair group (36% overall mortality), with Kaplan–Meier estimates of survival being: 80% at 1 month, 71% at 3 months, 64% at 1 year, 62% at 2 years, and 60% at 5 years (Fig. 14A-15). There were 32 deaths in the biventricular repair group (28% overall mortality), with survival estimated of 82% at 1 month, 77% at 3 months, 72% at 1 year, 71% at 2 years, and 70% at 5 years (Fig. 14A-15). Incremental risk factors for time-related death among those having embarked on a univentricular repair algorithm included a lower ascending aortic diameter, and the presence of moderate or severe tricuspid regurgitation. Incremental risk factors for time-related death among those having embarked on a biventricular repair algorithm included younger age, lower *Z*-score of the aorta measured at the sinuses of Valsalva, and a higher echocardiographic grading of severity of EFE. Having created separate multivariable hazard models for the initial intended operation (Norwood vs. biventricular repair), the authors predicted survival at 5 years for each patient in their dataset by applying each model twice for each patient, once for the Norwood pathway, and once for the biventricular repair pathway. This analysis revealed that 60 of the 116 patients (52%) who followed a biventricular repair pathway would have had a better predicted 5-year survival with a Norwood operation, and that 30 of the 179 patients (17%) who had an initial Norwood operation would have had a better predicted 5-year survival on a biventricular repair algorithm. Multiple linear regression analysis found that the following factors favored survival on a univentricular treatment algorithm vs. a biventricular repair: younger age, lower *Z*-score of the aortic valve and left ventricular length, higher grade of endocardial fibroelastosis, absence of important tricuspid regurgitation, and larger ascending aorta.

These studies highlight, it appears, that the method of relieving stenosis in critical aortic valve disease is probably of less importance than may have previously been estimated, as long as candidates are properly selected with isolated valve disease in absence of other left heart obstructive lesions. In those

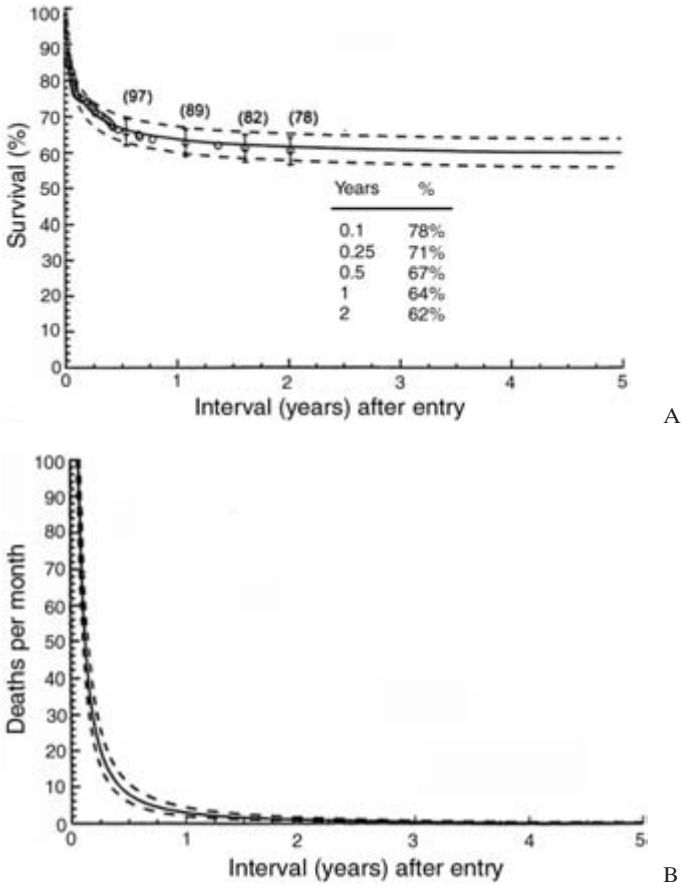


Fig. 14A-15 Survival after entry for patients who had an initial Norwood procedure ($n = 179$). The circles represent the Kaplan–Meier interval at each death, the solid lines represent the parametric determination of continuous point estimates, and the dashed lines enclose the 70% confidence interval. **A**, Per cent survival; **B**, hazard function. (Reprinted from Lofland *et al.*,[86] Copyright (2001) Mosby Inc., with permission from Elsevier.)

afflicted with EFE, or hypoplasia of the mitral valve apparatus, left ventricle, or ascending aorta and arch, careful consideration must be given to the adequacy of the heart for a biventricular repair. In some cases, Norwood's operation or cardiac transplantation may be indicated, accepting that long-term outcome is generally still less than desired in either of these algorithms. Future directions will likely include greater experience with other techniques, including the neonatal Ross procedure (pulmonary autograft)[215,216] or the Ross–Konno procedure[217,218] (discussed below), and these may come to supplant transplantation or univentricular repair for those in whom the left ventricular cavity and mitral apparatus are adequate.

Alternative surgical therapies

Aortic valvotomy provides excellent relief of obstruction in cases of isolated aortic stenosis, but is of limited use in cases that include, in addition to obstruction, moderate or severe aortic regurgitation. For such cases, valve replacement is required. A number of valves are currently available and include biological (stented and unstented, xenograft or homograft) and mechanical designs. While each valve design has advantages and disadvantages, the major issues surround: the durability of the valve,

the availability of a particular valve in small diameters for implantation in young children, the need for repeat valve replacement particularly in young children as they outgrow the implanted prosthesis, and the possible need for anticoagulation. While a detailed discussion of valve selection is beyond the scope of this text, certain generalizations apply. In general, mechanical valves necessitate anticoagulation, which is a significant drawback in young children due to the difficulty in maintaining therapeutic anticoagulation, the need for frequent blood studies for monitoring of anticoagulation (INR), and the risk of major hemorrhage in young children.[219] Current guidelines do not specify which valve type is best suited for a given age group or underlying lesion.[4] A more thorough discussion of valve replacement is provided elsewhere.[220–224] In selected cases with aortic insufficiency, aortic valve repair, rather than replacement may be feasible.[225, 226]

A particular type of aortic valve replacement deserves additional mention, the pulmonary autograft initially reported by Ross in 1967.[227] In the initial description, the pulmonary valve was harvested and implanted into the left ventricular outflow tract in the subcoronary position, with placement of a right ventricle to pulmonary artery conduit. A technical variation was later introduced, known as a root inclusion technique, in which the pulmonary autograft root was implanted within the native aortic root. Most centers now perform the Ross procedure as a root replacement technique, in which the free standing pulmonary autograft root is used to replace the native aortic root, or with reimplantation of the coronary arteries.[228] Theoretical advantages of the pulmonary autograft include: growth potential of the neoaortic valve, circumvention of an immunological reaction to a neoaortic valve with possible improved valve durability and avoidance of anticoagulation therapy.[229–231] Potential drawbacks include: ongoing concerns as to the fate of the neoaortic valve and the necessity for periodic replacement of the right ventricular outflow tract conduit. Concerns about the longevity of the neoaortic valve in patients undergoing the Ross procedure for rheumatic aortic valve disease have also been raised, given the possibility of recurrent rheumatic valvulitis involving the neoaortic valve.[232–234] Contraindication to the Ross procedure includes disorders with increased fragility of connective tissue such as the Marfan syndrome.[235] Perhaps one of the most significant concerns is the possibility of rapid enlargement of the neoaortic root with development of aortic regurgitation, as reported by several investigators.[236–238] It has been suggested that the risk of neoaortic root dilatation is greater among patients undergoing the Ross procedure for bicuspid aortic valve disease. Indeed, cystic medial necrosis has been found histologically both in the native pulmonary artery and in the native aortic root at the time of the operation, perhaps accounting for the greater propensity to neoaortic dilatation in this subset of patients,[239] although others have contested this observation.[240] Some have attributed the neoaortic dilatation to the surgical technique, finding greater neoaortic dilatation among patients undergoing the free standing root replacement technique.[241,242] Fixation of the neoaortic root at the sinotubular junction using a Dacron™ graft has been suggested as a means of reducing postoperative root enlargement, but this technique is not applicable in growing children, given that it would defeat the purpose of having an autograft capable of growth.[241]

Despite the theoretical concerns, most surgical series report good results. Ross's original series of 131 patients operated between 1967 and 1984 were reported in 1997,[243] with a mean duration of follow-up of 20 years. There were 3 deaths within the first postoperative year: 1 from severe autograft regurgitation, 1 from endocarditis on the homograft in the pulmonary position, and 1 sudden death. There were 38 late deaths, of which 13 were related to chronic heart failure, 6 due to acute myocardial infarction, and 8 deaths were sudden (14 late deaths were related to autograft regurgitation). Survival at 10 and 20 years was 85% and 61%, respectively. Of the cohort of 131 patients, 46 had reoperations (7 occurred within the first postoperative year, the remainder were late reoperations). Indications for early reoperation consisted of endocarditis in the pulmonary position ($n = 2$), myocardial ischemia ($n = 2$), severe autograft regurgitation ($n = 2$), and bleeding in 1. Indications for late reoperation included autograft regurgitation in 18 and pulmonary stenosis or regurgitation in 14. Retention of the original homograft in the pulmonary position was 89% and 80% at 10 and 20 years, respectively. Oswalt and colleagues had similar results, with actuarial survival of 90.2%, freedom from explantation of the autograft of 93.2%, and freedom from replacement of the homograft in the pulmonary position of 98.4% at 10 years.[244] Looking specifically at the experience with pediatric patients, Al-Halees and colleagues found an actuarial survival rate of 94% and an event-free survival rate of 93% at 10 years.[245] A randomized trial comparing aortic homografts to the Ross procedure was conducted by Aklog *et al. i*n a mixture of adult and pediatric patients.[246] A total of 182 patients were enrolled in the study: 97 in the pulmonary autograft group (root replacement technique was used), and 85 in the aortic homograft group, with a median follow-up of 33.9 months. Operative mortality was 1% for the autograft group and 4% for the homograft group, despite longer myocardial ischemic and cardiopulmonary bypass times. Results at 48 months were: actuarial survival and reoperation-free survival rates 97.8% and 94.2% for the autograft group, and 95.3% and 87.7% for the homograft group, respectively. While early results were encouraging, patients having undergone the Ross procedure will need continued vigilance for the development of autograft dysfunction (with or without neoaortic root dilatation), and stenosis or regurgitation of the homograft conduit in the pulmonary position.

In cases of left ventricular outflow tract obstruction not amenable to simple surgical valvotomy due to associated subvalvular or supravalvular stenosis, or because of annular hypoplasia, other surgical techniques have been applied to allow for unobstructed egress of blood from the left ventricle. One such technique is the creation of a double outlet left ventricle by anastomosing a conduit from the left ventricular apex to the aorta. Such procedures were initially conceptualized as early as 1910 by Alexis Carrel,[247] initially experimenting with a vein graft used as a conduit between the left ventricle and the thoracic aorta. By 1955, the technique was successfully applied in dogs.[248] Clinical series began appearing in the late 1970s.[249–251] Mortality rates in these early series, that included children, ranged from 12% to 22%, with excellent gradient reduction in the survivors.[252,253] Mortality in young children (< 2 years of age) was considerably higher and approached 100% in some series.[254,255] Describing a combined pediatric and adult experience with the technique, Sweeney *et al.* reported in 1986 a surgical mortality of 11%, with a 5-year survival rate of 78% and no major complications in 70%.[256] Survival in 80% of children < 2 years of age with apico-aortic conduits was reported in the late 1980s as experience with this technique continued to accrue

in some centers.[257] In a series of 20 pediatric patients from a single center, Frommelt and colleagues reported the natural history of apico-aortic conduits implanted between 1977 and 1987.[258] A surgical mortality of 10% (both patients were < 2 months of age) was reported. However, as survival rates improved, failure of the conduit valve due to degeneration and calcification emerged as a clinical concern. The authors reported a 3-year freedom from conduit failure rate of 80 ± 9%, while the 7-year rate was 52 ± 11%. There were no thromboembolic complications despite the absence of anticoagulation therapy. Eight patients underwent reoperation for conduit failure: 4 had replacement of the conduit, and 4 had an aortoventriculoplasty. Although apico-aortic conduits have generally been supplanted by other methods of alleviating systemic outflow tract obstruction, some recent series suggest that this technique retains merit when definitive repair is too difficult.[259] At the time of definitive repair, the apico-aortic conduit can be taken down surgically, or even occluded percutaneously in the cardiac catheterization laboratory if deemed surgically inaccessible.[260]

While apico-aortic conduits were being developed, other surgical approaches to deal with the hypoplastic aortic annulus evolved in parallel.[261] In the late 1970s, Konno *et al*.[262] and then Rastan *et al*.[263] published a method for enlarging the aortic annulus and subaortic area using a longitudinal incision in the aortic septum placed in the midportion of the two coronary ostia, followed by a vertical incision in the outflow tract of the right ventricle to join the septal incision. In so doing, enlargement of the aortic annulus for aortic valve replacement was possible, and the repair completed by patch reconstruction of both ventricular outflow tracts. Small series of pediatric patients having undergone the Konno procedure have been reported with good results.[264,265] The Konno procedure has also been successfully applied to aortic valve re-replacements.[266]

The Ross operation has been used in combination with the Konno aortoventriculoplasty in order to deal with complex left ventricular outflow tract obstruction or annular hypoplasia in children and adults.[215–218,267] These series are too few in number and the patients described within them span such a wide spectrum of ages and underlying cardiac lesions that meaningful comparisons between them is difficult. Of all the subgroups, neonates with critical aortic stenosis and significant hypoplasia of the left ventricular outflow tract pose the most formidable challenge, in that many of these infants have previously undergone some form of previous palliation for left ventricular outflow tract obstruction (either balloon or surgical valvotomy, and in some cases attempted valve repair) and the Ross–Konno procedure is considered a salvage operation.

Outcomes after percutaneous intervention for congenital aortic valve stenosis

Following the successful application of percutaneous balloon dilation for pulmonary valve stenosis described by Kan *et al*. in 1982,[268] Lababidi and colleagues used a similar technique in children with congenital aortic valve stenosis with surprisingly good results.[269,270] Subsequent reports demonstrated the feasibility, safety and efficacy of this mode of treatment as an alternative to surgery.[62,271–281] Due to its noninvasive nature, balloon dilation is generally considered the method of choice for initial palliation of non-calcific congenital aortic stenosis in neonates, children and young adults[84,85,282–312] (Fig. 14A-16). In this section, the outcomes after the use of this technique at differ-

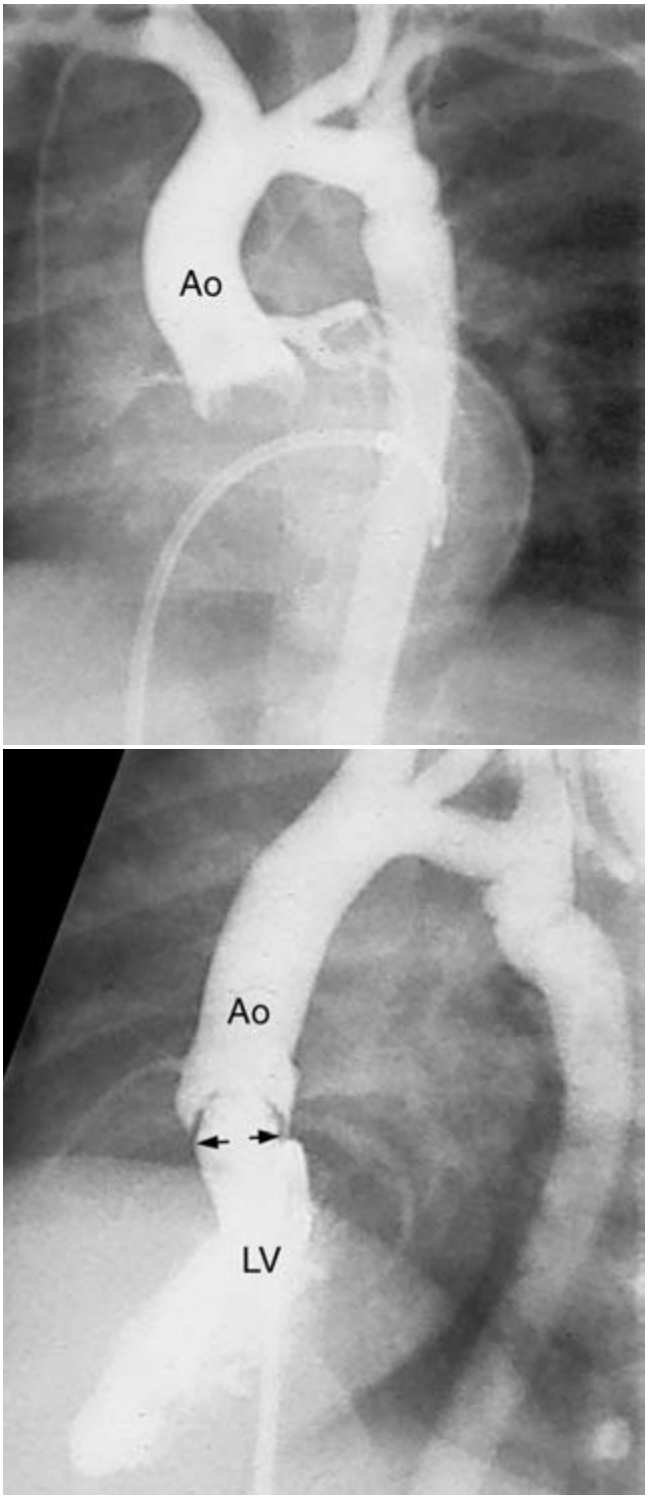


Fig. 14A-16 **A**. Ascending aortogram denotes a stenotic bicuspid aortic valve, and post-stenotic aortic root dilation. **B**. The corresponding left ventriculogram outlines the angiographic annulus, where the valve appears to attach to the annulus. The left ventriculogram is used to define the aortic annulus diameter for determination of the dilating balloon size.

ent ages will be reviewed. Although the procedure has been typically performed using a retrograde approach,[311,312] some technical modifications have been reported (Fig. 14A-17). As a detailed description of current techniques is beyond the scope of this review, only those technical issues that may affect the outcomes will be discussed.

The fetus and neonate

Indications for intervention

Although it is generally accepted that moderate to severe aortic stenosis in the older child requires intervention, quantification of the severity of obstruction in the neonate is problematic (Fig. 14A-18). The absolute transvalvar pressure gradient is not a uniformly reliable index of valvar orifice size, due to variable transvalvar flows, affected by left ventricular function, mitral regurgitation, left to right shunting through the oval foramen, right to left shunting through a patent arterial duct and cardiac output maintained by the right ventricle. Balloon dilation is indicated for neonates with critical aortic valve stenosis (defined as an arterial duct dependant systemic circulation), asymptomatic neonates, with Doppler-derived[313,314] or measured, peak-to-peak gradients > 60 mmHg.[315] Lower gradients in the setting of impaired left ventricular function do not reflect the severity of obstruction, and if valve mobility is clearly impaired on echocardiography, dilation should be attempted.

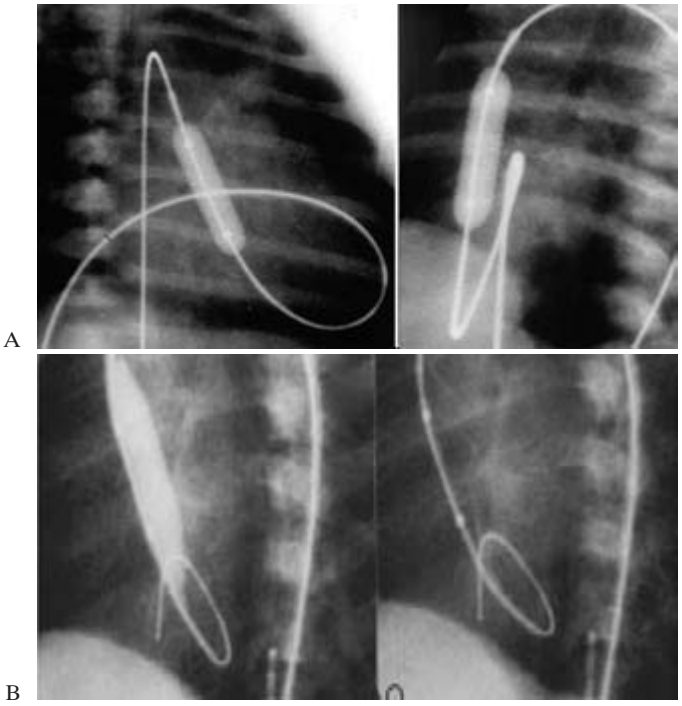


Fig. 14A-17 Balloon dilatation of aortic valve. **A**. Antegrade approach in a neonate. Right anterior oblique (left panel) and cranially angulated left anterior oblique (right panel) show an antegrade placement of the balloon with the guide wire in the inferior caval vein, atria, left ventricle and aorta. **B**. Standard retrograde approach in an older patient. Cranially angulated left anterior oblique views show a retrograde balloon across the valve, inflated (left panel) and deflated (right panel).

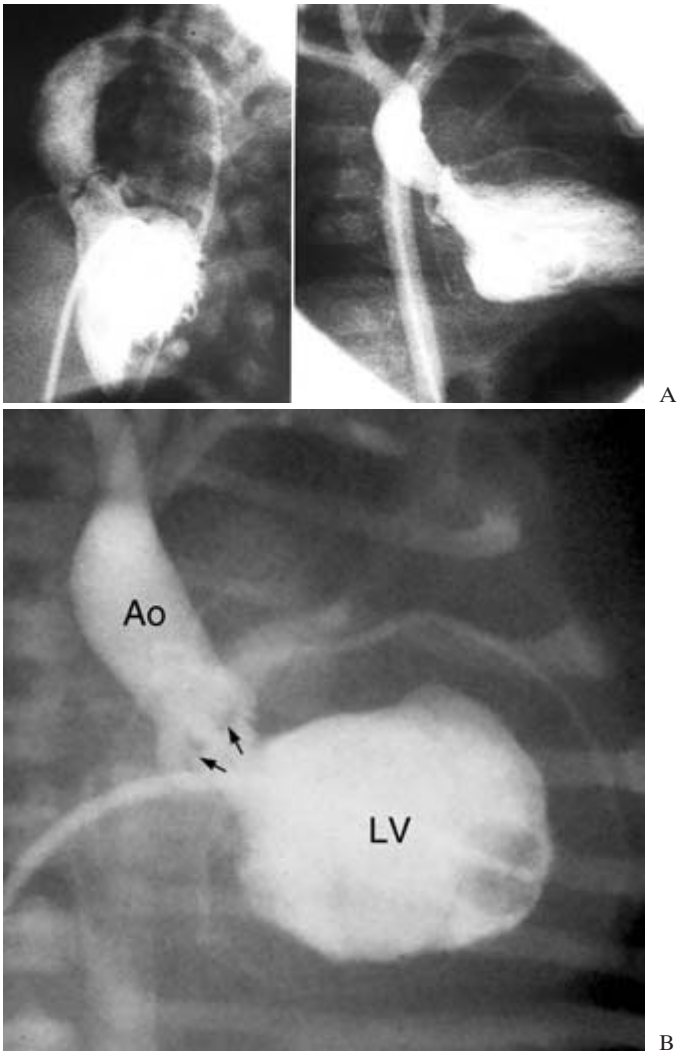


Fig. 14A-18 **A**. Left ventriculograms in a neonate with severe aortic valve stenosis. Note the thickened, dysplastic aortic valve leaflets. This patient had a normal left ventricular ejection fraction. **B**. Left ventriculogram from another patient, similarly with severe aortic valve stenosis, but profound left ventricular dysfunction and a morphologically malformed left ventricular chamber.

Patient selection

Severe aortic valve stenosis in the neonate is a complex disorder with varying degrees of left ventricular hypoplasia, functional and structural abnormalities of the mitral and aortic valves, and the presence of endocardial fibroelastosis.[52,316] Early surgical and interventional series (each with high mortality) included patients with small left sided structures, which retrospective analyses have defined as poor candidates for a two-ventricle repair. In this regard, suitability for a biventricular repair should be assessed according to the dimensions of the left ventricular inflow (mitral valve), left ventricular chamber (mass and volume) and left ventricular outflow (aortic annulus). These variables, measured by echocardiography, were incorporated into an equation that predicted which patients would have a successful outcome after a two ventricle repair by Rhodes *et al.* in 1991.[208] Other authors have used a similar approach to determine patient selection.[206,317] In a recent study from the Con-

genital Heart Surgeon Society (CHSS), Lofland *et al.*[86] identified risk factors that predicted whether a biventricular repair or Norwood pathway would result in the best survival. Younger age at entry, lower *Z*-score of the aortic valve diameter, reduced left ventricular length (apex to aortic valve), higher grade of endocardial fibroelastosis, absence of important tricuspid regurgitation, and larger ascending aorta were all considered independent factors associated with greater survival benefit for the Norwood procedure vs. biventricular repair. In this study, these characteristics were incorporated into a predictive equation and the outcomes were reviewed. Surprisingly, it was estimated that 50% of patients in the study cohort who had a biventricular repair should have had a Norwood procedure to achieve a better survival rate. On the other hand, predicted survival benefit favored biventricular repair in 20% of patients who had had the Norwood procedure. This reflects how difficult it is to determine treatment algorithm. Selecting the correct patient for the right management strategy for the best outcome remains a difficult task, even in the "modern" era of treatment of critical left ventricular outflow obstruction. Although a great deal has been learned in the last decade, many questions remain to be answered. No one would argue against the variables reflecting left ventricular size as proposed by Rhodes *et al.*,[208] however other anatomical, functional and clinical variables are probably as important in defining candidacy, as suggested by the study above.

Soon after its introduction in the late 1980s, balloon dilation rapidly became a widely accepted alternative mode of treatment for the neonate with severe aortic stenosis due to the high surgical mortality at that time.[85,282,285–294] The issue of which method (surgical or balloon) was a better treatment option dominated the early 1990s.[287,288] However, series comparing balloon to surgical therapy did not adjust for important differences in patient characteristics between groups which biased the results.[282,294] Because of the low frequency and the severe nature of the disease in neonates, along with different treatment protocols, prospective and randomized studies comparing the two strategies are not available in the literature. It was only recently, that larger series derived from either single[84] or multicenter[318] studies have became available, with proper adjustments for varying patient characteristics, allowing evaluation of the results of both procedures in this age group. Based on data derived from the CHSS registry, surgical and balloon therapies appear to have similar outcomes for neonates with critical aortic valve stenosis who are selected for biventricular repair.[318] Patients who underwent balloon dilation had a slightly greater degree of regurgitation compared to surgical valvotomy, but lower final transvalvular gradients. Therefore, the decision to proceed with either method essentially depends upon local institutional experience. Because balloon dilation avoids cardiopulmonary bypass, a shorter hospital stay and recovery periods,[318] it is less costly. Avoiding an early median sternotomy may be another important advantage, considering that these patients are likely to have some future surgical procedure on their valve.

Success rates

In a study by McCrindle for the Valvuloplasty and Angioplasty of Congenital Anomalies (VACA) registry investigators,[319] neonates and infants < 3 months of age were at risk for suboptimal immediate outcomes, defined arbitrarily as failure to perform the procedure, a residual gradient > 60 mmHg, a left ventricular to aortic pressure ratio of > 1.6, or major morbidity or mortality. In the same study, failure to perform or complete the procedure occurred in 16% of patients < 3 months of age. Earlier catheter series reported procedural failures due to a variety of causes, mainly inability to cross the aortic valve with either the guide wire or the balloon catheter.[85,282,285,286] With refinements in catheter technology, and institutional experience, these problems were overcome, and completion of the procedure has been achieved in > 95% of cases in recent reports.[84,297] To illustrate the effect of the institutional learning curve on outcomes, the same study by McCrindle[319] showed that earlier procedure date was also an independent factor for suboptimal immediate results. If one defines technical success as gradient reduction > 50% with no significant aortic regurgitation, this is achieved in > 70% of patients submitted to balloon dilation in more recent series.[84]

Gradient relief

Significant reductions in systolic pressure gradients across the valve can be achieved with immediate improvement in left ventricular function, when impaired, in most neonates.[315] However, suboptimal residual obstruction occurs more frequently in infants < 3 months of age when compared to older patients (18% vs. 8%).[319] The use of an undersized balloon (balloon to annulus ratio < 0.9) was also considered an independent predictor of a residual obstruction.[319] In general, the peak aortic valve gradient (in mmHg) can be reduced from the mid 60 or 70s to the high 20s or mid 30s (50–60% reduction).[84,85,282,285,286,289–297,308,309,311,312,315] Left ventricular end-diastolic pressure is also significantly reduced, usually by 20%.[84] Even in the setting of a unicommissural and dysplastic valve, the results of the procedure have been satisfactory.[316]

Early mortality

Mortality rates related to the procedure have varied over time, ranging from 9% to 30%.[84,85,282,285,286,289–297,308,309,311,312,315] Early series reported higher rates mainly due to technical difficulties, the occurrence of severe aortic incompetence or poor patient selection (small left sided structures).[85,282,285,286] Today, when balloon dilation is performed in appropriately selected patients, a low mortality rate, < 10%[84,297,315,318] can be expected.

In a study comparing the contemporary results of surgical to transcatheter valvotomy, McCrindle[318] found, as independent risk factors for mortality, the need for mechanical ventilation before valvotomy (reflecting the severity of the clinical status), the presence of a smaller aortic valve annulus, smaller subaortic diameter at the sinotubular junction and smaller subaortic region (reflecting anatomical features of a small left ventricle).

In a study by Robinson and colleagues,[297] from a multicenter registry of balloon dilation through a carotid cut down, duct dependent neonates had a higher mortality rate (38%) compared to the non-duct-dependent patients (5%). In uni- and multivariate analysis, they found an aortic valve diameter of < 6 mm, a left ventricle that did not form the cardiac apex and the presence of mitral stenosis as risk factors for death after completion of the dilation, or the need for univentricular heart palliation.

In general, the cause of death in such neonates with critical aortic stenosis was a low cardiac output syndrome due to inadequate left heart structures, reflecting in some patients that a single ventricle treatment algorithm[86] would have been a better strategy.

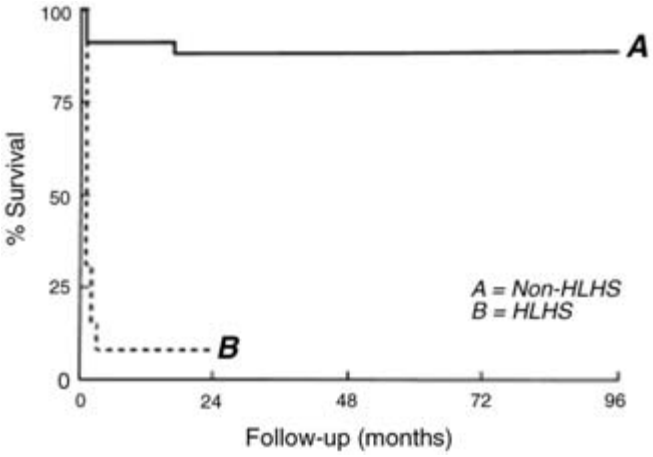


Fig. 14A-19 Kaplan–Meier survival curve for neonates after balloon dilation as initial treatment for critical aortic stenosis. HLHS(v) = hypoplastic left heart syndrome (variant group, echocardiographic score. > 2). (Reprinted from Egito *et al*.,[84] Copyright (1997), with permission from The American College of Cardiology Foundation.)

Complications and morbidity

When the procedure is performed through the femoral artery, the major complication is pulse loss with a varying incidence (40–100%),[84,85,282,285,286,315,320] which can usually be restored with heparin or thrombolytic therapy.[321,322] Evolving catheter technology has allowed improvements in this regard,[291] as will be discussed below.

De novo or an increase in aortic regurgitation is commonly observed after the procedure.[84,85,282,285,286,289–297,308,315] However, it is generally well tolerated, rarely requiring urgent surgery. This is not true when there is avulsion of 1 of the aortic cusps.[85] Induction of severe aortic regurgitation or an increase of 2 or more categories of the preexisting regurgitation occurs in 5–10% of patients.[84,311] A valve diameter < 8 mm was considered as an independent predictor of this complication in a study derived from the data pooled from the VACA registry.[319] This may be due to the more dysplastic changes observed in the smaller valves of the neonate. The presence of more than trivial preexisting aortic regurgitation and the use of oversized balloons (balloon to annulus ratio > 1) were also considered as risk factors for aortic regurgitation in the same study.[319] Some investigators have related the presence of unicommissural valves to the development of aortic insufficiency.[62] More often than not, the induction of aortic insufficiency in the neonate is due to wire perforation of a valve leaflet during attempts to enter the left ventricle from a retrograde approach, with subsequent tearing of the leaflet with dilation.

Major complications such as transection of the femoral or iliac artery, pericardial tamponade, perforation of the aorta or the left ventricle, bleeding requiring transfusion, arrhythmias, damage to the mitral valve apparatus resulting in mitral regurgitation, sepsis, stroke, and cardiac arrest have all been observed.[84,85,282,285,286,289–297,308,309,315] Younger patients (< 3 months) are at greater risk for such major complications.[318]

Mid to long-term results

From a large single center series, survival and freedom from intervention were 88% and 64% at 8 years, respectively[84] (Fig. 14A-19). At a mean 4 ± 2 years of follow-up (2–8 years), 83% of the survivors were asymptomatic. Echo-Doppler studies revealed a maximal instantaneous gradient of < 50 mmHg in 65% of patients and significant aortic regurgitation in only 14%. The need of reintervention was high (40%) primarily due to restenosis requiring redilation.[84]

Data derived from the large (95 infants) multicenter registry of balloon dilation through a carotid approach[297] revealed an actuarial survival and freedom from reintervention of 76 ± 6% and 67 ± 6% at 3 years, respectively. The 3-year actuarial survival and freedom from intervention were significantly different in duct-dependent infants compared to those not duct dependent (60 ± 9% vs. 93 ± 4%; $P = 0.0008$ and 59 ± 11% vs. 91 ± 5%; $P = 0.002$, respectively). In a mean follow-up of 2 years (0–9 years), the mean systolic gradient was 34 mmHg and moderate or severe aortic regurgitation was present in 15% of patients. Patency of the carotid artery was demonstrated by imaging in > 90% of patients during follow-up and none had clinical neurological sequelae.

In the study conducted by the CHSS comparing the contemporary results of surgical and balloon dilation valvotomy for critical aortic stenosis,[318] the authors found similar time related survival for both methods, which was 82% at 1 month and 72% at 5 years (Fig. 14A-20). Estimates for freedom from reintervention were 91% at 1 month and 48% at 5 years and did not differ significantly between groups (Fig. 14A-21). Predictors of reintervention were poor predilation clinical condition, lower weight and production of important aortic regurgitation after valvotomy.[318] Although similar outcomes were observed for both approaches, higher residual gradients were more commonly present after surgical valvotomy (36 [range 10–85] vs. 20 [range 0–85] mmHg; $P < 0.001$) and important aortic regurgitation was more often present after balloon dilation (18% vs. 3%; $P = 0.07$).[318]

A significant discrepancy in the length of the leg used for percutaneous arterial entry is occasionally seen in the follow-up.[84] Even after restoration of the distal pulses with heparin or thrombolytics, the prevalence of obstructive lesions detected by

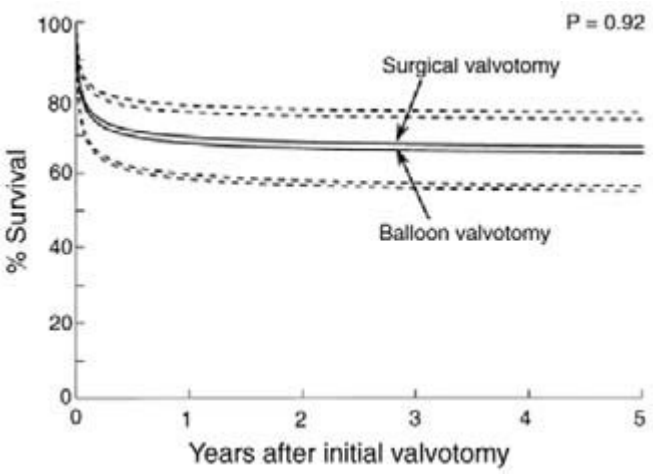


Fig. 14A-20 Time-related survival stratified by type of initial aortic valvotomy, adjusted for differences in group characteristics as reflected by a propensity score derived from multiple logistic regression. Solid lines represent parametric determination of continuous point estimates, and dashed lines enclose 70% CI. (Reproduced from McCrindle *et al*.,[318] copyright (2001), with permission from Lippincott Williams & Wilkins.)

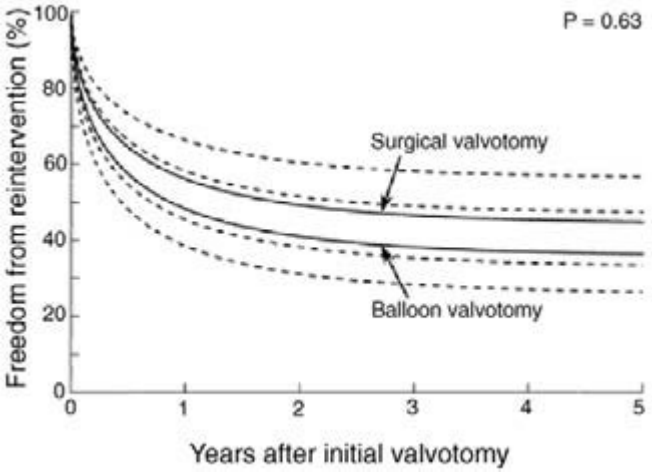


Fig. 14A-21 Time-related freedom from aortic valve–related reintervention stratified by type of initial aortic valvotomy, adjusted for differences in group characteristics as reflected by a propensity score derived from multiple logistic regression. Solid lines represent parametric determination of continuous point estimates, and dashed lines enclose 70% CI. (Reprinted from McCrindle *et al*.,[318] Copyright (1996), with permission from The American College of Cardiology Foundation.)

imaging modalities may be surprisingly high, however, with limited clinical impact.[323,324]

Technical issues that may affect outcomes: refinements in catheter technology are likely to reduce the incidence of arterial damage significantly. For example, balloon catheters up to 10 mm in diameter, on a 3 Fr shaft size, with a 0.014-in lumen are now available (Minityshak; Numed; Cornwall, Canada). Such catheters are suitable for different interventional procedures including aortic valve dilation in the neonate, although experience with their use is limited.

In order to expedite access to the left ventricle and minimize the risk of cusp perforation while crossing the aortic valve with a guide wire, some authors have advocated use of the carotid artery for dilation, with good short- and long-term results.[290,296,308,309297] Mortality and morbidity related to the procedure are reduced.[297] This approach also has the merit of sparing the femoral artery. In addition, the presence of the sheath introduced through the right carotid artery into the ascending aorta provides stability for the balloon during inflation, minimizing the risk of valve damage. As noted, no significant adverse neurological sequlae were seen after the use of this technique.[297]

In order to avoid arterial complications, valve perforations and better stabilize the balloon across the valve, the Toronto group has employed the antegrade technique with similarly good results.[315] Although it is technically more demanding with longer fluoroscopic times, it is associated with a lower incidence of pulse loss and significant aortic regurgitation. Proper balloon aortic valve annulus ratios are also of paramount importance to avoid this latter complication. In this regard, it is prudent to select a balloon diameter that is < 100% of the annulus diameter.[319]

Although arterial umbilical access has also been used for dilation to avoid femoral artery entry,[291] as has an axillary cutdown for access,[289] these approaches are associated with more difficult catheter manipulations, longer procedural times and local complications.[325] Transumbilical venous, antegrade, snare-assisted approaches have also been described,[326] although it carries similar disadvantages. The question of the easiest and safest access approach to perform the procedure in the neonate remains unsettled.[325]

Mitral valve damage is always a possibility when dilating the aortic valve[327] with either antegrade or retrograde techniques. It can be avoided by keeping a proper wire position in the left ventricular cavity, away from the mitral valve apparatus.

Patients that are considered to be too ill to be referred to a catheterization laboratory may benefit from bedside balloon dilation through the carotid artery under transesophageal ultrasound guidance.[328,329] Despite the recent use of high doses of adenosine (500 μg/kg) to lower the heart rate and achieve a better stabilization of the balloon across the valve,[330] the efficacy and safety of this approach remains to be determined in clinical trials. In neonates with critical obstruction and decreased left ventricular function, the role of high dose adenosine administration is probably limited.

The premature

Severe aortic stenosis requiring intervention has been reported in low weight premature neonates. Due to obvious access restrictions, due to the size of these patients, balloon dilation has been performed in an antegrade fashion,[331] through the carotid or umbilical arteries with good immediate outcomes.[332]

The fetus

In utero diagnosis of severe aortic stenosis with progression of obstruction and deterioration of left ventricular function, with fetal demise, has been well documented.[333–336] To improve the fate of such fetuses, prenatal ultrasound guided percutaneous balloon aortic dilation has been attempted in some centers with disappointing results.[333,335] In a recent report, Kohl *et al.*[336] reviewed the world experience with this procedure in 12 human fetuses, with severe aortic valve obstruction. The mean gestational age at intervention was 29 weeks (range 27–33). The mean time between initial presentation and intervention was 3 weeks (range 3 days to 9 weeks). Technically successful balloon dilations were achieved in 7 fetuses, none of whom had an atretic valve. Six patients who survived the prenatal intervention, died from cardiac dysfunction or at surgery in the first days or weeks after delivery, and only 1 patient remained alive at the time of the study. Of the 5 technical failures, 1 patient underwent successful postnatal intervention and remained alive at the time of the study. As discussed by the authors, the poor results were probably secondary to the severity of the disease, technical problems during the procedure, and high postnatal operative mortality in fetuses who survived gestation.[336] A clearer understanding of the hemodynamics, better patient selection, and technical refinements in interventional methods are needed before prenatal aortic balloon dilation can be advocated as a generally applicable technique.

Older infants, children, adolescents and young adults

Indications

The indications of balloon dilation for these patient groups are the same as those for surgical correction. An echo-Doppler derived or measured peak-to-peak systolic pressure gradient > 60–70 mmHg irrespective of symptoms or a gradient ≥ 50 mmHg with symptoms or electrocardiographic ST–T wave changes (at rest or after exercise) is generally considered an

indication for intervention.[62,272–281,283,284,299–307,310–314] The procedure is also indicated for infants in symptomatic heart failure or with impaired left ventricular function with "borderline" gradients. The presence of significant aortic regurgitation (equal or greater than moderate) is a contraindication for balloon dilation.[299,311] Previous surgical or balloon valvotomy does not affect the results unfavorably.[337–340]

Patient selection

The adequacy of left heart structures does not generally apply to these patients, almost all are suitable for dilation in the absence of annular hypoplasia and tunnel left ventricular outflow tract obstruction. Older infants, children, adolescents and young adults with congenital aortic valve stenosis usually have well formed left ventricles, with varying degrees of hypertrophy.[52] Functional and anatomic abnormalities of the mitral valve may be present.[52] Aortic valve pathology is variable, but typical findings include a normal sized valve annulus, a bicuspid valve with variable degrees of commissural fusion, and thickened and doming valve leaflets.[52] Calcification is uncommon.[52] The ascending aorta is usually dilated and isthmic hypoplasia with or without coarctation may also be present.[52] Balloon dilation is rarely contraindicated based upon the morphology of the valve.[312]

Success

Completion of the procedure is the standard, failures occurring in < 2% of cases.[319] Nevertheless, the procedure can be technically demanding due to difficulties in positioning and stabilizing the balloon across the valve.[312] Success, defined as a gradient reduction ≥ 40% or a residual peak-to-peak systolic gradient < 50 mmHg can be achieved in > 85% of patients.[299]

Immediate mortality

Procedural mortality is low, being < 1% in recent series.[283,284,299–303] Causes of deaths include aortic rupture, perforation of the valve or avulsion of valve leaflets, exsanguination from an arterial vessel disruption; cardiac arrest, malignant arrhythmias and myocardial ischemia due to coronary damage from inappropriate wire manipulation, or dissection of the valve annulus.[283,284,299–304,310]

Gradient reduction

Dilation reduces the peak-to-peak systolic gradient significantly, from the mid 70s to mid 30s or high 20s (in mmHg) with a mean per cent reduction of 50–60%.[62,272–281,283,284,299–307,310–312,319] Gradient reduction by 40% is achieved in at least 85% of patients.[299,312] Failure to reduce the gradient < 50 mmHg and < 60 mmHg occurs in 10–15%[299] and 6% of patients, respectively.[319] In one study, prior valvotomy was the only factor that significantly impaired the immediate gradient reduction after dilation.[299] Failure to reduce the gradient may also be related to some degree of annular hypoplasia seen in an occasional patient.[299,310] In the study by McCrindle *et al.* for the VACA registry, the presence of a predilation gradient over 80 mmHg was considered an independent risk factor for residual obstruction (odds ratio 3.53; CI: 1.46, 8.20) as was the use of an undersized balloon (balloon to annulus ratio < 0.9) (odds ratio 2.94; CI: 1.45, 5.97).[319] Acute reduction of left ventricular end diastolic pressure was also observed in one study,[301] however statistical significance was not reached in another.[299]

Complications/morbidity

Significant morbidity related to the procedure (beyond the neonatal period) has been remarkably low. Minor complications such as transient arrhythmias[341,342] (notably left bundle branch block, supraventricular and ventricular arrhythmias) and asymptomatic femoral artery occlusion are relatively common (13% and 7%, respectively).[299] Serious complications appear to occur in < 5% of patients.[62,272–281,283,284,299–307,310–312,319] These include cardiac arrest requiring defibrillation or resuscitation, aortic valve prolapse, valve leaflet tear, mitral valve injury, blood loss requiring transfusion, infective endocarditis, stroke and vascular damage requiring surgery.[62,272–281,283,284,299–307,310–312,319]

An increase in the degree of aortic regurgitation occurs in 10–58% of patients, usually being well tolerated.[62,272–281,283,284,299–307,310–312,319] Moderate to severe aortic regurgitation is observed in 5–13% of patients, rarely requiring surgery.[62,272–281,283,284,299–307,310–312,319] Prolapse of an aortic cusp may follow dilation as well,[277] although it is not clear what factors predict this occurrence. In a study derived from the VACA registry, the average balloon to annulus ratio was larger in patients who developed moderate to severe aortic regurgitation immediately after dilation.[279] It is important to point out, that at that time, investigators had yet to determine the ideal balloon diameter to valve annulus ratio (the maximal ratio was 1.5) and that the technical aspects of the procedure had not been standardized. Further analysis of the VACA registry data[319] demonstrated that three factors independently predicted the production of severe aortic regurgitation or an increase of two or more categories from preexisting aortic regurgitation. These included an increased balloon to annulus ratio (> 1), the presence of preexisting aortic regurgitation (graded mild or more) and larger valves (> 16 mm).[319] Previous surgical valvotomy was not considered a risk factor. It has been speculated that the presence of previous aortic regurgitation may signify valves with morphological abnormalities that would be exacerbated by the dilation. Larger valves encountered in older patients may also exhibits signs of secondary degenerative changes, which may predispose them to insufficiency. In addition, stabilization of the balloon across the valve is generally difficult in older patients (with normal ventricular function), which may damage the leaflets during the inflation, inducing regurgitation. In the study from Boston,[299] patients 1–5 years of age, with prior valvotomy, and with at least moderate regurgitation prevalvotomy, were considered to be at risk to have moderate to severe incompetence after dilation. Although the balloon to annulus ratio (0.68–1.37) was not a risk factor in this study, the authors made the point, stating that the average increase in aortic regurgitation seemed to be greater in patients in whom a balloon to annulus ratio of > 1.25 was used. This observation was in accordance with previous studies in animal models,[271] and in clinical models with intraoperative balloon dilation.[343] Injury to, and tears in, the aortic valve may follow overdilation.[344,345]

Mid to long-term results

Late mortality is uncommon after balloon dilation in patients beyond the neonatal period. In a large series (148 patients) from Boston, time-related survival was 97% at 5 years and 95% at 8 years[299] (Fig. 14A-22). Excluding young children with other significant left heart obstructive lesions, the occurrence of late deaths was rare, with a late survival rate of 99%. In the same

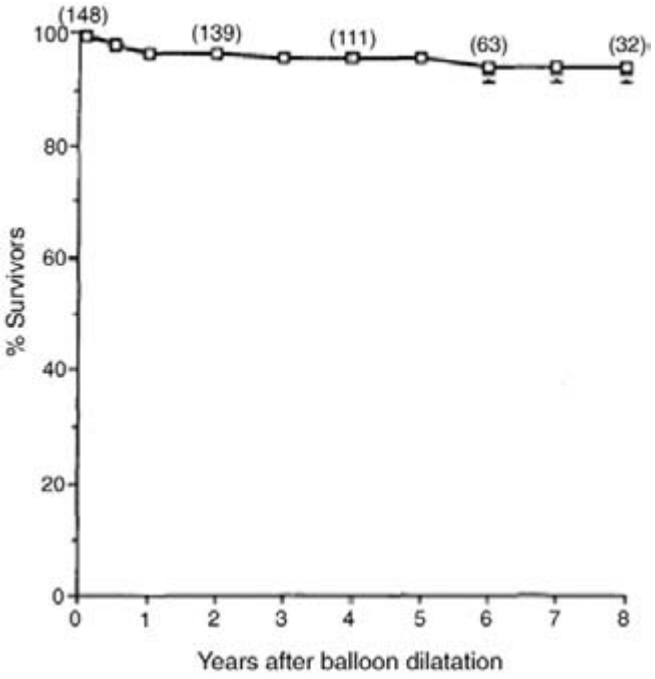


Fig. 14A-22 Survival after balloon dilation BD) for aortic stenosis in patients > 1 month old (n = 148). Percentages were calculated using the life-table approach. Error bars–1 SD. (Reprinted from Moore *et al*.,[299] Copyright (1996), with permission from The American College of Cardiology Foundation.)

study, over a mean follow-up of 31 ± 26 months, 25% required repeat intervention, 17% for restenosis (usually treated by redilation) and 8% for significant aortic regurgitation. Thirteen per cent of patients underwent surgery, mainly for significant aortic regurgitation. Time related freedom from repeat intervention was 80% at 4 years and 40% at 8 years after dilation (Fig. 14A-23). Seventy-six per cent of patients were free of aortic valve surgery at 8 years. At a mean follow up of 42 ± 24 months, there was no difference in the mean maximal instantaneous echo-Doppler gradient compared to immediately after dilation. However, the prevalence of grade 3+ or 4+ aortic regurgitation increased from 13% immediately after dilation to 38% in follow-up. In this study, factors that increased the risk of repeat intervention were the presence of symmetrically thin or thick aortic valve leaflets, regurgitation (grade 3) and a high residual gradient after dilation.[299]

In another single center study by Kuhn *et al.*,[300] outcomes were similar to those described in the Boston series. Median follow-up was 60 months in 22 children. Thirty-two per cent of the patients underwent redilation for restenosis, with good results. The actuarial freedom from repeat dilation was 50% at 60 months and 44% at 100 months. At late follow-up, 32% had an increase in aortic regurgitation to at least moderate degree, with 14% of patients undergoing surgery for functional deterioration of the aortic valve and severe aortic insufficiency. The actuarial freedom from aortic valve replacement was 90% at 60 months and 75% at 100 months.

Galal *et al.*[301] reported a mean follow-up of 72 ± 20 months (median 6 years) in 22 children. The restenosis rate was 23% and multivariable step-wise logistic regression analysis identified age < 3 years and immediate aortic valve gradient > 30 mmHg as predictors of restenosis. Significant aortic insufficiency developed in 27%, although none required surgical intervention. Logistic regression analysis suggested that the degree of echo-Doppler estimated aortic insufficiency the day following the dilation predicted aortic insufficiency at late follow-up. Actuarial intervention free rates at 1, 5 and 9 years were 80%, 76% and 76%, respectively.

More recent studies also confirm satisfactory follow-up outcomes. Demkow *et al.*[303] showed at 62 ± 30 months, gradient reduction persisted (50 ± 26 mmHg) in their 45 patient cohort, although 10 patients (22%) had gradients > 60 mmHg. Progression of aortic incompetence occurred in 13 patients (29%). There was no mortality. Fifteen patients (33%) required reintervention 51 ± 24 months after dilation due to restenosis, significant regurgitation or both. Actuarial freedom from reintervention at 2, 4, 6 and 8 years were 96%, 88%, 61% and 56% of patients respectively. The residual gradient after the procedure was the only predictor for reintervention for restenosis, with residual gradients > 40 mmHg carrying a sixfold increase in relative risk. The immediate degree of aortic regurgitation after the dilation was the only risk factor for reintervention for regurgitation, with grades > 2 carrying a 10-fold increase in relative risk. Jindal *et al.* [304] reported no long-term mortality at 6 ± 3 years (range 2–12) of follow-up, with 20% and 21% rates of restenosis and significant aortic regurgitation (> grade 3), respectively. These authors also identified the severity of aortic regurgitation and higher residual gradients immediately after

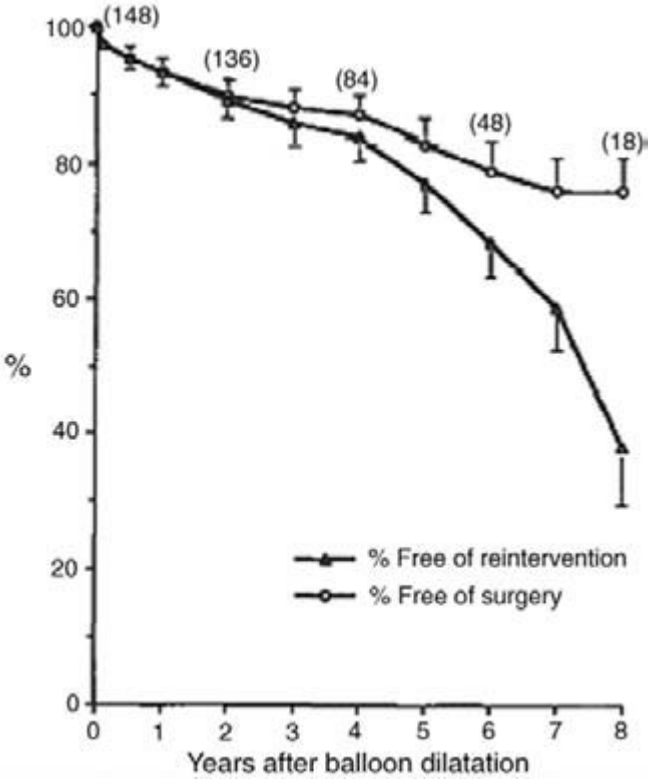


Fig. 14A-23 Per cent of patients free of any repeat intervention and those free of aortic valve surgery after balloon dilation (BD) for aortic stenosis in patients > 1 month old (n = 148). Percentages were calculated using the life-table approach. Error bars–1 SD. (From Moore *et al*.[299] with permission.)

the procedure as risk factor for late adverse events. Reintervention was performed in 14% of patients. The actuarial intervention free rates at 5, 7 and 12 years were 93%, 85% and 60%, respectively. In the case series reported by Borghi *et al.*,[302] survival and freedom from events was 88% and 75% for infants, and 96% and 64% for children at 6 and 8 years, respectively.

Other studies, with different numbers of patients and lengths of follow-up, demonstrated similar outcomes.[274–281,310] However, systematic comparison of different series and to historical surgical series are of limited value because of non-contemporary timeframes, lack of uniformity in defining restenosis and significant aortic regurgitation, inconsistent and variable techniques to assess aortic regurgitation, and variable criteria to determine the need of reintervention (either repeat balloon dilation or surgery). Although it has been suggested that aortic regurgitation may be more frequent after balloon dilation than surgical valvotomy,[299] data from The Hospital for Sick Children in Toronto, does not support this view.[283] To compare the characteristics of aortic regurgitation, the results of 213 procedures (110 aortic dilations and 103 surgical aortic valvotomies) performed in 187 patients between June 1981 through September 1993 for treatment of congenital aortic valve stenosis were reviewed. Whereas balloon dilation patients were older (median age 6 years vs. 3 months; $P = 0.0001$), there was no significant difference in median follow-up interval (3 years [range 0.5–7.2] for the balloon procedure vs. 4 years [range 0.6–10.4] for the surgical procedure; $P = 0.44$). The mean balloon to annulus ratio for dilation was 0.99 ± 0.09. An open valvotomy was performed in 83% of surgical cases. Acute systolic gradient reduction and subsequent increase at late follow-up was similar for both groups. Acutely, the mean regurgitant jet width ratio (echocardiographically determined) increased similarly in both groups ($P = 0.84$), being $9 \pm 15\%$ ($P = 0.0001$) for balloon dilation and $9 \pm 12\%$ ($P = 0.0003$) for surgical valvotomy, and was not related to the age at the procedure. At late follow-up, mean jet width ratio further increased significantly in both groups, although there was no difference ($P = 0.17$) in the amount of progression ($10 \pm 12\%$ for balloon; $P = 0.0001$ vs. $15 \pm 13\%$ for surgery; $P = 0.0002$). Similarly, freedom from reintervention was the same in both groups (Fig. 14A-24). In this study, it was concluded that balloon and surgical valvotomy produce similar degrees of aortic regurgitation with similar rates of progression.[283]

The observation that the degree of aortic regurgitation increases over time is universal and common to all catheter (and surgical) case series. Although risk factors for increasing aortic incompetence have not been defined, it has been speculated that this is an inevitable occurrence due to the intrinsically abnormal morphology of the aortic valve and reflects the modified natural history of this disorder. In other words, no matter what is done to alleviate the stenosis (surgically or percutaneously), an increase in the degree of aortic incompetence is a price to be paid. This is not surprising, considering that either the interventionalist's balloon or the surgeon's scalpel causes variable splitting of commissural fusion,[344,345] which is the primary mechanism for valvar obstruction.

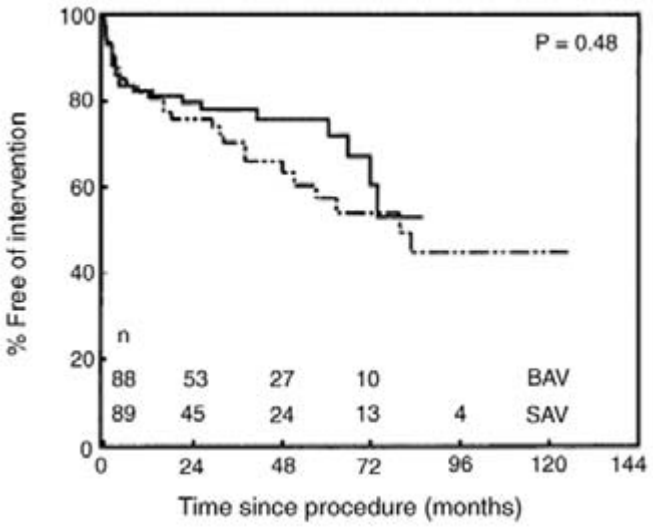


Fig. 14A-24 Kaplan–Meier curve showing freedom from subsequent intervention to the aortic valve after balloon valvotomy (BAV) (solid line) and surgical aortic valvotomy (SAV) (broken line). (Reprinted from Justo *et al.*,[283] Copyright (1996), with permission from Excerpta Medica.)

Technical issues that may affect outcomes

Because crossing the small hemodynamic orifice within the stenosed valve can be difficult, a variety of catheters and wires are used.[52] When retrograde catheterization of the left ventricle is fruitless, some authors have used a transeptal approach, with flotation of a catheter balloon from the left ventricle to the ascending aorta, and exteriorizing a wire out of the femoral artery forming a femoral vein–femoral artery loop.[346] Antegrade snaring of the guide wire has also been described.[347]

As already discussed above, the use of oversized balloons may be associated with the occurrence of significant aortic regurgitation.[319] Therefore, it is recommended that a balloon diameter of 90% of the annulus should be employed, at least in the first inflation. If the gradient is still > 50 mmHg or has fallen < 40%, and the degree of aortic regurgitation has not been changed, the operator may consider increases to the balloon to annulus ratio.[299,312] Detailed analysis derived from the VACA registry revealed the optimal balloon to valve annulus ratio to be 0.9–1.0, with undersized balloons resulting in a significant residual obstruction and oversized balloons resulting in significant aortic regurgitation.[319]

With the availability of large diameter balloons mounted on a "low" profile catheter shafts, the issue of arterial damage is less of concern today. For example, balloons up to 18–20 mm in diameter, 4–6 cm long, mounted on 7–8 Fr shafts with inner lumens accepting a 0.035-inch wire are available (Tyshak II, NuMed, Cornwall, Canada). To eliminate the risk of arterial trauma, some authors have performed the procedure in an antegrade fashion.[348,349] However, this approach has potential drawbacks such as the need for transeptal puncture (outside the neonate period) catheter advancement through the left heart, injury to the mitral valve, and hemodynamic instability due to catheter induced mitral regurgitation.

In order to better control the effective dilating diameter and to minimize the risk of femoral artery damage, other investigators have used a double balloon technique, with two low profile balloon catheters introduced through both femoral vessels[350,351] (Fig. 14A-25). Although it is technically demanding (sometimes three or four operators are required in the field), this approach also permits better systemic and coronary flow during the dilation process.[352] An increase in the degree of aortic regurgitation does not seem to be an issue with this approach.[319] In general, only when the aortic annulus > 20 mm, the double balloon tech-

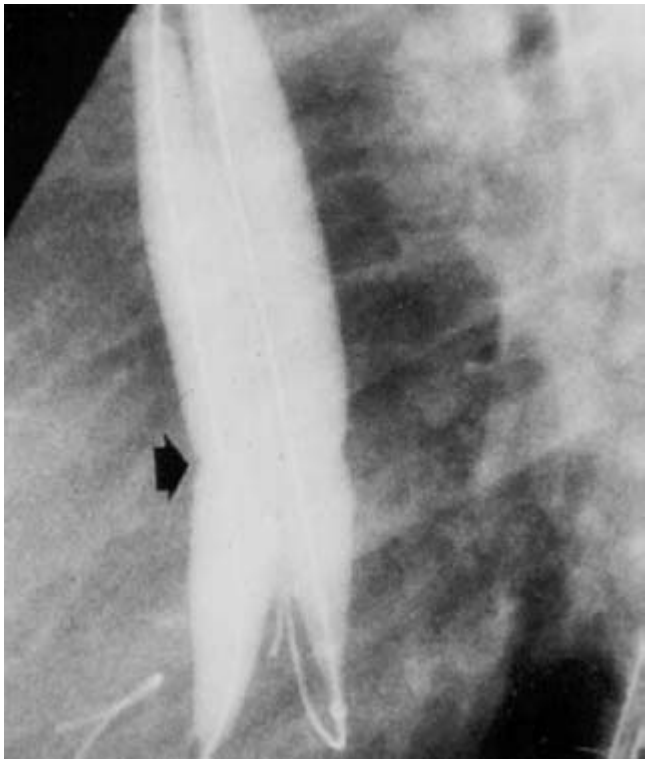


Fig. 14A-25 Two retrograde balloons across a stenotic aortic valve, inflated during valve dilation. Note the indentation (arrow) at the valve annulus level.

nique is employed routinely.[52] As a simple rule of thumb to calculate the adjusted combined balloon diameter, the sum of the two balloon diameters should be 1.3 times the aortic annulus.[353,354]

It is speculated that poor stabilization of the balloon across the valve during inflation with to and fro movements, may result in damage to the aortic valve, potentially increasing the degree of aortic regurgitation.[310] To circumvent this problem, attention to technical details is of paramount importance. Longer (4–6 cm) and highly compliant balloons should be used for stabilization and quick inflation/deflation cycles.[312] An extra stiff guide wire with a large curve, shaped on its tip should be used to provide support to the catheter balloon while it is advanced during inflation.[312] A long sheath may be positioned in the ascending aorta close to the proximal part of the balloon to avoid movement by the hyperdynamic left ventricle.[310] Recently, some investigators have advocated the use of high doses of adenosine (500 µg/kg) to lower (or even stop) the heart rate for better positioning and stabilization during balloon inflation.[330] Although this may be an option in difficult cases (generally adolescents and young adults), its efficacy and safety remains to be seen in trials. Needless to say, care should be taken while positioning the wire in the left ventricular cavity near the septum, away from the mitral valve, to avoid damage to this structure.[312]

Interestingly, McCrindle[319] studied the effect of operator and institution on outcomes after dilation, and showed that experience makes a difference when it comes to dilating aortic valves, with an operator's evolving experience most predictive of improved results.[319] Despite this observation, improved results were unrelated to the total number of cases, or the time period over which the procedures had been performed. This suggests that well trained and experienced operators at small centers will have similar results to those in larger volume academic centers.

Infants 3–12 months

The results of the procedure in this age group are similar to those seen in older children.[298] However, because femoral arterial complications seem to occur more frequently in this age group,[280,281,311] some authors have advocated the use of the carotid artery for entry.[297,298,309,310] As observed in neonates, favorable neurological outcomes are also seen in infants. Despite this, it is difficult to determine the upper age limit at which the procedure can be done safely through the carotid artery. Because improvements in catheter technology reduce the risk of arterial complications significantly, the conventional femoral approach may as well be a safer access option.

Adolescents and young adults

Congenital aortic stenosis may require relief in older patients as well. Unlike the elderly, in whom aortic stenosis is caused by a degenerative calcium laden valve, in the adolescent and young adult with congenital aortic stenosis the primary anatomic lesion remains fusion of the commissures.[305–307] Although calcification does occur more frequently with aging, even in patients with congenital aortic stenosis,[305] case series have demonstrated that the short and intermediate term outcomes of balloon dilation for adolescents and young adults with congenital aortic stenosis are similar to those observed in children.[305–307] Significant gradient relief is observed immediately after the procedure, and persists at intermediate follow-up, postponing the need for surgical intervention.[305–307] This is in contrast to the results of balloon dilation of the acquired calcific aortic stenosis in the elderly, which is invariably followed by restenosis within a short period of time, with no impact on mortality or the need for aortic valve replacement.[355–358] Nevertheless, patients with congenital stenosis with valvar calcification tend to have higher echo-Doppler gradients at follow-up following balloon dilation and a lower likelihood of remaining incident-free[305] (Fig. 14A-26). As such, the procedure can benefit older patients (> 16 years of age) providing that the valve leaflets are not severely calcified.[307] Balloon dilation has also been performed in late childhood and adolescence for critical patients in severe heart failure with restoration of the left ventricular function and favorable outcomes.[359]

Because of their size, arterial trauma secondary to balloon entry is not an issue in the older and larger patient. On the other hand, the diameter of the aortic annulus is invariably > 20 mm, requiring the application of a double balloon technique. Stabilization of the balloon across the valve may be a difficult task in this age group due to the hyperdynamic ventricular contractions secondary to the longstanding obstruction. The administration of high doses of adenosine may prove to be helpful to circumvent this problem. Its impact on decreasing the degree of aortic regurgitation remains to be determined.

The Inoue-Balloon™ (Toray Inc., Japan), commonly employed for balloon dilation of rheumatic mitral valve stenosis, has also been used for antegrade, transeptal, stepwise dilation of the aortic valve in congenital stenosis.[360,361] Although it may offer some technical advantages, the need for routine transeptal approach is a drawback. As aortic regurgitation does not seem to develop less frequently with this technique, its

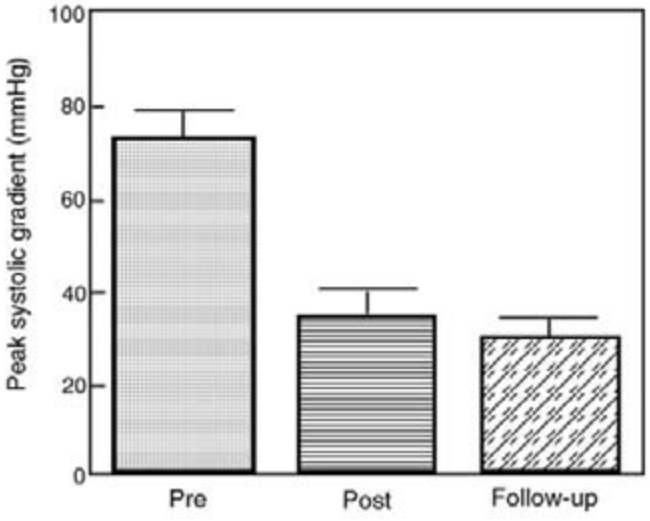


Fig. 14A-26 Peak systolic gradients before and in follow up after balloon aortic valve dilation in young adults. (Reprinted from Sandhu *et al*.,[307] Copyright (1995), with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

superiority over more conventional approaches remains to be proven in further and larger series.

Balloon dilation under special circumstances

Balloon dilation of the aortic valve is safe and effective when applied to patients with restenosis following previous surgical or balloon valvotomy.[311,312,337–340] Immediate gradient reduction and development of aortic regurgitation are comparable to results reported for primary balloon dilation.[337–340] Gradient relief persists at follow-up and, as would be expected, some patients do require surgical intervention due to progressive aortic insufficiency.[337–340] Therefore, it seems reasonable to manage patients with restenosis either after surgical or balloon valvotomy with a catheter procedure.

Although there are some reports of balloon dilation for discrete membranous subaortic stenosis [362–366] with good short and intermediate-term results, the procedure does not seem to provide sustained relief of obstruction and does not deal with the aortic incompetence issue. These patients are probably better served with surgical intervention. Finally, balloon dilation has a limited role in alleviating obstructions within biological or mechanical prosthetic valves in the aortic position.[311,367]

Congenital aortic insufficiency

Congenital aortic insufficiency is a rare condition.[368–392] Perhaps the most common cause of pure aortic regurgitation in the newborn is the aortico-left ventricular tunnel and this entity is considered elsewhere in this volume (see Chapter 15A). Aortic regurgitation may complicate the course of the patient with either a perimembranous ventricular septal defect or a doubly committed subarterial ventricular septal defect (see Chapter 3) or defects of the sinus of Valsalva (see Chapter 15B). Some patients with congenital aortic stenosis will develop *de novo* progressive regurgitation while in others it may develop subsequent to infective endocarditis. Aortic regurgitation is a well-known consequence of surgical aortic valvotomy or balloon valvuloplasty.

Pure congenital aortic regurgitation in the setting of a fully biventricular heart usually reflects absence of one aortic valve leaflet or on occasion a dysplastic aortic valve leaflet.[368–392] In this latter setting isolation of a coronary ostium has been well documented.[371,375,381] Other causes of pure aortic regurgitation have been attributed to a quadricuspid aortic valve;[372,373,378,379,384] to unusual stretching of an aortic cusp, the so-called "kite anomaly";[368] or to a fibrous band between the aortic cusp and aortic wall.[370,377] Understanding that pure congenital aortic regurgitation is rare, some patients will present early in infancy, their condition requiring immediate intervention, while in others surgical intervention can be postponed or deferred for some time with anticongestive therapy. An absent aortic valve leaflet has also been found in the patient with interruption of the aortic arch and DiGeorge syndrome,[393] double-outlet right ventricle,[394] and very rarely both aortic and pulmonary valve leaflets may be absent[395,396] (see also Chapter 13A). Congenital absence of the aortic valve is also well documented in the hypoplastic left heart syndrome, and this confounding feature has been recognized in the fetus as well[395–405] (see also Chapter 31). The prognosis for the neonate with absent aortic valve leaflets complicating the hypoplastic left heart syndrome is very poor, although there has been an occasional report of successful Norwood-type palliation.[402]

Finally, in any discussion of severe neonatal aortic insufficiency, one must consider the diagnosis of neonatal Marfan syndrome. This diagnosis is unlikely to be omitted from consideration as these babies are usually profoundly dysmorphic and the clinical features have been amply described.[406–413] Mutations in the gene for fibrillin-1 (FBN1) cause Marfan syndrome, an autosomal dominant disorder of connective tissue with prominent manifestations in the skeletal, ocular, and cardiovascular system.[414–416] There is a remarkable degree of clinical variability both within and between families with Marfan syndrome as well as in individuals with related disorders of connective tissue caused by FBN1 mutations and collectively termed type-1 fibrillinopathies. The so-called neonatal region in FBN1 exons 24–32 comprises one of the few generally accepted genotype–phenotype correlations described to date. In this work, we report 12 FBN1 mutations identified by temperature-gradient gel electrophoresis screening of exons 24–40 in 127 individuals with Marfan syndrome or related disorders.[414–416] These reports document a significant clustering of mutations in exons 24–32. Although all reported mutations associated with neonatal Marfan syndrome and the majority of point mutations associated with atypically severe presentations have been found in exons 24–32, mutations associated with classic Marfan syndrome occur in this region as well. It is not possible to predict whether a given mutation in exons 24–32 will be associated with classic, atypically severe, or neonatal Marfan syndrome.[414–416] Any of the four cardiac valves may be involved, but in the neonatal expression of the disease, mitral or aortic regurgitation may on occasion be particularly severe.[406–413] Aortic regurgitation in this setting is accompanied by profound dilatation of the aortic root.

All references can be found at the end of the book. See pp. 661–71 for Chapter 14A.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

14B

Robert M. Freedom and Shi-Joon Yoo

Supravalvular Aortic Stenosis

Of aortic valve stenosis, the fixed forms of subaortic stenosis, and supravalvular aortic stenosis, this last form is certainly the least common. It is usually but not invariably associated with Williams syndrome, and even the largest institutions see relatively only modest numbers of these patients.[1–10] Supravalvular aortic stenosis is an important feature of the Williams–Beuren syndrome, but is also found in a familial form, in twins or in sporadic cases.[9,11–16] Supravalvular aortic stenosis is usually an autosomal-dominant inherited disorder causing obstructive arterial disease in the systemic and often the pulmonary circulations. As summarized by Keating, the most pronounced effects of this disorder are on large vessels, the aorta and pulmonary arteries, but this genetically-determined condition has the potential for involving all so-called conducting arteries.[11] Morris has recently reviewed the genetic aspects of supravalvular aortic stenosis, a most interesting disorder.[13] Supravalvular aortic stenosis occurs as an autosomal dominant trait or as part of the phenotype of the usually sporadic condition Williams–Beuren syndrome. Supravalvular aortic stenosis is the result of mutation or deletion of the elastin gene located at chromosome 7q11.23. Thus, supravalvular aortic stenosis may be more appropriately termed an elastin arteriopathy. Studies have demonstrated various point mutations and intragenic deletions of elastin gene resulting in nonsyndromic supravalvular aortic stenosis. Individuals with Williams syndrome are hemizygous for the elastin gene, owing to a 1–2 Mb deletion of a portion of the long arm of chromosome 7 that encompasses the elastin gene. This submicroscopic deletion is readily detected by fluorescent *in-situ* hybridization, useful in the diagnosis of Williams syndrome. The severity of supravalvular aortic stenosis is quite variable, both in series of Williams syndrome patients and within supravalvular aortic stenosis kindreds, suggesting that other genetic factors are involved in expression of the phenotype. Experiments with elastin knockout mice will likely yield clues regarding the role of elastin in arterial morphogenesis and the pathogenesis of obstructive vascular disease.[13]

Anatomically, supravalvular aortic stenosis has been classified into three subtypes: 1. the hourglass type; 2. diffuse hypoplasia of the ascending aorta; and 3. membranous or diaphragmatic form (Fig. 14B-1).[3–8] Abnormalities of the aortic valve, subaortic region, and coronary arteries are common as well as pointed out by Stamm and his colleagues and by McElhinney and his colleagues.[17–19] Supravalvar aortic stenosis may present in early infancy but uncommonly in the newborn period. In early infancy it occasionally presents as: (1) an isolated, autosomal dominantly inherited form;[12] (2) part of the spectrum of cardiovascular anomalies seen in association with the rubella syndrome; (3) part of the spectrum of cardiovascular anomalies seen in the Williams–Beuren syndrome.[1–14] The latter association is by far the most common. The involvement of the supraortic area and the pulmonary arteries are by the far the best known aspects of this syndrome (Fig. 14B-2). The most common systemic arterial anomalies consist of stenoses in the proximal aortic arch vessels (Fig. 14B-3). Rein and colleagues have used intravascular ultrasound imaging to demonstrate the severe wall thickening with secondary luminal narrowing that is so characteristic of the diffuse arterial involvement of this syndrome.[20] These vascular changes may involve virtually all the major conducting arteries, including the renal arteries, etc.[21,21A] Radford and Pohlner have called attention to the "middle aortic syndrome" as an important component of Williams syndrome,[21] as many of these patients will have diffuse hypoplasia of the abdominal aorta.

The Williams–Beuren syndrome first described in 1961 as mental retardation, peculiar (elfin) facies and supravalvar aortic stenosis,[1] was soon recognized to have peripheral pulmonary stenosis, dental anomalies and idiopathic hypercalcemia as frequent findings.[1–14] Recent works have reviewed the cardiac[22] and non-cardiac[9] spectrum of anomalies in this syndrome. Aortic aneurysms may develop in the patient with supravalvular aortic stenosis.[23] In the patient recorded by Beitzke and his colleagues, these aneurysms developed between 1 and 4 years of age. Bleiden, Becker, and their respective colleagues have observed uniform thickening of the mitral valve in patients with supravalvular aortic stenosis.[4,6] Pulmonary hypertension associated with portal hypertension has also been reported in a child with Williams syndrome, reminiscent of the patient with Alagille syndrome and cirrhosis.[24] Pathological changes in the coronary arteries have received considerable attention in patients with supravalvular aortic stenosis, and the rare instances of sudden death may be related to these coronary artery involvement (Figs 14B-4, 14B-5).[25–30] Coronary ostial stenosis has been well documented in patients with supravalvular aortic stenosis.[17–19,25–30] Amongst 80 patients with supravalvular aortic stenosis seen at the Mayo Clinic, dilatation of the right coronary artery was found in 29% of the patients, and dilatation of the left coronary artery in 20%.[31] This difference reflects the higher incidence of left coronary ostial stenosis. There are other changes in the coronary arteries reflecting high systolic pressure in the aortic root including intimal hyperplasia and atherosclerosis. Sun and colleagues have reported a 3-year 9-month-old patient with supravalvular aortic stenosis who died suddenly.[26] At post-mortem, a somewhat dysplastic right aortic valve was fused to the supravalvular aortic ridge nearly isolating the right coronary artery, and responsible for an

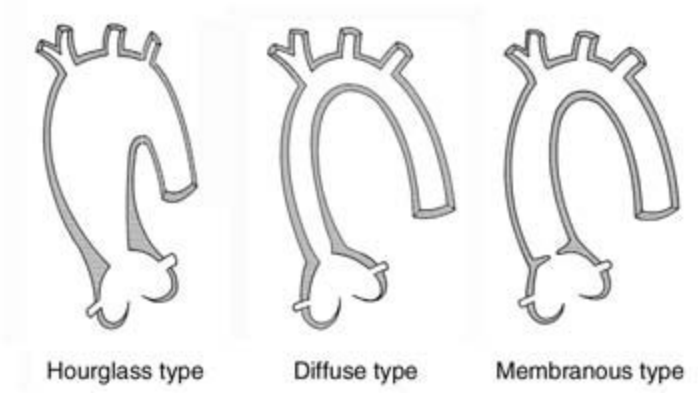


Fig. 14B-1 Types of supravalvular aortic stenosis.

acute myocardial infarction. Others have described myocardial infarction because of coronary ostial occlusion in these patients.[25–30] Rarely, progressive left main coronary artery obstruction resulting in myocardial infarction in a patient with Williams syndrome will occur in the absence of supravalvular aortic stenosis.[27] The coronary arterial involvement peculiar to those patients with supravalvular aortic stenosis must be distinguished from coronary ostial obstruction due to fusion of the aortic cusp to the aortic wall.[32–36] This latter situation is most uncommon and in the few patients described, most have had mild commissural abnormalities of the aortic valve, but supra-aortic obstruction has been absent. A dissection of the aorta has occurred following aortography in a patient with elastin arteriopathy.[37] Cerebral arterial stenoses causing strokes have been seen in the patient with Williams syndrome.[38–40] A pulmonary sling has been observed in the patient with Williams syndrome.[41] There is some suggestion that males are more severely affected than females in terms of cardiovascular involvement.[41A] In an occasional nonsyndromic patient supravalvular aortic stenosis and supravalvular pulmonary stenosis may be complicated by coronary artery stenosis and multiple systemic vascular stenoses.[41B]

Outcome analysis

This is a diagnosis that is uncommonly made in the fetus, and thus there is little information about fetal outcome.[41C] We have recently reviewed our experience with this syndrome of supravalvular aortic stenosis and pulmonary arterial stensoses and found that over a mean period of 75 months of follow-up a definite tendency for the peripheral pulmonary artery stenosis to improve spontaneously was seen.[10,42–48] Supravalvular aortic stenosis on the other hand remained static in most cases and worsened in others with no tendency toward spontaneous improvement being seen.[10,42–48] Similar observations have been published showing rapid progression of supravalvular aortic stenosis and spontaneous improvement in the peripheral pulmonary arteries.[8,15] Vascular lesions may progress in patients with the Williams–Beuren syndrome, sometimes malignantly so.[15] Ino and his colleagues have documented the progression of coarctation of the aorta in one patient, and renal artery stenosis in another.[44] Boxer and his colleagues have reported the role of magnetic resonance imaging in the diagnosis and assessment of the vascular involvement of this syndrome.[49] Because of the reality of coronary ostial stenosis as well as stenoses within other major conducting arteries, there remains a role for cardiac catheterization with angiography.[50]

The outcome of patients with supravalvular aortic stenosis reflects the multi-system arterial involvement of this disorder. As stated earlier, there is some evidence to suggest spontaneous improvement in the severity of pulmonary arterial stenoses, and the tendency to worsening of the supra-aortic obstruction. Failure of growth of the sinotubular junction might be responsible for the progression of the aortic lesion. Indeed, progression of renal arterial stenosis or carotid artery obstruction may subject the patient to renovascular hypertension or adverse neurological events. Sudden death is also well described in this syndrome, likely related to the coronary ostial pathology common to this syndrome, or to severe bilateral outflow tract obstruction, or both.[17–19,25–30] There is some suggestion that progression of the aortic lesion at the level of the sinotubular junction may be associated with involvement of the coronary ostia. Bird and colleagues reported on ten cases of sudden death in Williams syndrome.[30] In most of these cases, but not all, there was clinical and/or necropsy evidence of important supravalvar aortic stenosis, usually with coronary artery or ostial involvement. Their first patient was interesting in that despite absence of supravalvular aortic stenosis, subtotal fibrous obliteration of both coronary ostia was found at autopsy.[30] Similarly, their case 4 showed no significant pulmonary artery stenosis or supravalvular aortic stenosis. Yet the coronary arteries had focal areas of stenosis resulting from intimal fibrosis.[30] These well-defined instances of sudden death in some patients with elastin arteriopathy, but without supravalvular aortic stenosis are very concerning. The inference is that there is the potential for sudden cardiac death, likely ischemic, in any patient with elastin arteriopathy. Kitchiner and his colleagues have published data on survival of patients with mild, moderate and severe disease, with worsening outcome related to severity of the obstruction (Fig. 14B-6).[48]

Subsequent to the first surgical repair of supravalvular aortic stenosis carried out by McGoon and his colleagues in 1956,[51] there have been numerous reports of surgical outcomes and modification of surgical technique.[18,31,52–58] Most have evolved from a single sinus to multiple sinus reconstructions with improved outcome. Stamm and his colleagues from the Boston Children's Hospital reviewed the outcome of 75 patients with supravalvar aortic stenosis operated there between 1957 and 1998.[59] The median age at operation was 7.4 years. Surgical procedures included patch enlargement of the noncoronary sinus only in 34, inverted bifurcated patch plasty in 35 and three-sinus reconstruction of the aortic root in 6. There were 7 early deaths. Among those surviving the operation, 100% were alive at 5 years, 96% at 10 years, and 77% were alive at 20 years (Fig. 14B-7). Diffuse stenosis of the ascending aorta was a risk factor for death and reoperation (Fig. 14B-8). Residual gradients were lower after multiple-sinus reconstruction as was the prevalence of moderate aortic regurgitation. Fourteen operations were carried out during the follow-up period. Kaplan–Meier estimates of freedom from reoperation were 98% at 5 years, 86% at 10 years, and 66% at 20 years (Fig. 14B-9). From this and other papers, one can conclude that survival is poorer and freedom from reoperation is worse in the more diffuse form of supravalvular aortic stenosis, and that surgical results improved in the evolution from single to multiple sinus reconstruction.

In a subsequent paper from the same group, Stamm and colleagues reported the outcome of 33 patients with elastin arteriopathy who underwent surgery for bilateral outflow tract obstruction between 1960 and 1999.[60] Fifteen of these patients

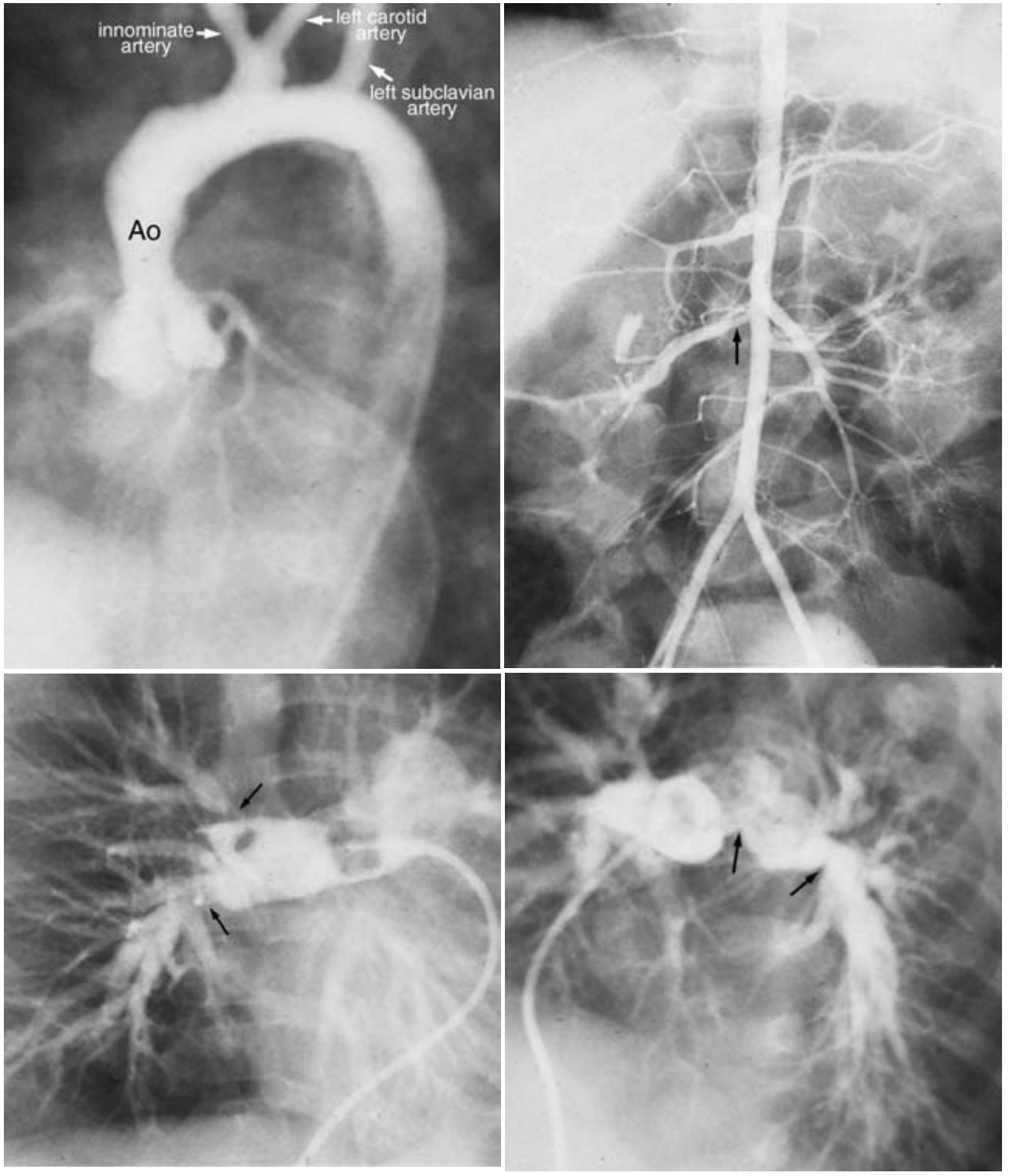


Fig. 14B-2 Williams syndrome involving ascending aorta, origin of the right innominate artery, renal artery and pulmonary artery. **A**. Aortogram shows supravalvar stenosis of the ascending aorta (Ao). The innominate and left carotid arteries have a common origin from the aortic arch. The innominate artery origin shows mild stenosis. **B**. Abdominal aortogram shows small abdominal aorta and stenosis of the right renal artery origin (arrow). **C** and **D**. Right and left pulmonary arteries show multiple peripheral pulmonary arterial stenosis (arrows).

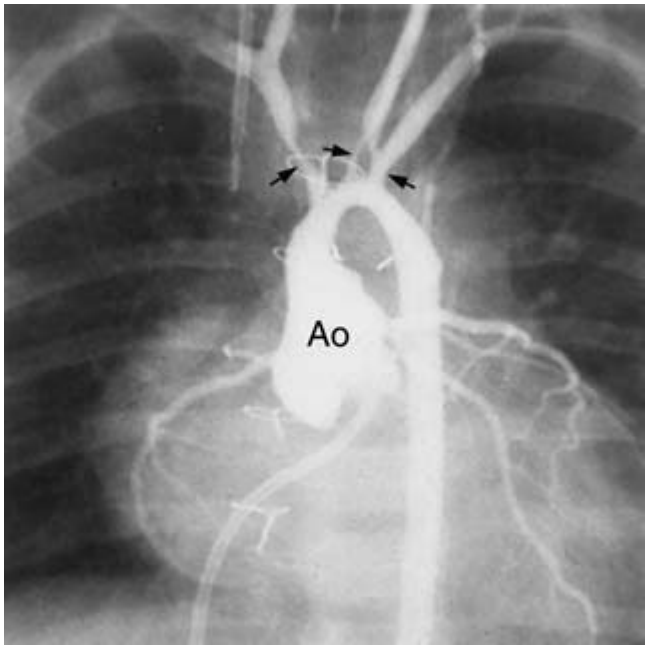


Fig. 14B-3 Williams syndrome involving the aortic arch and its head and neck branches (arrows). The supravalvular aortic stenosis has been repaired. Ao, aorta.

with only moderate right-sided obstruction underwent operation for supravalvular aortic stenosis only, while 18 patients underwent surgical relief of pulmonary arterial stenosis or right ventricular outflow tract obstruction in addition to operations for supravalvar aortic stenosis. Eight patients had undergone preoperative balloon dilatations of stenotic pulmonary arteries. There were 6 early deaths and 1 late death in this series. Survival at 10 and 20 years was 76% (70% confidence interval (CI), 68–84%) and freedom from re-intervention was 59% (70% CI, 46–71%) at 10 years and 49% (70% CI, 35–62%) at 20 years. Multivariate analysis showed that patients with a right ventricular/descending aortic pressure ratio of 1.0 or more were at higher risk for re-intervention, but not for death.[60] The Pediatric Cardiac Care Consortium operated on 102 patients with supravalvar aortic stenosis. Fourteen of these patients were infants from 2 to 12 months of age, and 3 of these died following operation. Eighty-five were children from 1 to 21 years of age, and 2 children, both < 2 years of age died.[61] Brown and his colleagues have reported on the outcomes of 101 consecutive

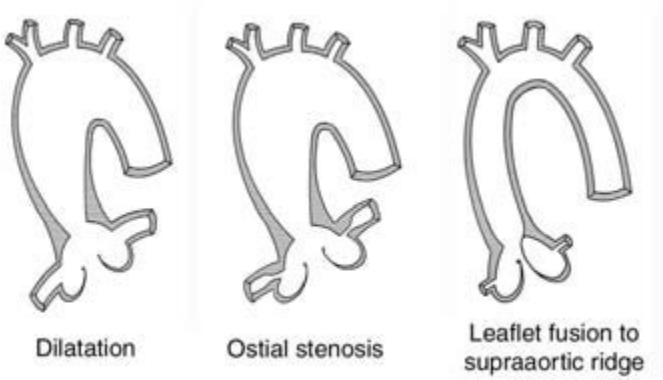
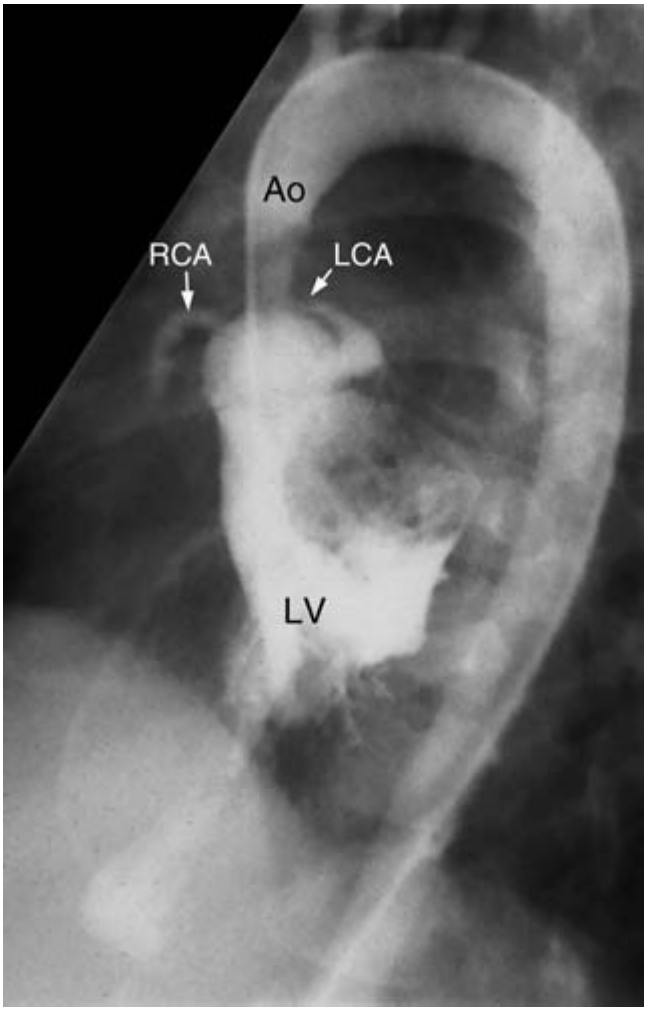


Fig. 14B-4 Coronary arterial involvement in Williams syndrome.



Fig, 14B-5 Coronary arterial involvement in Williams syndrome. Left ventriculogram shows severe supravalvular stenosis of the ascending aorta (Ao). The left coronary artery (LCA) origin shows mild stenosis. The left ventricle (LV) is hypertrophied and hypercontractile. RCA, right coronary artery.

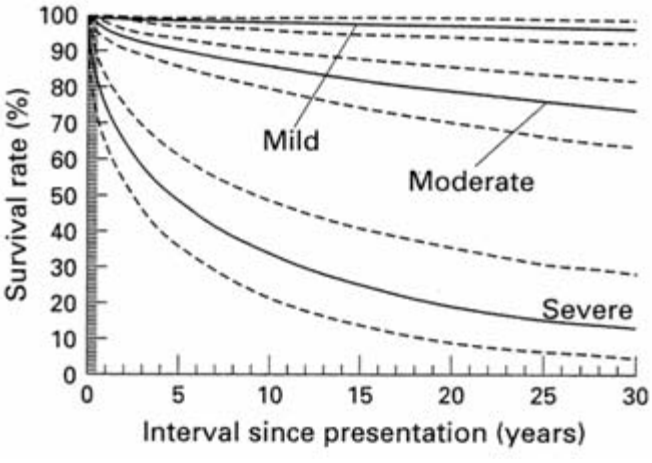


Fig. 14B-6 Kaplan–Meier showing predicted survival of patients with supravalvular aortic stenosis depending on severity at presentation. (Reprinted from Kitchiner *et al.*,[48] Copyright (1996), with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

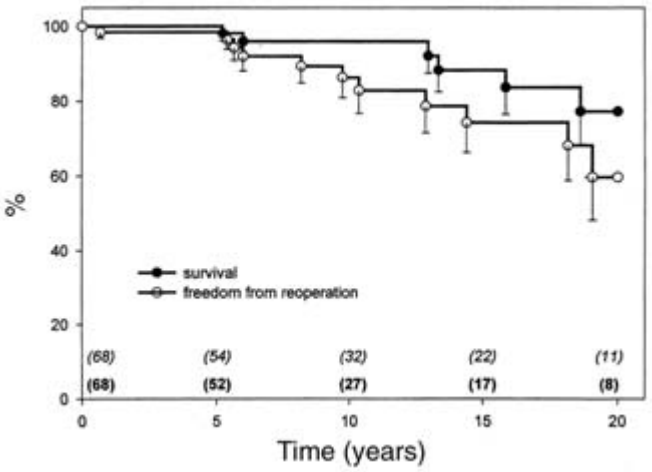


Fig. 14B-7 Kaplan–Meier 20-year estimates of survival and freedom from reoperation, excluding operative deaths. Error bars indicate lower half of 70% CL. Numbers of patients at risk are in italics (survival) and bold (freedom from reoperation). (Reprinted from Stamm *et al.*,[59] Copyright (1994) Mosby Inc., with permission from Elsevier Inc.)

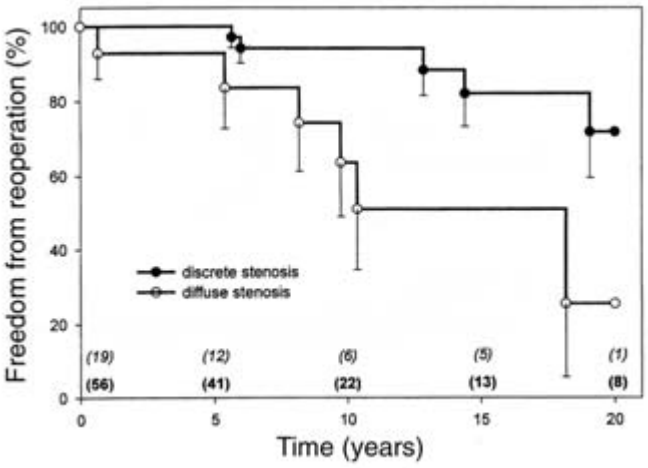


Fig. 14B-9 Kaplan–Meier 20-year estimates of freedom from reoperation according to type of stenosis ($P = 0.002$ log-rank test. Error bars indicate lower half of 70% CL. Numbers of patients at risk are in italics (diffuse stenosis) and bold (discrete stenosis). (Reprinted from Stamm *et al.*,[59] Copyright (1994) Mosby Inc., with permission from Elsevier Inc.)

patients with supravalvular aortic stenosis operated between 1962 and 2000, 14 of whom (14%) had Williams syndrome.[55] Sixty-one were males (60%) and the patients ranged in age at operation from 3 months to 17 years (median 6.1 years). A variety of operations including 5 with an apical aortic conduit operated early in the experience were performed depending on the severity of the supravalvular aortic stenosis, with 1 early death, 2 late deaths, and 14 patients underwent one or two additional operations at a medium of 9.4 years. Overall survival including operative mortality was 98% at 10 years, 97% at 20 and 30 years. Nine of the 14 patients with Williams syndrome underwent pulmonary artery patch augmentation as well.[55] Thistlethwaite and her colleagues have reported the various surgical approaches to the management of congenital obstruction of the left main coronary artery in these patients.[61A] Three approaches were taken depending on the pathology of the obstruction.[61A] These included patch aortoplasty in those with circumferential ostial thickening and obstruction; excision of the fused leaflet in patients with this pathology; and bypass grafting and aortoplasty in patients with diffuse narrowing of the left main coronary artery.

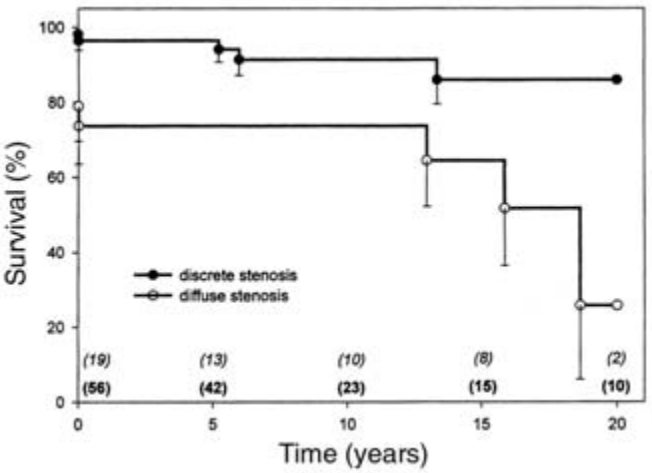


Fig. 14B-8 Kaplan–Meier 20-year estimates of survival according to type of stenosis ($P = 0.002$ log-rank test). Error bars indicate lower half of 70% CL. Numbers of patients at risk are in italics (diffuse stenosis) and bold (discrete stenosis). (Reprinted from Stamm *et al.*,[59] Copyright (1994) Mosby Inc., with permission from Elsevier Inc.)

Again, the review of the San Francisco experience serves to underscore the abnormal nature of the aortic root in patients with supravalvular aortic stenosis, and the need in some of these patients for a more radical approach to the rehabilitation of the left ventricular outflow tract.[18] Although balloon dilatation and surgical intervention for diffuse pulmonary arterial stenoses may help to remodel and restore the pulmonary arteries, the arteriopathy is usually so diffuse that functional and physiological abnormalities will persist after intervention[62] (see Chapter 13B). Finally, there has been limited experience with balloon angioplasty for the membranous form of supravalvular aortic stenosis.[63] We would caution against this approach because visual inspection of the coronary ostia is important to the surgical management of this disorder. Furthermore, if an intimal flap is raised, this could dissect into the adjacent coronary ostia, resulting in an acute coronary event.[17,19] For those patients with diffuse involvement of the neck arteries, unifocalization procedures have been used.[64]

On occasion systemic hypertension may be particularly severe. This could reflect renal artery stenosis, the middle aortic syndrome and the diffuse vasculopathy that renders the systemic arterial bed non-compliant.[20,21,39,65–70]

All references can be found at the end of the book. See pp. 671–3 for Chapter 14B.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

14C

Robert M. Freedom and Shi-Joon Yoo

Fixed, Short-segment Subaortic Stenosis

This chapter will deal with the so-called fixed or short-segment form of subaortic stenosis as is found in hearts with normal segmental and sequential anatomy. This is a peculiar and fascinating disorder, certainly congenital, but only rarely detected in the fetus or newborn.[1] Indeed, some have questioned whether the fixed form of subaortic stenosis is a congenital abnormality, or an acquired one.[2] Furthermore, as pointed out by Kitchiner in a recent editorial, "authors use the same terminology to denote different conditions and a variety of names of the identical lesions. Some terms are descriptive, others histological or anatomical."[3] One will not be surprised, then, that the optimal medical management, timing for surgery, and even the methodology of intervention remains controversial. Left ventricular outflow tract obstruction in atrioventricular septal defect is discussed in Chapter 5; with coarctation of the aorta in Chapter 22 and interrupted aortic arch in Chapter 23; isolated atrioventricular discordance in Chapter 26B, in anatomically corrected malposition in Chapter 27, and in patients with cardiac neoplasms in Chapter 40.

Morphology of the fixed forms of subaortic stenosis

The fixed forms of subaortic stenosis have been characterized as discrete, fibrous or membranous, fibromuscular, and tunnel forms, but clearly there is a continuum between these forms, and one form may progress or evolve from a less diffuse to a more diffuse and extensive form (Fig. 14C-1).[1] We are reminded by Somerville who has had a long interest in this disorder that the discrete form of so-called fibrous subaortic stenosis is rarely simple and discrete, and it is neither membranous nor diaphragmatic.[4–6] The fixed, short form of subaortic stenosis is a complex condition whose basic nature has both congenital and acquired features.[1,3–21] The prevalence of the fixed forms of subaortic stenosis in isolation or in association with other forms of congenital heart disease has been estimated to range from 5% to 10%, or higher. Rarely, as in the report of Abdallah and colleagues and others the occurrence of a discrete subaortic membrane will be familial.[22–24] Petsas and coworkers suggest that the mode of inheritance in the particular family they reported could be autosomal dominant.[24] It is unusual for the fixed forms of subaortic stenosis to be detected in the fetus or in the newborn, taking some months or years to develop.[25,26] Of the many considerable series of patients with the fixed forms of subaortic stenosis in isolation, relatively few infants are included. The fixed forms of subaortic stenosis may occur in isolation but they have been found with a wide range of associated cardiac malformations, including ventricular septal defect with or without divided right ventricle, aortic valve stenosis, etc. Perhaps the most frequent association is with either a ventricular septal defect or a bicuspid aortic valve.[27] There is a male predilection.[4,7,8]

The normal spectrum of aortic–mitral fibrous continuity was defined years ago by Rosenquist and his colleagues and then they went on to demonstrate the spectrum of aortic–mitral separation in discrete subaortic stenosis, providing anatomic evidence of increased separation in patients with the fixed expressions of subaortic stenosis (Fig. 14C-2).[28,29] Gewillig and his colleagues in 1992 using Doppler echocardiographic studies suggested that discrete subvalvular aortic stenosis might be caused by a chronic flow disturbance in a small left (and? elongated) ventricular outflow tract.[30] They also suggest that even after surgery the substrate for reoccurrence persists: i.e. an abnormal left ventricular outflow tract. Kleinert and Geva found that the left ventricular outflow tract malformation is characterized by a wider mitral–aortic separation, an exaggerated aortic override and a steeper aortoseptal angle.[15] These features are present in patients with ventricular septal defect or coarctation of the aorta, or both, who develop subaortic stenosis. Furthermore, the histopathologic and ultrastructural features of the so-called fibrous ring in these patients is consistent with the observation that turbulent fluid shear stress induces vascular endothelial cell turnover *in vitro*.[15,30–32] Borow and Glagov in an editorial to the Gewillig paper summarize the data supporting the view that subaortic stenosis is both acquired and congenital.[33] Cape and his colleagues have proposed a four-stage etiology for subaortic stenosis that: combines (1) morphologic abnormalities; (2) elevation of septal shear stress; (3) genetic predisposition and (4) cellular proliferation in response to shear stress.[34] They showed that variations in the aortoseptal angle produced marked elevations in septal shear stress (from 103 dynes/cm^2 for 150º angle to 150 dynes/cm^2 for 120º angle for baseline conditions). This effect was not dependent on the convergence angle in the outflow tract (150–132 dynes/cm^2 over full range of angles including extreme case of 0º). A ventricular septal defect enhanced this effect (150 to 220 dynes/cm^2 at steep angle of 120º and 3 m/s shunt velocity), consistent with the high incidence of ventricular septal defects in patients with subaortic stenosis. The position of the ventricular septal defect was also important, with a reduction of the distance between the ventricular septal defect and the aortic annulus causing further increases in septal shear stress (220 and 266 dynes/cm^2 for dis-

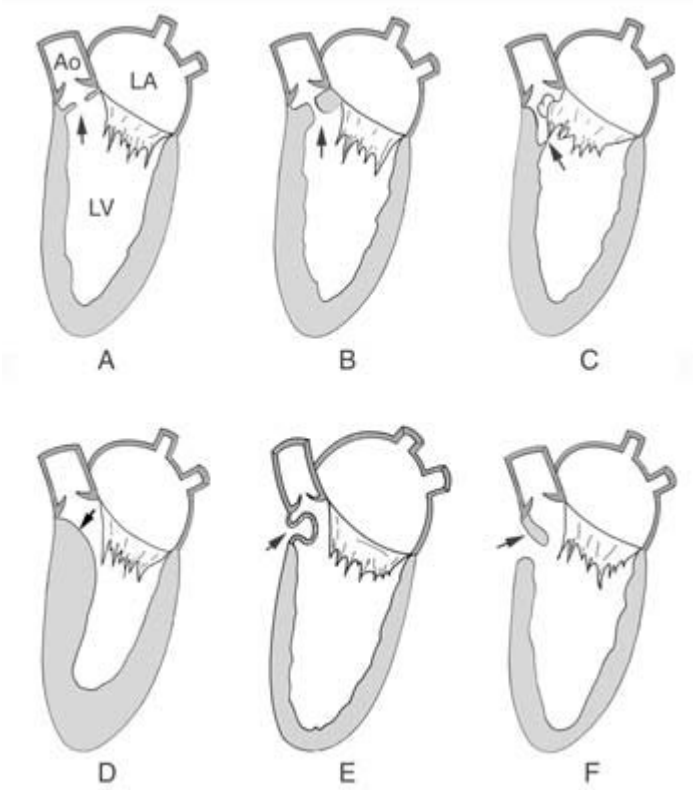


Fig. 14C-1 Types of subaortic stenosis. **A**. Discrete fibrous membrane. **B**. Fibromuscular tunnel. **C**. Mitral valve tissue or its tension apparatus attached to the septum. **D**. Hypertrophic obstructive cardiomyopathy. **E**. Tissue derived from the membranous septum or tricuspid valve herniating into the left ventricular outflow tract through a ventricular septal defect. **F**. Posterior displacement of the infundibular septum. Ao, aorta; LA, left atrium; LV, left ventricle.

tances of 6 and 2 mm from the annulus, respectively). This group showed that small changes in aortoseptal angle produce important changes in septal shear stress (Fig. 14C-2B). The levels of stress increase were consistent with cellular flow studies showing stimulation of growth factors and cellular proliferation. They concluded that a steepened aortoseptal angle was likely a risk factor for the development of subaortic stenosis.[34] In addition to an abnormally elongated left ventricular outflow tract, some have shown that the aortic valve annulus is hypoplastic in patients with subaortic stenosis.[35,36] A prominent left-sided ventriculoinfundibular fold (the anterolateral muscle bundle of Moulaert) may contribute to the morphologic substrate of subaortic stenosis by promoting an elongated and narrowed left ventricular outflow tract; this area is vulnerable to injury as resection may take the surgeon outside the heart (Fig. 14C-2A).[37]

Some years ago, we reported the rapid and fatal development of subaortic stenosis in a young infant who underwent in the neonatal period successful repair of a thoracic coarctation of the aorta.[38] While we characterized the left ventricular outflow tract in this patient as normal, the degree of aortic–mitral separation seems in retrospect excessive, supporting the findings of Rosenquist and Gewillig and their respective colleagues.[28–30,39] However Krishnan and colleagues also reported a case of rapid evolution of discrete subaortic stenosis in infancy, commenting that their patient had no other discernible anomalies of the left ventricle.[40] Salim and colleagues report the acquisition of discrete subaortic stenosis in two patients after successful treatment of congenital aortic valve stenosis.[41] In these patients the left ventricular outflow tract was also initially characterized as normal. Referring to their case 1, figs 2 and 4, the left ventricular outflow tract appears elongated, and abnormal mitral–aortic separation is evident, a harbinger for subaortic stenosis.[41] Ruchelli and Anderson have commented on the significance of aortic–mitral separation in patients with ventriculoarterial concordance[42] and Cilliers and Gewilleg have provided a timely review of the rheology of discrete subaortic stenosis.[43]

Other mechanisms promoting subaortic stenosis

We have summarized elsewhere those mechanisms responsible for promoting subaortic stenosis.[44–66] Anderson and his colleagues examined 25 hearts from the cardiovascular pathology registry of the Children's Hospital of Pittsburgh with coarctation of the aorta and ventricular septal defect, asking whether such defects actually compromised aortic blood flow.[67] Twenty of the 25 hearts demonstrated a particular form of perimembranous ventricular septal defect with aortic override. These defects were partially closed or restricted by tricuspid valve tissue, and the left ventricular outflow tract was further compromised by various anatomic lesions including abnormal left ventricular muscle bundles, the anterolateral muscle bundle of

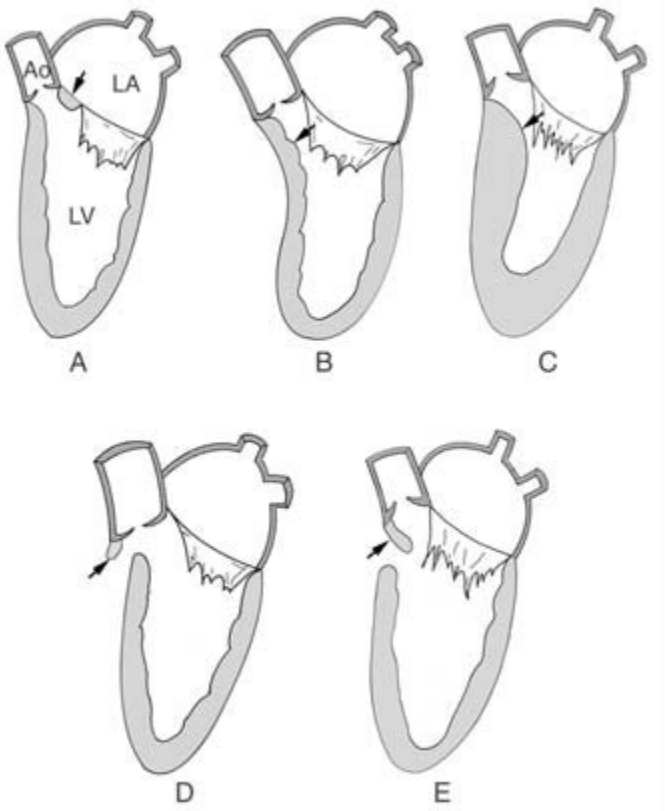


Fig. 14C-2 Anatomical substrates for development of subaortic stenosis. **A**. Aortomitral separation with an anterolateral muscle of Moulaert. **B**. Steep aortoseptal angle. **C**. Hypertrophied septum. **D**. Anterior malalignment type of ventricular septal defect with aortic override. **E**. Posterior malalignement type of ventricular septal defect. Ao, aorta; LA, left atrium; LV, left ventricle.

Moulaert, anomalous subaortic trabeculae, a discrete septal bulge, and mitral valve abnormalities. Tissue derived from the membranous septum or tricuspid valve may herniate or protrude into the left ventricular outflow tract causing subaortic stenosis (Fig. 14C-1E). This has been observed more frequently in those patients subjected to previous pulmonary artery banding.

Zielinsky and his colleagues have studied the role of ventricular septal malalignment in the genesis of a subaortic ridge (Figs 14C-2D, 2E).[68] Thirty-two of 295 patients with a ventricular septal defect in their series had a subaortic shelf at the time of presentation and all of these 32 patients had a malalignment-type of ventricular septal defect. Anterior malalignment was present in 28 and posterior malalignment in the remaining 4 patients. Indeed, in many patients the subaortic stenosis seemingly develops on the substrate of a ventricular septal defect. Vogel when in Toronto reviewed 41 patients with ventricular septal defect and subaortic stenosis (excluding interruption of the aortic arch).[69,70] The mechanisms responsible for subaortic stenosis in these patients included a fixed fibromuscular form in about 75%; left ventricular muscular abnormalities in about 10%; tricuspid valve tissue in about 5%; and miscellaneous causes in the remainder. Amongst those patients undergoing serial catheterizations, the mean gradient increased from 9 to 36 mmHg. Some of this change was reflected in progressive reduction in size of the ventricular septal defect, but none the less, even when associated with ventricular septal defect, the morphological basis and hemodynamic severity of left ventricular outflow tract obstruction seemed progressive. Silverman and colleagues have further characterized the nature of the fibrous obstruction within the left ventricular outflow tract associated with left ventricular septal defects.[64] They found a ridge of tissue within the left ventricular outflow tract in 37/188 specimens with ventricular septal defect. Kitchiner and his colleagues have studied the morphology of the left ventricular outflow tract in patients with subaortic stenosis and a ventricular septal defect.[14] Slightly more than half of the patients in this study had obstructive and deviated muscular structures in the left ventricular outflow tract (Figs 14C-2D, 2E).

Ventricular septal defect, subaortic stenosis, and divided right ventricle

A well-known relationship in patients with a perimembranous ventricular septal defect, a divided right ventricle, and a fixed subaortic abnormality has been defined[1,44,66–70] (see also Chapter 21). We have addressed in an echocardiographic study this association in 36 patients with perimembranous ventricular septal defect and right ventricular anomalous muscle bundles. Eighty-eight per cent of these patients had echocardiographic evidence of an associated subaortic abnormality, and in a number of these patients, Doppler evidence of progression of the left ventricular outflow tract gradient was provided. We have observed progression of a subaortic deformity initially producing no obstruction, and some years later causing severe left ventricular outflow tract obstruction after surgical closure of a ventricular septal defect ± resection of anomalous muscle bundles of the right ventricle.

In the era of cross-sectional echocardiography, the incidence of primary subaortic stenosis in Malta was 0.25 per 1000 live-births.[71]

Outcome

Much has been learned about the genetics, pathology and outcome of subaortic stenosis in the dog.[72] Pyle and his colleagues found that in the Newfoundland hound predisposed to subaortic stenosis, the left ventricular outflow tract appears normal in the first few weeks of life. However it begins to demonstrate some verrucous changes from 3 to 6 weeks, continuing to develop more moderate changes from 6 to 12 weeks, and when older than 6 months of age, subaortic stenosis was moderate to severe in two-thirds of the dogs.[72] While the timetable is certainly different in the human, the tendency for progression in severity is likely similar, at least in childhood. Kienle and coworkers have studied the natural clinical history of canine congenital subaortic stenosis.[73] Breeds found to be at increased relative risk for the development of subaortic stenosis include the Newfoundland hound, boxer and golden retriever. Dogs with mild gradients (16–35 mmHg) and those that developed infective endocarditis or left heart failure were diagnosed at older ages than those with moderate (36–80 mmHg) and severe (> 80 mmHg) gradients. Of 96 untreated dogs, 32 (33.3%) had signs of illness varying from fatigue to syncope; 11 dogs (11.3%) developed infective endocarditis or left heart failure. Exercise intolerance or fatigue was reported in 22 dogs, syncope in 11 dogs, and respiratory signs (cough, dyspnea, tachypnea) in 9 dogs. In addition, 21 dogs (21.9%) died suddenly. Sudden death occurred mainly in the first 3 years of life, primarily but not exclusively, in dogs with severe obstructions (gradient, > 80 mmHg; odds ratio, 16.0; $P < 0.001$). Infective endocarditis (6.3%) and left heart failure (7.3%) tended to occur later in life and in dogs with mild to moderate obstructions.[70] Perhaps the one issue not mentioned in these studies of the canine model of subaortic stenosis is the development and progression of aortic regurgitation.[72,73]

The fixed, short forms of subaortic stenosis tend to be progressive in childhood.[1,6–8,10,18,20] Occasionally the progression can be extremely rapid.[36,37] What has been difficult to predict, however, is which patient will demonstrate progression because the clinical course can be quite variable. Bezold and his colleagues have developed an echocardiographic model for predicting the progression of subaortic stenosis in children.[74] The features that were used in the logistic regression equation were the initial Doppler-derived gradient in mmHg; absence (0) or presence (1) of mitral leaflet involvement; and indexed distance between aortic valve and subaortic membrane in mm/body surface area. Using a complex regression equation, they felt that they could distinguish between patients who would progress and those who would not progress. They also felt that this methodology could distinguish between those in a so-called intermediate group and those who would not progress. This methodology assumes, and we believe incorrectly, that one can accurately measure the distance between the membrane and the aortic valve. This would seem to be unreliable because the membranous tissue can be so diffuse as we and others have observed in post-mortem specimens, or at surgery.[4–6,44,75]

As one surveys the outcomes of patients with the discrete forms of subaortic stenosis, what are the major issues that need to be scrutinized?

- What is the optimum management?
- What is the optimum timing for surgery to prevent recurrence and progressive damage to the aortic valve? Does early

intervention reduce the rate of recurrence that ranges from 7% to 27%?

- What is the optimum methodology for intervention? Surgery or balloon?
- If surgery is considered the optimum mode of therapy, myotomy, myomectomy, both, etc.
- Does intervention reduce the incidence of endocarditis?

The surgical procedures for the fixed, short forms of subaortic stenosis have continued to evolve and results continue to improve. The earlier favored myotomy has been replaced with a more aggressive approach of myotomy/myomectomy.[76–90] There is relatively little mortality in any of the recently published series, and most would agree that this aggressive approach is justified. Some patients may require a Konno-type operation to widen the outflow tract,[76–90] especially for those with tunnel-form subaortic stenosis.[83–90] There is always the risk of damaging the aortic valve and the anterior (aortic) leaflet of the mitral valve in the resection of the fibromuscular tissue as this tissue frequently extends on to the base of the aortic cusps and on to the anterior mitral leaflet, resulting in a circumferential ring.[75] The diagnosis of the short form of subaortic stenosis has evolved from the catheter laboratory to non-invasive imaging with cross-sectional echocardiography and Doppler interrogation, and the extent of the disorder is easily discerned from this imaging modality.[91–99] In addition one can ascertain the presence and severity of aortic regurgitation (or less frequently aortic valve stenosis), the dimension of the aortic annulus, mitral valve function, and the performance of the left ventricle. Intra-operative transesophageal echocardiography will confirm the adequacy of the myotomy/myomectomy and will provide information about the aortic and mitral valves as well.[96–99] Surgery is routinely conducted in childhood on the basis of echocardiographic examination.[44,99]

There remains considerable discussion as to the timing of the operation. The majority of children with the fixed forms of subaortic stenosis are asymptomatic, and if there are symptoms, they are generally vague. For those with resting ST–T wave changes or exercise-induced ischemia, and assuming that one can exclude a coronary artery anomaly as the etiology of the ischemic changes, surgery is indicated. But there is no consensus as to what Doppler-derived pressure gradient should be the arbiter of surgical intervention in the otherwise asymptomatic patient. Some take the approach that since this disorder is a progressive one, early intervention even with a low pressure gradient is justified. It is apparent that intervention should ideally be carried out before there is important damage to the aortic valve and before there is damage to the contractile elements of the left ventricle. Some have taken the position that early operation at lower levels of obstruction reduces the rate of recurrence and reduces secondary damage to the aortic valve. Indeed, the most commonly recognized complications of fixed subaortic stenosis include infective endocarditis and aortic regurgitation. Considerable scrutiny has been focused on those factors promoting aortic regurgitation in the fixed forms of these conditions.[1,3–8,44,62,75,100–106] The incidence of aortic regurgitation, estimated to be as high as 50% in affected patients, is not static. There are also data that once aortic regurgitation develops it progresses with time.[107] At least two mechanisms have been implicated as causal to the aortic regurgitation. Aortic valvular incompetence results from repetitive trauma caused by the jet of blood through the subvalvular stenosis impinging on the aortic valve at the beginning of systole. Feigl and associates from the laboratory of Dr Jesse Edwards suggest extensions of fibroelastic tissue from the site of the discrete subaortic stenosis towards the base or superior to the base of one or more cusps with deformity of a cusp will result in valvular aortic insufficiency.[75] Motro and his colleagues have tried to correlate the distance from the subaortic membrane to base of the right aortic valve cusp and the development of aortic regurgitation in mild discrete subaortic stenosis.[108] Their data indicate that patients with mild subaortic stenosis in whom the membrane is remote from the aortic valve (≥ 11 mm) are more likely to develop aortic regurgitation than those with a shorter distance between membrane and valve. Remembering the cautions of Somerville about the complex nature of the fixed forms of subaortic stenosis[4] and the morphological observations of Feigl,[75] the observations of Motro should be accepted or interpreted with some caution.[108]

Some years ago we defined an institutional policy of early resection and myomectomy for treatment of fixed subaortic stenosis in order to prevent recurrence of subaortic stenosis and distortion of the aortic valve and aortic regurgitation.[107] Between May 1975 and November 1989, 37 patients underwent operation for a fixed form of subaortic stenosis at the Toronto Hospital for Sick Children. The mean preoperative systolic pressure gradient of these patients was 40 ± 20 mmHg, and in 13 of the 37 patients the gradient was < 30 mmHg. Our data showed that early surgical intervention did not prevent the risk of recurrence, but did reduce the risk of aortic regurgitation.[107] Brauner and her colleagues from the University of California in Los Angeles have presented data indicating that early surgical resection of fixed subaortic stenosis before the development of a pressure gradient > 40 mmHg may prevent recurrence, reoperation and secondary progressive aortic valve damage with aortic regurgitation.[109] Others as well have provided data indicating that operative age and gradient are predictors of late aortic valve incompetence. Rizzoli and colleagues have addressed the relationship of operative age and left ventricular outflow tract gradient and the development of late aortic incompetence.[110] Their data indicated that the probability of aortic incompetence at follow-up was significantly and simultaneously related to: (1) older age at operation; (2) higher preoperative gradient; (3) cardiomegaly; (4) surgical myomectomy. Serraf and his colleagues have reported a 17-year surgical experience with the treatment of 160 patients with subaortic stenosis.[111] There were 5 early (3.1%) and 4 late (4.4%) deaths. They found that recurrence and reoperation were influenced by coarctation and immediate postoperative left ventricular outflow tract gradient.[105] Before the operation the mean left ventricle–aorta gradient was 80 ± 35 mmHg, and at a median follow-up of 13.3 years, the mean left ventricle–aorta gradient was 20 ± 13 mmHg. They also found that relief of the subaortic stenosis improved the degree of the aortic regurgitation in 86% of those with preoperative aortic incompetence. Actuarial survival and freedom from reoperation rates at 15 years were 94% ± 1.3% and 85% ± 6%, respectively. De Vries and his colleagues did not find any benefit from early surgical intervention.[103] Even among those who advocate early intervention, there is not agreement on the level of the systolic pressure gradient as the arbiter of the timing of intervention.

Rohlicek and his colleagues published in 1999 their experience with 92 children from five tertiary care pediatric cardiol-

ogy units in eastern Canada diagnosed with fixed subaortic stenosis between 1985 and 1998.[112] The mean age at diagnosis was 5.3 years and the mean of the echocardiographically derived left ventricular outflow tract gradient was 30 mmHg, with aortic regurgitation at presentation in 22%. They found that many patients with mild subaortic stenosis with gradients < 21 mmHg did not progress and similarly in these patients little change in the amount of the aortic regurgitation was noted during the course of the 4-year follow-up. However, those children with more important gradients of 40 mmHg did show more progression. Endocarditis was not seen in their patients, acknowledging a relatively short period of follow-up, but this is the generally accepted experience that surgical relief of severe subaortic stenosis reduces this particular risk. To this point, we have discussed intervention in terms of surgical intervention. There is some experience with balloon therapy of the fixed form of subaortic stenosis,[113–115] but we would agree with Ritter and others that this form of therapy is rarely if ever justified.[115,116]

The tunnel or diffuse forms of fixed subaortic stenosis have been difficult to treat. The usual approach of myotomy/myomectomy is palliative at best, and many patients so-treated were left with substantial residual gradients and the sequelae thereof.[87] Some patients with tunnel and other complex forms of left ventricular outflow tract obstruction have been treated with an apical left ventricular–aortic conduit, but for a variety of reasons this procedure has been largely abandoned.[117–125] The fate of the conduit, the impact of the surgery on the left ventricle, and the introduction of new surgical procedures contributed to the "near extinction" of this technique. Some still use this approach for very selected patients, and there is no doubt that this approach afforded reasonable palliation.[125] Over the past two decades the approach of aortoventriculoplasty with or without aortic valve replacement has offered these patients a substantially improved outlook.[80–89] Van Son and his colleagues about a decade ago reviewed the experience of the Mayo Clinic with 169 patients with discrete (n = 108) and tunnel forms of subaortic stenosis (n = 61) seen between 1957 and 1992.[90] For all patients, early mortality was 4.7% (2.7% since 1961), and during follow-up extending to 29 years, there have been 16 late deaths. Twenty-six patients underwent a second or third operation for recurrent left ventricular outflow obstruction, including 11 of the 154 who had their primary operation at the Mayo Clinic (7.1%). Among the 21 patients who had a discrete lesion at initial repair and required reoperation, 19 (92%) were noted to have tunnel obstruction at reoperation. At late follow-up, the left ventricular outflow tract gradient was higher in patients with tunnel vs. discrete obstruction (33 ± 5 vs. 24 ± 17 mmHg, P < 0.04), and 10-year survival was poorer (79% vs. 91%, P < 0.02). Ten-year survival was worse in patients with tunnel lesions and associated cardiac anomalies vs. those with isolated tunnel subaortic stenosis (64% vs. 92%, P < 0.005). Some degree of aortic valve insufficiency was seen at late follow-up in 26% of patients, but in most cases this was mild. For patients with discrete subaortic stenosis, the risk of late aortic insufficiency was 38.6% after isolated membranectomy, 27.8% after membranectomy and myotomy, and only 7.3% after membranectomy and myectomy (P < 0.004). Progression of aortic insufficiency requiring aortic valve replacement occurred in only 6 patients. Their results support the use of myectomy in conjunction with membranectomy for discrete subaortic stenosis. For restenosis and tunnel obstruction, they suggest that more complete relief of subaortic stenosis is afforded by extended resection or a modified or classical Konno–Rastan (Figs 14C-3, 14C-4). Others suggest that these procedures may improve late survival and reduce the incidence of recurrent subaortic stenosis and late aortic valve insufficiency.[86] Roughneen and colleagues reported their experience with the modified Konno–Rastan procedure in 16 children.[85] One late death occurred secondary to pneumonia 2 years after operation (6.2% mortality rate). The mean follow-up period was 62 ± 39 months. All patients had complete relief of preoperative symptoms and were in New York Heart Association (NYHA) class I. One patient underwent a successful redo modified Konno–Rastan procedure 7 years after the first operation for residual left ventricular outflow tract obstruction immediately below the aortic valve. One patient was waiting reoperation for aortic incompetence unrelated to conal enlargement 1.5 years after the first procedure. These experiences indicate the benefit of conal enlargement in selected patients.

Jahangiri and colleagues have also reported the outcomes of their management strategies for complex and tunnel-like

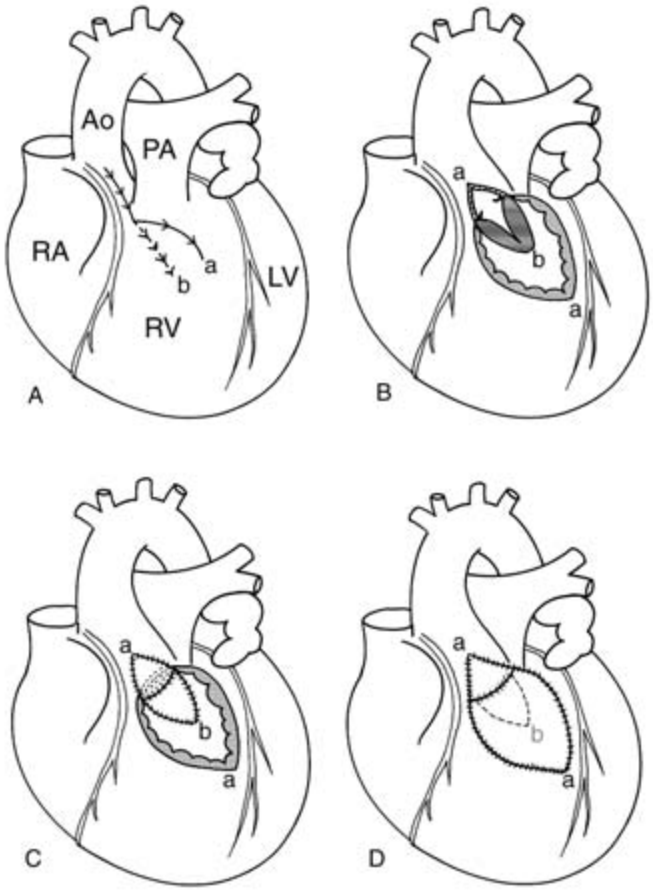


Fig. 14C-3 Classic Konno–Rastan operation. **A**. The vertical aortotomy is extended into the anterior wall of the right ventricle (solid line with arrows, marked a), and the aortic incision is also extended through the ventricular septum (interrupted line with arrows, marked b). **B**. The two incisions create a view of the interior of both right and left ventricular outflow tracts. **C**. The left ventricular outflow tract is augmented by applying a patch in the ventricular septum and aorta. A prosthetic valve (dotted circles) is placed in the enlarged annulus. **D**. The right ventricular outflow tract is closed with a pericardial patch. Ross–Konno modification uses the pulmonary valve autograft instead of placing a prosthetic valve. Ao, aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

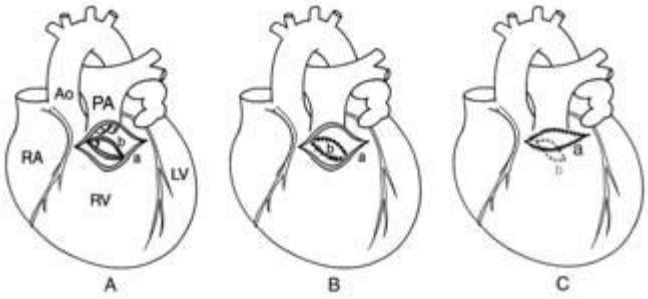


Fig. 14C-4 Modified Konno–Rastan operation. The modification preserves the native aortic valve. **A**. The ventricular septum is incised (b) through the right ventricular outflow tract incision (a). **B**. The subaortic left ventricular outflow tract is augmented by resecting the left side of the septum and placing a patch in the incised septum. **C**. The right ventricular outflow tract is augumented with a patch. Ao, aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

subaortic stenosis.[89] Forty-six patients who underwent surgery for complex and tunnel-like subaortic stenosis between January 1990 and November 1998 were reviewed. In 45 of the 46 patients subaortic stenosis developed following repair of a primary congenital heart defect and only 1 patient presented with *de novo* tunnel-like subaortic stenosis (Fig. 14C-5). Fifteen of the 45 patients had undergone repair of double-outlet right ventricle and the remaining 30 had undergone repair of a variety of defects. The median age at the time of surgery was 5 years. The modified Konno procedure was performed in 15 patients, Konno procedure in three, Ross–Konno procedure in 2 and resection of the conal septum in 12 patients. Five patients with double-outlet right ventricle underwent replacement of the intraventricular baffle and 2 patients underwent an aortic valve-preserving procedure in conjunction with mitral valve replacement. There were no deaths. None of the patients had an exacerbation of aortic regurgitation and none developed complete heart block. The median follow-up was 3 years (range 1 month to 8.5 years). Two patients developed recurrent subaortic stenosis defined as a gradient of 40 mmHg or greater diagnosed by transthoracic echocardiography. Freedom from recurrent subaortic stenosis at 1, 3 and 5 years was 100, 94 and 86%, respectively. This group favors the modified Konno procedure and conal resection to the Konno or the Ross procedure, since insertion of a prosthetic valve or homograft is avoided and aortic valve function is preserved. Excellent relief of tunnel-like subaortic stenosis was achieved in this experience without damage to the conduction tissue.[85] The operations of the Konno-type involve incisions in the infundibular septum and the septal perforator coronary arteries are subject to injury.[126]

In childhood, patients with the fixed forms of subaortic stenosis develop aortic regurgitation (either operated or non-operated), demonstrate a frequent relationship with a closing or closed ventricular septal defect, show a tendency towards progression and are uncommonly identified as neonates.[127] There is little doubt that the formation of subvalvular outflow tract obstruction occurs at the interface between rheology and morphology as shown so nicely in the work of Ozkutlu and colleagues.[128]

Yet when one compares the fixed forms of subaortic stenosis in children with adults, there are some interesting differences. In contrast to children, adults with the fixed forms of subaortic stenosis seem to show less progression.[129] Furthermore from the study of Oliver and colleagues, while aortic regurgitation is common, it is often mild and does not appear to progress as it does in children. And finally, aortic regurgitation is more conspicuous in patients after surgical intervention than in unoperated patients.[129] In follow-up one must be reminded that a discrete membrane can recur many years after surgery,[130] and in conditions where subaortic stenosis is rare, before and after surgery.[131–133] Further "food for thought" is the issue raised by Delius and colleagues who asked: "Should a bicuspid aortic valve be replaced in the presence of subvalvar or supravalvar aortic stenosis?" Their data suggest the answer to the question is a tentative yes.[134] Finally, some patients will have the combination of anomalies embraced by the designation of Shone's syndrome.[135–137] The outcomes of these patients reflect the severity of the left ventricular inflow and outflow tract anomalies (see also Chapters 12 and 22).

In summary:

- The short, fixed forms of subaortic obstruction have both congenital and acquired features.
- This disorder is far more complex than a discrete membrane.
- It can accompany and complicate the management of other cardiac anomalies, particularly ventricular septal defect ± a divided right ventricle; coarctation of the aorta; congenital abnormalities of the mitral valve.
- The often elongated and geometrically disadvantageous left ventricular outflow tract predisposes both to progression in

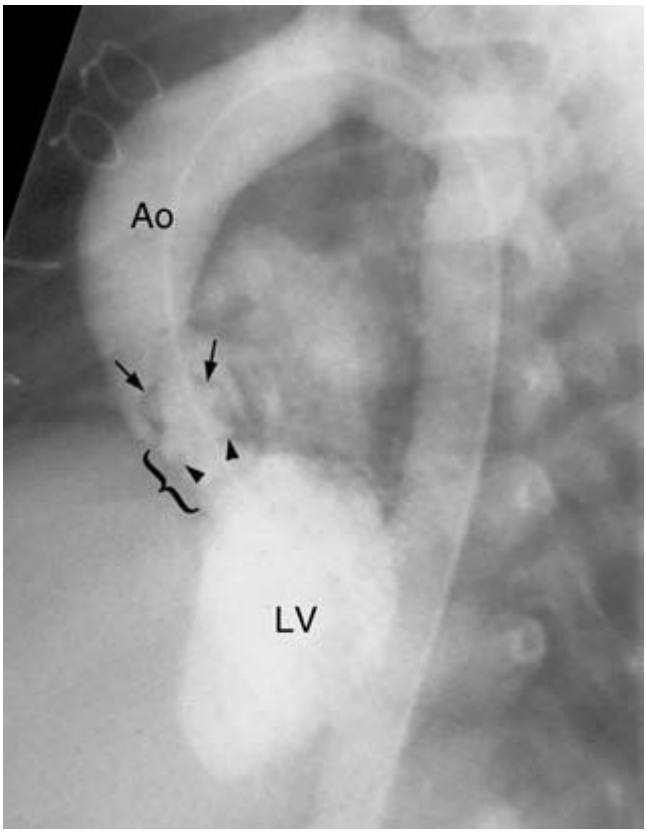


Fig. 14C-5 Residual and recurrent stenosis after repair of subaortic stenosis. There is tunnel obstruction (parenthesis) in association with a discrete ridge (arrowheads) and aortic valvular stenosis (arrows). Ao, aorta; LV, left ventricle.

severity and recurrence. Aortic–mitral separation and an abnormal aorto-ventricular angle contribute to the "disordered" left ventricular outflow tract.

- Progression is more commonly a pediatric phenomenon and there seems to be a tendency to less progression in adulthood.
- Longstanding subaortic obstruction tends to damage the aortic valve, resulting in aortic regurgitation.
- Most consider the presence of aortic incompetence (assuming a once normal aortic valve) and systolic gradients ≥ 40–50 mmHg as indications for intervention.
- There is no agreement in the absence of symptoms or aortic incompetence as to the lower limit of systolic pressure gradient to intervene.
- Because of the frequency of recurrence after resection, most have adopted surgical myotomy and myomectomy to treat this disorder.
- Patients with diffuse or tunnel-type subaortic stenosis may require a Konno–Rastan procedure.
- There is limited experience with balloon dilatation of the short, fixed forms of subaortic stenosis. The basic pathology of the obstruction and the desirability of complete relief of the obstruction are contraindications to this approach.
- Patients with unoperated or surgically-treated subaortic stenosis require lifelong surveillance with regard to recurrence, aortic incompetence, and infective endocarditis.

All references can be found at the end of the book. See pp. 673–6 for Chapter 14C.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

15A

Robert M. Freedom and Shi-Joon Yoo

Aortocameral Communications

Aortocameral communications are uncommon congenital communications between the root of the aorta and any of the cardiac chambers (Fig. 15A-1). Perhaps the best known and most common of these infrequent conditions is the aorto-left ventricular tunnel.[1–54A] This is followed in frequency by the aorto-right atrial tunnel;[47,55–59] aorto-right ventricular tunnel;[60–67] and finally by the aorto-left atrial tunnel.[68–70] Sinus of Valsalva aneurysms will be considered in a separate chapter (see Chapter 15B).

Congenital aortocameral communications

- Aorto-left ventricular tunnel
- aorto-right atrial tunnel
- aorto-right ventricular tunnel
- aorto-left atrial tunnel.

All of these conditions produce the physiology of congenital aortic insufficiency, but when the tunnel connects to a right heart chamber, an important left-to-right shunt is also produced. Finally there are rare instances of true congenital aortic insufficiency. These have been described in patients with a congenitally absent aortic valve and in those with quadricuspid aortic valves, etc.[71–83]

Some years ago we reported several patients with congenital communications between the root of the aorta and the right atrium, and we acknowledged that in some patients it may be difficult to differentiate this condition from a congenital coronary artery–cameral fistula.[56] The final arbiter in these cases would be selective coronary arteriography. In addition these congenital tunnels may be confused with ruptured sinus of Valsalva aneurysms.[84–125]

No single institution has any significant experience with these congenital aorto-cameral communications. We have not identified any patient with a congenital aorto-left atrial tunnel; only 3 or 4 patients with an aorto-right atrial tunnel; 1 or 2 patients with an aorto-right ventricular tunnel and less than half a dozen patients with an aorto-left ventricular tunnel (in the past 40 years).

Aorto-left ventricular tunnel

This is the most frequent of these uncommon conditions.[1–54] While the aorto-left ventricular tunnel usually occurs in isolation, we have seen it in the patient with an associated ventricular septal defect and others have reported it in patients with aortic stenosis or aortic atresia with variable left heart hypoplasia, and in a patient with pulmonary valvar or subpulmonary obstruction. When occurring in isolation, the usually severe aortic insufficiency results in neonatal congestive heart failure, and thus it is uncommon for patients to present later in life, although this has been reported in the older child and rarely the adolescent. Indeed, the aorto-left ventricular tunnel has been recognized in the fetus.[52] There are numerous reports of successful surgical intervention in these patients, but data about

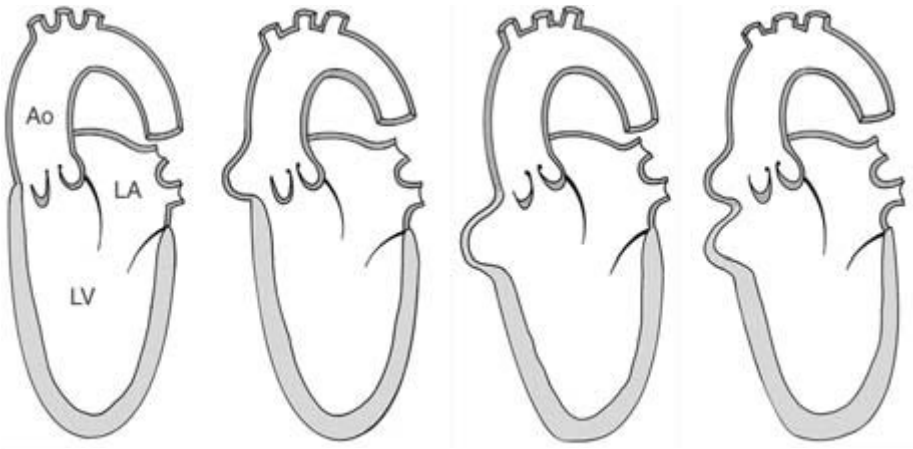


Fig. 15A-1 Various types of aorto-left ventricular tunnel. Ao, aorta; LA, left atrium; LV, left ventricle. (From Hovaguimian *et al*.[17] with permission.)

follow-up is quite sparse.[4,17,20,33,34,36,123] Both from the literature and from our own experience, survivors of early surgical repair are at risk to develop progressive aortic insufficiency. The reasons for this include both some intrinsic abnormality of the aortic valve and a distorted aortic root, preventing normal aortic leaflet coaptation. Thus in the long-term surveillance of these patients, attention must be paid to the form and function of the aortic valve and the impact of chronic aortic regurgitation on left ventricular function. There has been one report of transcatheter closure of the tunnel using an Amplatzer device.[54A]

We reported a number of years ago our experience with congenital aorto-right atrial tunnels.[56] This condition promotes both aortic insufficiency and a left-to-right shunt. The several patients we reported presented with a loud to-and-fro systolic and diastolic murmur along the mid-left sternal edge and the diagnosis was confirmed in these patients with aortic root and selective coronary angiography. Surgical intervention effectively closed the tunnel, and of the three patients we reported, only one in follow-up developed trivial aortic regurgitation. The anatomy of these peculiar malformations lends itself to catheter-based device closure as has been achieved in the patient with sinus of Valsalva aneurysms.[89] Our experience with a congenital aorto-right ventricular tunnel is limited to one infant who underwent surgical closure of the defect and we have not seen any patient with a congenital aorto-left atrial tunnel,[47] although we have seen an acquired aorto-left atrial communication secondary to infective endocarditis and an aortic root abscess with vegetations on the aortic and mitral valves. The coronary artery, particularly the right, but occasionally the left, may be intimately related to the tunnel, and thus follow-up considerations include the possibility of progressive aortic incompetence and myocardial ischemia secondary to distortion of the coronary artery or its orifice.[65–67] Finally, McKay and her colleagues have recently published an excellent review of the anatomic, investigative and surgical outcomes of patients with aorto-ventricular tunnels.[126]

All references can be found at the end of the book. See pp. 676–9 for Chapter 15A.

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15B

Robert M. Freedom and Shi-Joon Yoo

Sinus of Valsalva Aneurysm

Among the earliest descriptions of the ruptured sinus of Valsalva aneurysms were the reports of Hope in 1835[1] and Thurnam in 1840.[2] Abbott was likely the first to suggest that these malformations were congenital in origin, not acquired secondary to syphilis or endocarditis.[3] Congenital aneurysms of the sinus of Valsalva are rare, and when occurring in isolation are infrequently seen in the neonate or young child.[4–102] The etiology of the aneurysm of the sinus of Valsalva is thought to result from absence of normal elastic and muscular tissue which leads in turn to thinning of the wall of the aortic sinus.[4–7] Operations to treat sinus of Valsalva aneurysms account for < 0.5% of all cardiopulmonary bypass operations. In the experience of the Pediatric Cardiac Care Consortium, 18 patients with congenital aneurysms of the sinus of Valsalva underwent 19 operations from 1984 to 1994 among the 27 678 operated patients (< 0.07%).[8] This malformation occurs more frequently in males by as much as 3:1.[9] While aneurysms of the sinus of Valsalva are uncommon in the occidental, they seem more common in patients of Asian and Indian origins.[9,13,14–17,28,29,53,62,63,76,80,88] These deficiencies of the aortic root permit intracardiac and extracardiac communications, and must be distinguished from congenital aortocameral tunnels, etc. Aneurysms of the sinus of Valsalva may be of congenital or acquired basis, or acquired changes may be superimposed on a congenital abnormality (i.e. infective endocarditis or calcification of a previously unruptured aneurysm of the sinus of Valsalva). Subsequent to the elegant and comprehensive review of the anatomy and classification of congenital aneurysm of the sinus of Valsalva by Sakakibara and Konno,[17] an extensive literature details the anatomy, site of rupture and communication, surgical strategies to repair this anomaly, and follow-up information.[4–16,18–101] Dilatation of the sinuses of Valsalva occurs as a normal phenomenon of aging, and this occurs more frequently in males, and in those that are hypertensive.[95,96] Profound dilatation of the sinuses of Valsalva may occur in patients with Marfan's syndrome, in those with annuloaortic ectasia, ankylosing spondylitis, Ehlers–Danlos syndrome, amongst other disorders of connective tissue.[98] The weakened walls of the sinus of Valsalva progressively dilate under systemic pressure, usually producing a windsock deformity that may eventually rupture into a low pressure cardiac chamber, pulmonary artery, interventricular septum or rarely into the pericardium (Fig. 15B-1).[5,7–9,13–18,28,31,39,45–47,49,53,59,75,87] It is evident from the normal spatial relationships between each of the aortic sinuses of Valsalva and the cardiac chambers why each of the sinuses has its own pathological venue for protrusion and rupture.[5,7–9,13–18,28,31,39,45–47,49,53,59,75,87] Pathological rupture of a sinus of Valsalva most frequently involves the right sinus, followed by the noncoronary or nonfacing sinus, and the least likely to congenital deformity and rupture is the left sinus of Valsalva.[5,7–9,13–18,28,31,39,45–47,49,53,59,75,88,89] Thus one is not surprised that rupture of a sinus of Valsalva into right-sided heart chambers is far more common than pathological communication with left heart chambers. The right ventricle or right atrium are the common sites for rupture of the right and nonfacing sinus of Valsalva. When rupture of the right sinus of Valsalva occurs into the right ventricle, it commonly protrudes through the infundibular septum, and the noncoronary sinus may rupture into a similar location, or into the right atrium. The left sinus may rupture into the left ventricle or left atrium. The right or nonfacing sinus may erode into the interventricular septum, and the left sinus may rupture into the left ventricular outflow tract. Rupture of the nonfacing sinus into the left atrium has also been observed. Myocardial ischemia may reflect the aortic insufficiency from the ruptured sinus of Valsalva, frank or dynamic coronary artery compression, or dissection into the coronary artery.[14,20,21,25,61,64,70] Some of these aneurysms may reach "gigantic" dimensions.[91,102,103] Beck and his colleagues using an experimental model showed that the sinuses of Valsalva play an important role in minimizing stress in the leaflets of the aortic valve.[97] Rupture of a sinus of Valsalva aneurysm has been reported in a newborn, and has been observed in the patient with Noonan's syndrome.[36,38]

Deformation and rupture of the sinus of Valsalva is associated with ventricular septal defect in about 50% of patients. The right sinus of Valsalva may prolapse through a doubly committed juxta-arterial ventricular septal defect, and both the right and nonfacing sinus may prolapse through a perimembranous defect. Soto and Pacifico point out that when an aneurysm of the sinus of Valsalva is associated with a ventricular septal defect, the aortic insufficiency is almost always owing to prolapse and subsequent deformity of the aortic valve.[45] The extensive experience of the Hospital for Sick Children in the diagnosis and therapy of ventricular septal defect and aortic regurgitation indicates that while there is overlap in the pathology of sinus of Valsalva aneurysm with rupture and prolapse, aortic regurgitation reflects primarily prolapse with distortion of the aortic valve.[50,51] Of the 70 patients ranging in age from 1.96 years to 35.9 years (mean 10.1 years) who underwent repair of ventricular septal defect and aortic insufficiency reported by Trusler and colleagues, rupture of the sinus of Valsalva was not observed.[50,51] Yet others have found a ruptured sinus of Valsalva aneurysm in the setting of a ventricular septal defect and aortic regurgitation.[9,15–17,28,29,37,45,49,59,79,80]

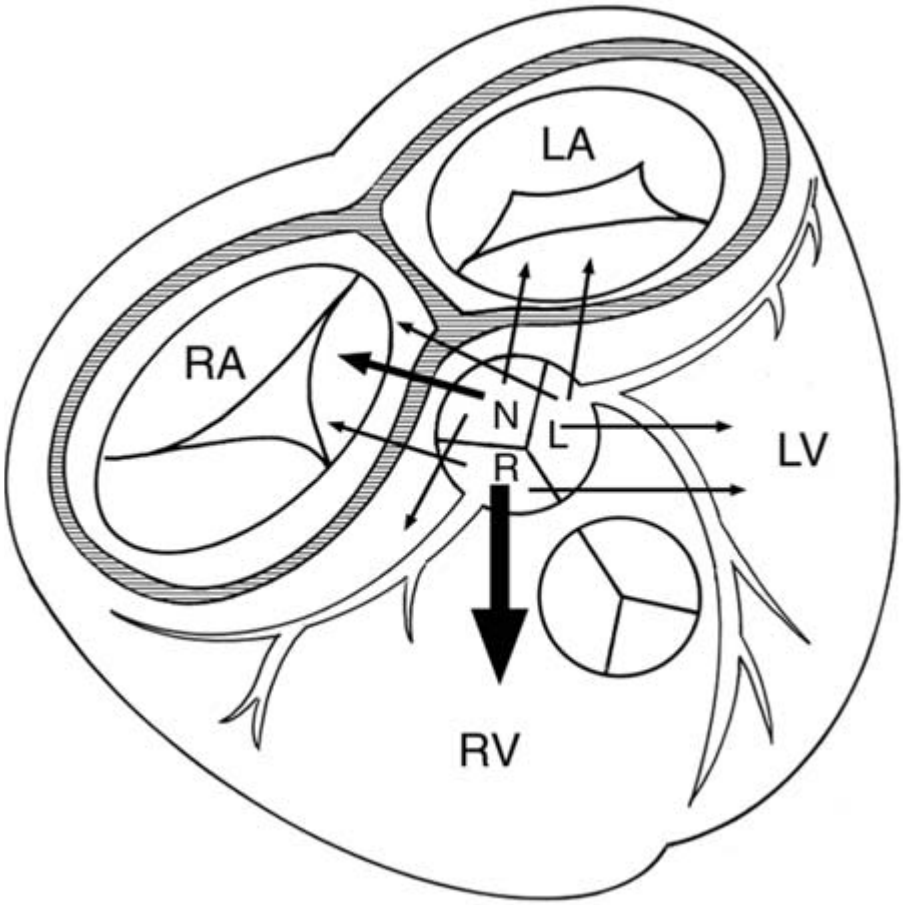

Fig. 15B-1 Normal anatomy of the base of the ventricles showing the potential sites for the sinus of Valsalva aneurysm to protrude or rupture. The right coronary sinus (R) is most frequently involved and ruptures most commonly into the right ventricle (RV). The noncoronary sinus (N) is the second most frequently involved and ruptures most commonly into the right atrium (RA). The left coronary sinus (L) is the least commonly involved. The arrows indicate the potential sites of aortic sinus rupture. Rarely, the rupture is into the pericardial cavity. LA, left atrium; LV, left ventricle.

There is now considerable experience with ruptured and non-ruptured sinus of Valsalva aneurysms. As with the ruptured sinus of Valsalva aneurysm, the unruptured aneurysms originate primarily from the right sinus of Valsalva, followed by the noncoronary and lastly the left sinus of Valsalva.[24,30,35,43,48,52,56,59,60,62,71,73,74,77,78,80A,81,95] Thus unruptured sinus of Valsalva aneurysms protruding into the right ventricular outflow tract can simulate pulmonary outflow tract obstruction,[8,9,11,52,74] and those protruding into the left ventricular outflow tract, subaortic stenosis.[9,40,73] Right ventricular outflow tract obstruction may result from either a ruptured or unruptured sinus of Valsalva aneurysm.[8,9,11,35,52,55,57,60,71,74,77] Anomalous origin of the right coronary artery from the pulmonary artery has been identified in a patient with rupture of the nonfacing sinus of Valsalva into the right ventricle.[44] van Son and colleagues have recently reported the entire Mayo Clinic surgical experience with repair of sinus of Valsalva aneurysm.[53] Of their 31 patients, aneurysms originated in the right sinus in 24 and nonfacing sinus in 7, entering the right ventricle in 21 and right atrium in 10.[53] There was no hospital mortality and overall survival at 20 years was 95%.

One of the more common associations with a ruptured sinus of Valsalva aneurysm is aortic regurgitation whether or not a ventricular septal defect is present.[8,9,11–18,26,27,29,47,49,53,59,62–64,80,88,100] The presence of a ruptured sinus of Valsalva deprives the aortic sinus and annulus of its support. In addition, the runoff through the rupture produces a Bernoulli effect which tends to pull the related aortic cusps away from their line of closure or apposition, producing incompetence. Shu-Hsun and colleagues reported the presence of aortic regurgitation in 35% of their cases.[16] Furthermore, aortic incompetence seems to be more common when there is an associated ventricular septal defect (43.3%) as compared to 25.9% when the interventricular septum is intact. Choudhary and his colleagues found aortic incompetence in 43.3% of their patients and in 17 (37.8%) it was severe.[59] Other associated malformations include left superior vena cava[67] pulmonary stenosis, infundibular pulmonary stenosis, tetralogy of Fallot; coarctation of the aorta, atrial septal defect, bicuspid aortic valve, valvular and supravalvular aortic stenosis, and fixed from of subaortic stenosis.[11,59] In the experience of Choudhary and colleagues, the ventricular septal defect was doubly committed and subarterial in nearly 61% of those with an associated ventricular septal defect. The Mayo Clinic found that of the 31 patients with ruptured sinus of Valsalva aneurysms, a ventricular septal defect was identified in 16, and in 15 of these, the ventricular septal defect was of the doubly committed subarterial type.[53]

The results of surgery for ruptured sinus of Valsalva are generally very good with a number of series reporting no mortality. Choudhary and his colleagues summarizing the literature suggests the average surgical mortality is *c.* 3.0–3.5%.[59] In many of the larger clinical series, repair of the ruptured sinus of Valsalva requires repair or replacement of the aortic valve.[9,11–17,26,29,53,59,63,66,75,79,82] In the large experience of Choudhary and colleagues who reported surgical results in 104 patients with sinus of Valsalva aneurysms, 7 cases were found in

children from 0 to 10 years of age.[59] Aortic incompetence was found in 45 patients (43.3%). The defect was closed through the aortic root alone in 24 patients (23.1%) and through both the aortic root and the chamber of rupture in the remaining 80 patients. Six patients required repair of the aortic valve and 21 aortic valve replacement.[59] It is of interest that in this series, 12 aneurysms were unruptured. There were 2 operative deaths and no late deaths. These authors state that in the majority of patients, long-term follow-up was uneventful.[59] Naka and his colleagues found that a substantial number of patients developed progressive aortic regurgitation from 7 to 13 years after repair of the ruptured sinus of Valsalva aneurysm.[63] These authors found that of the 27 patients in their series, 23 had coexistent cardiac lesions, including 21 with ventricular septal defect. Of the total of 16 patients with associated aortic regurgitation, 13 had a ventricular septal defect.[63] A recurrent fistula is most uncommon in the current era, although this complication has been recorded in the past.[11,53] Both pre–and postoperative rhythm disturbances have been well documented in patients with ruptured sinus of Valsalva aneurysms. Those aneurysms eroding into the interventricular septum are well known to precipitate complete heart block.[11,12,39,58,59,63,69,75,82,85,86,92]

The methodologies to diagnose the ruptured and unruptured sinus of Valsalva aneurysm continue to evolve, and evolve to less invasive imaging modalities. Angiography[45,46,54,76] has been in large part replaced by transthoracic and transesophageal echocardiography, magnetic resonance imaging and helical computed tomography.[14,23,24,35,49,59,65,73,84,99,100] There has been only limited experience with transcatheter closure of a ruptured sinus of Valsalva aneurysm.[22]

Thus in follow-up, patients must be assessed for progression of the severity of aortic regurgitation and the potential requirement for late aortic valve replacement and its impact on the left ventricle, arrhythmias, prosthetic valve endocarditis, and progressive congestive heart failure.

All references can be found at the end of the book. See pp. 679–82 for Chapter 15B.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom and Shi-Joon Yoo

Tetralogy of Fallot

As in virtually all forms of human endeavor, congenital heart disease is an elegant witness to evolution. Indeed, in many ways, tetralogy of Fallot serves as one of the more important paradigms for one's appreciation of the evolution in our understanding of the morphology, natural history, and changing surgical algorithms germane to a congenital heart defect. The evolution in our understanding of the morphology is paralleled by those achievements in therapy: from palliation as the only form of therapy nearly 60 years ago, to repair of this malformation, tetralogy of Fallot, at almost any age today. The classic morphologic tenants of the tetralogy of Fallot: right ventricular outflow tract obstruction, right ventricular hypertrophy, ventricular septal defect and aortic override, have undergone considerable scrutiny since the seminal description of this disorder.[1–10] There is a wonderful history about tetralogy of Fallot,[11–31] and there remains discussion as to who originally described the entity now bearing the surname of Etienne-Louis Arthur Fallot.[11] Perhaps the earliest description of what was to become the tetralogy of Fallot was described by Stenson (Nils Steno) in 1671 (1638–86),[16] followed by Sandifort in 1777,[19,20] and Hunter in 1784.[18] The late Helen B. Taussig (1898–1986) in her Neuhauser lecture published in 1979 stated that to the best of her knowledge, Eduardus Sandifort was the first to provide a clinical and pathological description of what later became known as a tetralogy of Fallot.[22] Interestingly, according to Taussig, Sandifort suggested the ductus Botalli may have lessened the cyanosis of this $12\frac{1}{2}$-year-old boy. But it was Etienne-Louis Arthur Fallot (1850–1911), a French physician and pathologist in a lecture at the Academy of Medicine in Marseille, who suggested apparently for the first time that one could make the clinical diagnosis of this disorder.[11] Again, according to Taussig, the condition became known as the tetralogy of Fallot as Fallot had commented on those four aspects of morphology lending themselves to a clinical diagnosis, designating them in fact as a "tetralogy."[22] Fallot actually considered designating hearts with this tetralogy as *la maladie bleu*. But according to Van Praagh it was likely Maude Abbott who in 1924 coined the more convenient designation of tetralogy of Fallot.[13,25] In this respect, Maude Elizabeth Seymour Abbott (1869–1940) also contributed very importantly to the early history of this disorder amongst many other forms of congenital heart disease that she had studied (see also Chapter 1). These observations culminated in the publication of her now famous *Atlas of Congenital Heart Disease* in 1936 under the auspices of the American Heart Association.[23–27,29–31] The paths of the two great pioneering women of congenital heart disease crossed in 1931 when Taussig first met Maude Abbott at the New York Academy of Medicine where Abbott was exhibiting some congenital malformations of the heart. Taussig states that after that initial meeting she visited Abbott frequently, visiting her in Montreal in the spring of 1938, where Abbott demonstrated a specimen of Fallot's tetralogy with a right aortic arch, as Taussig had asked to see a specimen of tetralogy with a right arch.[22] Abbott told Taussig that 20% of patients with tetralogy had a right aortic arch and as well showed her a radiograph of a patient with a right aortic arch, also fluoroscoping a patient with a right arch.[22] It is so sad that Maude Abbott died just a few years before Blalock and Taussig irrevocably altered the natural history of patients with tetralogy of Fallot by the "creation" of a ductus Botalli.[31A,31B,32] She was alive, however, when Gross [1905–1988] of Boston first successfully ligated a large arterial duct of L.S., a girl of 7 years on August 26, 1938, this date ushering in the "modern" era of congenital heart surgery.[33] The many publications of Maude Abbott were reprinted from *J Pathol Bact* 1941; **52**: 394–400 in Waugh's biography of Abbott.[29] MacDermott also published a wonderful memoir about Maude Abbott shortly after her death.[31A] In addition, Bauer and Astbury have published a comprehensive bibliography of the 1000 cases analyzed in Maude Abbott's Atlas with an index.[31B]

Prevalence

The prevalence of tetralogy of Fallot has been studied widely, both its prenatal and postnatal incidence[34–36] (see also Chapter 2). Some of the differences between the studies reflect the methods of ascertainment. The diagnostic frequency for tetralogy of Fallot of 0.214 per 1000 live births was provided from the New England Regional Infant Cardiac Program,[37] and data from the more recently completed Baltimore–Washington Infant Study provided a prevalence of 0.262 per 1000 live births.[38] The Alberta Heritage Study indicated a live-born prevalence of 0.184 per 1000 live births for tetralogy of Fallot.[39] The prospective Bohemia Survival Study found a live-born prevalence of 0.21 per 1000 live births and these accounted for 3.36% of all congenital heart malformations in this survey.[40] Hoffman some years ago conducted an exhaustive survey of the postnatal incidence of many congenital heart malformations.[34,35] The median percentage of this survey for tetralogy in live-born children was 5.5%. Recently Hoffman and Kaplan reviewed 41 studies and identified the mean incidence for tetralogy of Fallot as 421 per million live births.[36] The standard deviation was 188. Data from the Toronto Hospital for Sick Children found that tetralogy of Fallot accounted for 9.7% of congenital heart malformations (1426 of 15 104 cases from 1950 to 1973).[41] Francannet and colleagues sur-

veying the epidemiology of tetralogy of Fallot found the incidence to be 0.22 per 1000 live births.[42]

Tetralogy of Fallot is not considered an inheritable disorder.[43] Yet there are a number of reports of tetralogy in siblings and in successive generations, as well as in monozygotic twins.[43–50] The inheritance pattern or etiology in a number of these reports is considered either multifactorial, autosomal recessive or dominant. Evaluation of candidate loci in a large kindred segregating autosomal dominant tetralogy of Fallot with reduced penetrance culminated in identification of a mis-sense mutation (G274D) in JAG1, the gene encoding jagged1, a Notch ligand expressed in the developing right heart.[51–55] Nine of 11 mutation carriers manifested cardiac disease, including classic tetralogy of Fallot, ventricular septal defect with aortic dextroposition and isolated peripheral pulmonic stenosis (PPS). All forms of tetralogy of Fallot were represented, including variants with pulmonic stenosis, pulmonic atresia and absent pulmonary valve.[51–54]

Recent reports have implicated mutations in the transcription factor NKX2.5 as a cause of various forms of congenital heart disease including tetralogy of Fallot.[51–54] In this regard, Goldmuntz and her colleagues have estimated the frequency of NKX2.5 mutations in tetralogy patients and they further investigated the genotype–phenotype correlation of NKX2.5 mutations.[52] To accomplish this study, they genotyped 114 TOF patients. Patients were recruited prospectively and tested for a 22q11 deletion; those with 22q11 deletion or recognized chromosomal alteration were excluded from the study. Patients were then screened for NKX2.5 alterations by conformation-sensitive gel electrophoresis and sequencing of fragments with aberrant mobility. Four heterozygous mutations were identified in 6 unrelated patients with cases of tetralogy, including 3 with pulmonary atresia and 5 with right aortic arch. None of the patients had ECG evidence of PR interval prolongation. Three of four mutations (Glu21Gln, Arg216Cys, and Ala219Val) altered highly conserved amino acids, of which two mapped in the conserved NK2 domain. The fourth mutation (Arg25Cys) was identified in three unrelated probands in the present study and has been previously reported. No homeodomain mutations were identified. They found that NKX2.5 mutations are the first gene defects identified in nonsyndromic tetralogy patients. NKX2.5 mutation was present in > / = 4% of tetralogy patients. Mutations identified in this study mapped outside of the homeodomain, were not associated with atrioventricular conduction disturbances, and were not fully penetrant, in contrast to mutations previously reported that impair homeodomain function.

Association with 22q11 microdeletion

As with some patients with common arterial trunk, interruption of the aortic arch, isolated anomalies of aortic branch laterality and branching, there is a well-known association between tetralogy of Fallot with microdeletion of the 22nd chromosome, the velocardiofacial syndrome, etc.[56–62] Goldmuntz and her colleagues found a 22q11 deletion in 15.9% of patients with tetralogy of Fallot.[60,61] The same studies found this deletion in 50% of patients with interruption of the aortic arch (see Chapter 23); 34.5% of patients with common arterial trunk (see Chapter 6); and only 1 of 20 patients with double-outlet right ventricle (see Chapter 28). McElhinney and his colleagues found that 24% of patients with an isolated anomaly of aortic arch laterality or branching had a 22q11 deletion.[59]

Recurrence risks

Golmuntz has summarized the literature addressing recurrence risks for tetralogy of Fallot.[63] Nora and Nora combining their data with those of 9 additional studies suggested a recurrence risk of 2.5% if 1 sibling was affected and 8% if 2 or more siblings were affected.[64] A similar risk of recurrence of 2.2% was calculated by Burn and colleagues,[65] and Digilio and coworkers found a recurrence risk of 3.1% in patients without identifiable genetic syndromes or chromosomal abnormalities.[66] There are also data of recurrence if 1 parent has had tetralogy of Fallot.[67,68] The recurrence risk ranges from 1.2% to 8%. Nora and Nora found a recurrence rate for tetralogy of Fallot of 4.2% if 1 parent had tetralogy of Fallot.[69] Zellers and coworkers found the rate of recurrence of congenital heart disease with 1 parent with tetralogy of Fallot to be 1.2%.[70] There is debate as to whether the recurrence risk is higher when the affected parent is the mother or father, with some studies giving a higher risk when the mother is the affected parent. Nora and Nora in 1987 found a slightly higher risk for recurrence if the mother was the parent with tetralogy of Fallot.[71] Data provided from Whittemore and her colleagues did not find a difference between affected maternal and paternal parents.[72]

Morphology

Numerous reviews of the anatomy of tetralogy of Fallot and its variations have been published.[1–10] The most frequent segmental anatomy of tetralogy of Fallot is levocardia, normal atrial situs, with concordant atrioventricular and ventriculoarterial connections. Tetralogy of Fallot in situs invs. totalis is uncommon (< 5%), and tetralogy of Fallot with isolated dextrocardia is also uncommon. Tetralogy of Fallot has been infrequently diagnosed in those patients with incomplete visceral lateralization, usually left isomerism with or without polysplenia. Tetralogy of Fallot with inverted normal great arteries is an uncommon form of tetralogy.[73,74] The connections between atria and ventricles and ventricles and great arteries are concordant in this variant, but with the infundibuloarterial inversion, the right coronary artery traverses the stenotic right ventricular outflow tract.[73]

Those morphological findings of tetralogy of Fallot include pulmonary stenosis of a specific infundibular character; a ventricular septal defect located between the anterior and posterior limbs of the trabecular septal band; overriding of the aorta; and right ventricular hypertrophy (Fig. 16-1).[1–10] Right ventricular hypertrophy is progressive, reflecting the myocardial response to both right ventricular outflow tract obstruction and to the large, nonrestrictive ventricular septal defect. More than three decades ago Van Praagh and his colleagues suggested that tetralogy of Fallot is really a "monology" of Fallot resulting from this displaced infundibular or outlet septum, and that in tetralogy the outlet septum is "too short, too narrow, and too shallow."[1] The malalignment of the infundibular septum is now considered the essence of tetralogy of Fallot (Fig. 16-1**)**. The leftward or septal end of the infundibular septum is displaced anteriorly, inserting in front of the left anterior division of the septal band rather than between its two divisions as in the normal heart. The rightward aspect of the infundibular septum is rotated anteriorly and passed anteriorly and superiorly to reach the free wall of the right ventricle so that the infundibular septum and its parietal extension lie almost in a sagittal plane

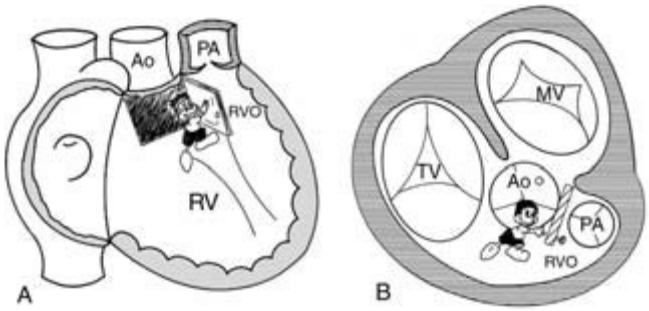


Fig. 16-1 Pathologic features of tetralogy of Fallot. The key pathology of tetralogy is the anterior, leftward and superior displacement of the infundibular septum (trap door) relative to the rest of the septum. It results in an anterior malalignment type of ventricular septal defect, narrowing of the subpulmonary outflow tract (RVO) with a small pulmonary valve annulus, and overriding aortic valve. Ao, aorta; MV, mitral valve; PA, pulmonary artery; TV, tricuspid valve.

rather than the usual frontal plane Others, while agreeing that tetralogy reflects this malalignment of the outlet septum, do not agree that invariably the outlet septum is hypoplastic.[2] Geva and his colleagues have recently published a prospective longitudinal echocardiographic study of those quantitative features characteristic of progressive infundibular obstruction in tetralogy of Fallot.[9] Their data showed that the subpulmonary infundibulum in tetralogy of Fallot, when compared with healthy infants, is characterized by a smaller volume, shorter and thicker infundibular septum, and anterosuperior deviation of the infundibular septum. The character of the pulmonary stenosis is clearly related in typical cases to this deviation of the infundibular septum, and thus this obstruction by definition is muscular. The infundibular obstruction in many patients is worsened by a hypoplastic pulmonary valvular annulus, pulmonary valve stenosis with a bicuspid valve with thickened cusps and fused commissures, anomalous muscle bundles and varying degrees of hypoplasia of the main pulmonary trunk and its branches.[10] Those patients with absence of the outlet septum are not really classical examples of tetralogy of Fallot, despite similar hemodynamics.[75–78] An overriding aorta is also consistently identified in the patient with Fallot's tetralogy of Fallot, and Kirklin and Barratt-Boyes indicate that the overriding varies from about 30% to 90%, with usually about 50% of the aortic orifice above the right ventricle.[79,79A] Kirklin and Barratt-Boyes also point out that aortic override is associated with a variable degree of clockwise rotation of the aortic root as viewed from the ventricular apex.[79] This rotation moves the base of the noncoronary cusp rightward and superiorly on to the posterosuperior margin of the ventricular septal defect and away from the base of the anterior or aortic leaflet of the mitral valve.[79] The rightward rotation of the left aortic cusp results in more of it becoming continuous with the anterior mitral leaflet, while the superiorly positioned right cusp moves to the left. The degree of overriding and clockwise rotation of the aortic root relates to the degree of underdevelopment or hypoplasia of the right ventricular outflow tract and to malalignment of the infundibular septum. Of the morphological variables influencing surgery, one must focus attention on the nature of the pulmonary circulation,[80–83] and also on epicardial distribution of the coronary artery circulation.[83–111] As we will discuss, most of the confounding features of the pulmonary circulation and coronary artery abnormalities have with time been effectively neutralized. Tremendous variability in pulmonary artery size is evident in any large cohort of patients with tetralogy of Fallot. The smallest confluent pulmonary arteries (1.0 mm in diameter) are seen in those patients with tetralogy of Fallot and pulmonary atresia (see Chapter 18). That even very small arteries reflect underfilling because of severe outflow tract obstruction is supported by results of surgical repair of tetralogy of Fallot in the first months of life. Multiple diffuse calibre abnormalities, arterial stenoses, the so-called arborization abnormalities, can be evident in the patient with tetralogy of Fallot and a perforate outflow tract, but these are much more common in patients with pulmonary atresia and multiple aortopulmonary collaterals (see Chapter 18). Small indirect aortopulmonary collaterals and enlarged bronchial arteries are easily identified in the older infant and child, reflecting increasing hypoxemia and polycythemia. It is uncommon to identify large direct aortopulmonary collateral vessels originating from the descending thoracic aorta in the patient with "uncomplicated" tetralogy of Fallot, but like the observations of Ramsay and colleagues, we also have identified a number of such patients.[83,112] Numerous collaterals develop after thoracotomy performed to construct a systemic-to-pulmonary artery anastomosis. Stenosis of the left pulmonary artery at the site of ductal insertion has been observed with increasing frequency in patients with tetralogy of Fallot, although the initial observations were again in patients with pulmonary atresia and ventricular septal defect.[83,113–118] The incidence of ductal-related pulmonary artery coarctation has been estimated to be as high as 25%.[115] Waldman and his colleagues have also documented spontaneous acquisition of discontinuous pulmonary arteries related to ductal tissue in patients with many forms of complex right heart obstruction, stating that this complication developed in as many as 29% of such patients studied by this group.[117] In other patients with classic tetralogy, the right and left pulmonary arteries may be nonconfluent with one pulmonary artery, usually the left originating from the ascending aorta (see Chapter 7), or it may have a distal ductal origin. And with ductal closure the ipsilateral pulmonary artery becomes isolated (see Chapter 8). Significant naturally occurring multiple aortopulmonary collaterals while uncommon in tetralogy of Fallot with confluent pulmonary arteries, are also well documented in the absent pulmonary valve variant (see Chapter 17).[119] Origin of the left pulmonary artery from the right pulmonary artery (so-called pulmonary sling) has been seen in the patient with tetralogy of Fallot (see Chapter 13C). The hypogenetic right lung complex with right pulmonary artery hypoplasia and abnormal connection of the right pulmonary veins, the scimitar syndrome (see Chapter 24B), has also been observed in the patient with tetralogy of Fallot.

Coronary artery anomalies assume importance in tetralogy of Fallot because of their potential for interruption or damage at the time of right ventriculotomy.[83–111] The most common important abnormality complicating repair of tetralogy of Fallot is origin of the left anterior descending coronary artery from the right coronary artery, occurring in about 5% of patients (Fig. 16-2).[83] In this situation, the anterior descending coronary artery crosses the right ventricular outflow tract a variable distance from the pulmonary valve. We have seen an accessory anterior descending originating from the right coronary artery in about 2.5% of patients with tetralogy of Fallot. Less commonly are instances of a single right or left coronary artery,

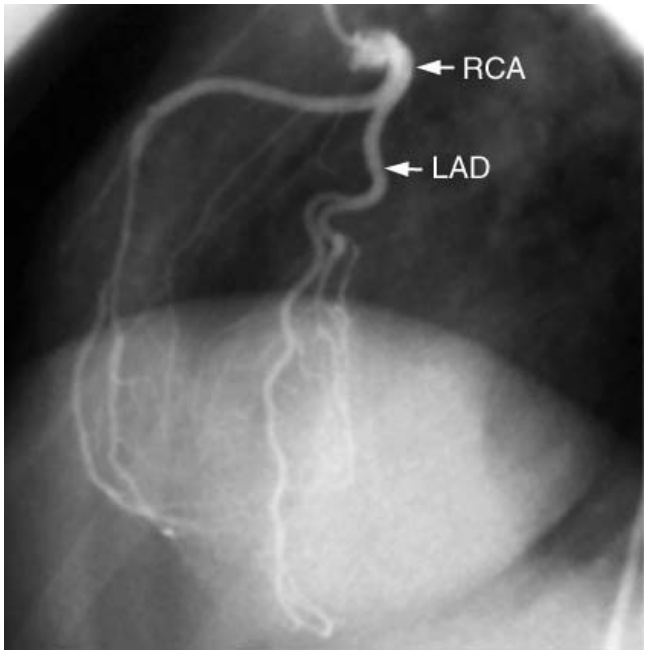


Fig. 16-2 Origin of the left anterior descending coronary artery (LAD) from the right coronary artery (RCA) in a patient with tetralogy of Fallot.

anomalous origin of the left coronary artery or the anterior descending coronary artery from the main pulmonary trunk, origin of both coronary arteries from the pulmonary trunk; or multiple coronary artery–cameral fistulae.[83–111] In the rare variant of tetralogy of Fallot with infundibuloarterial inversion, the stenotic pulmonary outflow tract is to the right of the aorta. Thus the right coronary artery must cross the right ventricular outflow tract to reach the right atrioventricular groove, positioning this artery in a disadvantageous way.[73,74] Sharma and colleagues addressed collateral arteries originating from the coronary arteries in tetralogy of Fallot.[104] Semi-selective aortic root and some selective coronary angiographic studies were performed in 330 patients with tetralogy of Fallot over a period of 4 years. Collateral vessels arising from the coronary arteries were found in 11 cases and a direct communication between the coronary artery and pulmonary arteries in 1 case (3.6%). Tetralogy of Fallot with anomalous origin of the right coronary artery has been described by Moss and colleagues.[105] In this 8-year-old child, the right coronary artery did not have an aortic origin. Rather, it originated from the right anterior sinus of the pulmonary artery. Flow from the left coronary artery was to the right coronary artery and then into the main pulmonary artery, and this connection was the sole source of pulmonary blood flow.

A left aortic arch is found in about 75% of patients with tetralogy of Fallot, and in these patients the arch branching pattern is usually normal, although one should always exclude aberrant origin of the right subclavian.[1–10,83] Twenty-five per cent of patients with tetralogy of Fallot will have a right-sided aortic arch. In the patient with a right-sided aortic arch and an aberrant left subclavian artery, the anomalous subclavian artery almost always originates directly from the descending aorta, not from an aortic diverticulum. In classic tetralogy of Fallot, an arterial duct is usually present, but closes physiologically as in the normal individual. The left subclavian artery may be isolated from its normal aortic arch origin, having instead its origin from the left pulmonary artery (see Chapter 41I). With closure of the left arterial duct the left subclavian artery will be isolated, filling from a left vertebral and subclavian steal. Bilateral arterial ducts have been diagnosed in the patient with tetralogy of Fallot.[83,120] Isolation of the right subclavian artery is far less common than isolation of the left subclavian artery. Rarely coarctation of the aorta or interruption of the aortic arch have been described in the patient with tetralogy of Fallot, confounding the general rule of fourth and sixth aortic arch reciprocity.[121–124] A cervical aortic arch, double aortic arch, vascular ring with and without bronchial compression have all been observed in the patient with tetralogy of Fallot.[83] Amongst patients with a cervical aortic arch and tetralogy of Fallot, one must be aware of this association with 22q11 deletion, CATCH 22, and velocardiofacial syndrome.[58–62] A fifth aortic arch has also occasionally been observed in the patient with tetralogy of Fallot [125,125A] (see also Chapter 41D).

The pulmonary vascular bed in tetralogy of Fallot

Perhaps there is less emphasis on the pulmonary vascular bed in patients with Fallot's tetralogy because even modest degrees of pulmonary vascular disease can be well tolerated at the time of repair. This reality is not true in patients undergoing Fontan-like surgery as this procedure is less forgiving of pulmonary vascular disease (see Chapter 36). None the less, a number of publications have studied the nature of the pulmonary vascular bed in patients with tetralogy of Fallot, both shunted and non-shunted.[81–83,126–128] Findings published by Hislop and Reid have shown that the branching pattern of the airways, pulmonary arteries and veins are normal in tetralogy of Fallot.[129] At all ages of the patients studied, there was a decrease in total lung volume and in both pulmonary artery and vein size. In the intra-acinar region, the small pulmonary arteries and veins were increased in number, but the alveolar number was decreased.[129] The studies of Hislop and Reid and Rabinovitch and her colleagues both showed some degree of increased pulmonary arterial muscularity, usually very mild, in contrast to the findings of Ferencz.[82,126,127] Ferencz also stressed the rather common finding of intrapulmonary thrombosis in patients with tetralogy of Fallot and the frequent evidence of recanalization, observations published earlier by Rich and also by Best and Heath.[128,130] Ferencz and others have studied the effects of a systemic-to-arterial shunt on the pulmonary vascular bed.[82,127] The findings depend on the time of death related to the shunt, shunt patency, duration of the shunt and its size.[127] A surgically created shunt causes abnormal extension of muscle into peripheral pulmonary arteries, and increased muscularity as well.[82,127] Rabinovitch and her colleagues also demonstrated more severe pulmonary vascular changes with shunts of longer duration and caliber.[82]

Associated anomalies

Associated anomalies are particularly common in tetralogy of Fallot, and these have been amply and widely catalogued. These include a patent ovale foramen or true atrial septal defect, the latter being found in about 5% of patients with tetralogy (designated by some pentalogy of Fallot); left superior vena cana with unroofed coronary sinus; anomalies of the tricuspid valve including Ebstein's, cleft, straddling and overriding, as well as

tricuspid valve hypoplasia or stenosis; right ventricular hypoplasia; anomalies of pulmonary venous connections including partial and total anomalous pulmonary venous connections; mitral valve anomalies including isolated cleft; mitral stenosis and supravalvular stenosing mitral ring; multiple ventricular septal defects; atrioventricular septal defect, usually Rastelli type C (see Chapter 5); left ventricular outflow tract obstruction; asymmetric septal hypertrophy; and aorticopulmonary window; omphalocele with cardiac diverticulum, etc.[83]

Outcome analysis

Fetal experience

There is now considerable literature on the prenatal diagnosis of tetralogy of Fallot and its more common variants (absent pulmonary valve; pulmonary atresia, aortic origin of the left pulmonary artery, etc).[131–139] Tometzki and colleagues amongst others have shown that prenatal diagnosis of tetralogy of Fallot and other forms of conotruncal anomalies is readily accomplished with accuracy, and there are also data suggesting that additional features can be used to predict 22q11 status of fetuses with tetralogy of Fallot.[131] Those additional features used by Boudjemline and coworkers to predict the 22q11 deletion status include increased nuchal translucency, polyhydramnios and intrauterine growth retardation as well as pulmonary arterial abnormalities.[57] These abnormalities were found more frequently in fetuses with tetralogy of Fallot with associated 22q11 deletion than in fetuses with tetralogy but without the deletion. They suggest that 22q11 deletion can be predicted with a sensitivity of 88%.[57] Many patients once the fetal diagnosis of tetralogy of Fallot is established choose to terminate the pregnancy. Data of Allan and Sharland provided by Hornberger revealed that of 125 cases of prenatally diagnosed tetralogy of Fallot with and without pulmonary atresia at least 25% had associated chromosomal abnormalities or severe extracardiac malformations.[140] The chromosomal abnormalities included trisomies 18, 21, 13, triploidy and microdeletion of chromosome 22. Those extracardiac malformations were most commonly omphalocele, tracheoesophageal fistula, VATER and CHARGE syndromes.[140] Of 74 cases of tetralogy without pulmonary atresia, pregnancy was terminated in 22; there were 9 intrauterine deaths, 7 neonatal deaths, 4 deaths in infancy, and 3 lost to follow-up. If the FISH is positive, it is likely that the decision for pregnancy termination could increase. Others have studied the fetal dimensions of the aorta and pulmonary arteries, providing additional support for the diagnosis of congenital heart disease.[132,141,142]

Postnatal outcome

Natural history

Tetralogy of Fallot is a progressive disorder, and most patients will become symptomatic in infancy and childhood. The outlook for children born with tetralogy of Fallot and untreated is indeed bleak. According to data compiled by Bertranou, 66% of patients with tetralogy of Fallot not treated surgically live to age 1 year, 48% to age 3 years, and 24% to age 10 years[143] (Fig. 16-3). Samanek has studied the probability of natural survival of patients born with tetralogy of Fallot in central Bohemia.[144] These data were compiled before the era of reparative surgery in that region. He found that 88% survived the first week, and

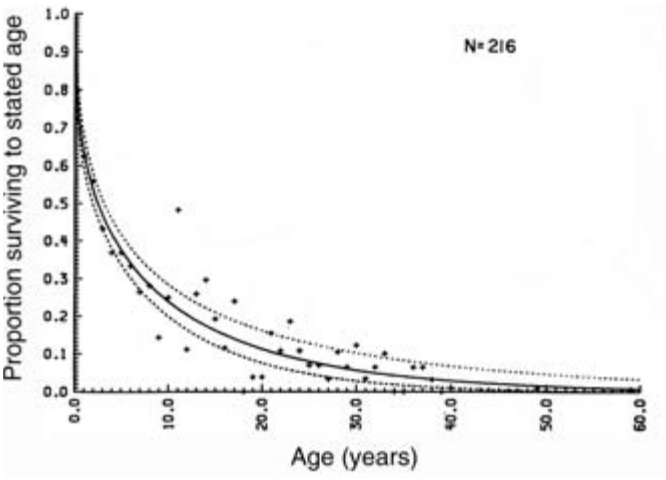


Fig. 16-3 Life expectancy of unoperated patients with tetralogy of Fallot based on data from the Danish populations study. Crosses, data points calculated in that study; solid line (with its 70% CL enclosed by dashed lines), parametric analysis of this data. (Reprinted from Bertranou *et al.*,[143] Copyright (1978), with permission from Exerpta Medica, Inc.)

84% to the first month. The actuarial survival rate at 1 year was 64%, 49% at 5 years, 23% at 10 years, and only 4% at 15 years.[144] As one might anticipate survival overall is considerably worse in those patients with tetralogy and pulmonary atresia (see Chapter 18). Unusual longevity has been seen, however, in some untreated patients with tetralogy of Fallot or pulmonary atresia.[145–149] White and Sprague reported in 1929 the case of a Mr Henry Gilbert, the American composer, who died with tetralogy of Fallot 8 days following the onset of left hemiplegia within a few months of his 60th birthday.[147] White and Sprague reminded us that the oldest patient in Fallot's original series was 36 years old, and in a personal communication from Maude Abbott to the authors she was not aware of any patient older than in their report.[147] This gentleman's picture is reproduced in Maude Abbott's Atlas.[148] Rygg and colleagues have reviewed the life history of the patient with tetralogy of Fallot in Denmark, commenting on the patients reported in Abbott's Atlas and other case series in the literature, with a particular focus on longevity.[148A] From Abbott's compilation the median age at death for the 85 patients with tetralogy of Fallot was 9 years, ranging from 11 days to 60 years. For those 30 patients with pulmonary atresia, the median age at death was 11 months, ranging from 9 days to 30 years. The entirety of her experience comprised 115 patients, with a median age at death of 7 years, ranging from 9 days to 60 years.[148A,148B] Rygg *et al.* identified 177 unoperated patients with tetralogy of Fallot in Denmark in 1949 and compared their cumulative age distribution curve to that of the total population of Denmark.[148A] The median age of the entire population of Denmark at that time was 32 years, while that of the group with tetralogy was only 7 years, and < 5% of the tetralogy patients were older than 30 years. This is depicted dramatically in fig. I of their paper.[148A] Bain reported an unoperated patient with tetralogy of Fallot who died at 69 years of age.[150] In another report a 54-year-old man's prolonged survival without surgical intervention was likely secondary to a large volume congenital systemic-to-pulmonary artery shunting from his right internal mammary and accessory internal mammary arteries to his right pulmonary artery.[150A] Also as Gasul

and his colleagues recognized nearly 50 years ago some patients initially thought to have a high flow ventricular septal defect do acquire important pulmonary outflow tract obstruction, culminating in cyanosis and/or frank cyanotic or hyperpneic spells.[151] The incidence of this transformation is unclear, but it is not uncommon. As we pointed out > two decades ago the mechanism more commonly associated with this transformation was related to the hypertrophy of right ventricular anomalous muscle bundles rather than to hypertrophy of a displaced infundibular septum.[152] Some patients with very severe infundibular obstruction will over time acquire complete atresia of the pulmonary valve and distal infundibulum, with the patients surviving on a previously constructed shunt or small indirect and direct aortopulmonary collateral and bronchial arteries.[153–156] This phenomenon today is very uncommon with strategies of early primary repair of tetralogy of Fallot.

As we will show in a subsequent chapter (see Chapter 25A) the outlook for the patient with simple transposition of the great arteries can be linked to a variety of medical and surgical maneuvers. These maneuvers forever dramatically changed the fortunes of these patients although there is still attrition of these patients:

- the Senning procedure in 1959 (see specific references in Chapters 25A and 25B)
- the Mustard procedure in 1963
- balloon septostomy in 1966
- prostaglandin therapy 1979
- arterial switch 1975
- neonatal arterial switch 1983.

Similarly, the fortunes of patients with tetralogy of Fallot were altered by a series of primarily surgical maneuvers:

- the Blalock–Taussig shunt 1945[157]
- the Potts shunt 1946[158]
- primary repair 1954[159]
- the Waterston shunt 1962[160]
- prostaglandin therapy 1976[161]
- primary repair of the infant 1973.[162]

But even these signal accomplishments do not prevent loss or attrition. The "promise" is only that and reality is far different. One of the important differences between patients with transposition of the great arteries and those with tetralogy of Fallot beyond the cardiac malformation itself is that the latter have a far greater association with important extracardiac anomalies that influence outcome.[163] Karr and her colleagues have documented a 28% attrition for patients with tetralogy of Fallot registered in the Baltimore–Washington Infant Study from 1981 to 1985, and this study showed that major additional cardiac anomalies, low birth weight, major noncardiac anomalies and prematurity were significant risk factors for death.[163] In the era after the beginning of palliation and before the era of prostaglandin therapy, it is likely that the attrition would be even more considerable.

Palliation

The systemic-to-pulmonary artery anastomosis

The Blalock–Taussig shunt

The outcomes of patients born with tetralogy of Fallot were forever changed by the clinical acumen of the late Dr Helen Taussig.[22,28] She was persuaded that creation of a "ductus" would improve some patients with cyanotic congenital heart disease, as she had witnessed clinical deterioration in some cyanotic patients coincident with closure of the arterial duct.[28] Knowing that Gross of Boston had first successfully ligated the arterial duct,[164] she tried to persuade him to consider constructing a "duct," but he was apparently unwilling to do so. She then returned from Boston to Baltimore and discussed this with Alfred Blalock (1899–1964), and this discussion culminated in the clinical application of the first systemic-to-pulmonary shunt performed on November 29, 1944.[157] Eileen Saxon, born August 3, 1943, greatly benefited from this surgical ingenuity of Dr Alfred Blalock and Mr Vivien Thomas (1910–85). How fortunate that Blalock when at Vanderbilt was interested in producing an animal model of pulmonary artery hypertension.[165–167] Attempts to create this model in the dog were achieved by surgically connecting the proximal end of the divided left subclavian artery to the distal end of the divided left pulmonary artery.[165] While this model did not result in pulmonary artery hypertension, the technical approach matured into the "blue baby" operation. But about Mr Vivien Thomas.[166,167] He was Blalock's chief laboratory technician, a very talented individual who forsook thoughts of college and medical school because of the great depression.[165–167] His technical ability and manual dexterity provided the perfect interface for the collaboration with Blalock. The collaboration began when he met Dr Alfred Blalock on February 10, 1930, and then participated in the surgery to create this animal model of pulmonary hypertension. Thomas supervised the surgical laboratories at Johns Hopkins for over 35 years.[165] In recognition of the contributions of Mr Vivien Thomas to the origins of Pediatric Cardiovascular Surgery members of the Old Hands Club (former Halsted residents at Johns Hopkins) in 1969 agreed to commission the painting of his portrait, and the presentation of this portrait occurred on February 27, 1971. In 1976 he was appointed instructor in surgery at the Johns Hopkins University School of Medicine and also in the same year, he was awarded the honorary degree Doctor of Laws, by the Johns Hopkins University. Upon his retirement in 1979, he became instructor emeritus of surgery. Appropriately Vivien Thomas's achievements were widely recognized by his colleagues, and in 1996 the First Vivien Thomas Young Investigator Award was given at the annual American Heart Association meeting. A fitting tribute indeed!

The classical Blalock–Taussig shunt was constructed using the right subclavian artery in the patient with a left aortic arch and the left subclavian artery in those with a right aortic arch.[79,157] The ability to improve the oxygen saturation and reduce polycythemia following construction of the classic Blalock–Taussig shunt was shown clearly in the 1947 publication of Taussig and Blalock.[157A] An aberrant origin of the subclavian artery or those rare cases with isolation of the subclavian artery could confound this approach (see Chapter 41I). The evolution from the classical Blalock–Taussig shunt to the modified form of the shunt took place in the mid 1970s,[168,169] and most centers adopted the use of the modified Blalock–Taussig shunt using polytetrafluoroethylene.[79] Others introduced in 1975 the subclavian arterioplasty so that a classical Blalock–Taussig shunt could be performed ipsilateral to the aortic arch without kinking and distorting the subclavian artery.[170,171]

The Potts and Waterston shunts

Subsequent to the publication of the benchmark paper by Blalock and Taussig experience with this form of palliation rapidly expanded and other forms of systemic-to-pulmonary artery shunts were then devised. These included the Potts shunt

between the left pulmonary artery and descending thoracic aorta performed in 1946,[158] and the Waterston shunt between the ascending aorta and right pulmonary artery in 1962,[160] this latter shunt modified by Cooley and his group.[172] We reviewed in 1975 our experience with systemic-to-pulmonary artery shunts in infants < 30 days of age with obstructive lesions of the right heart chambers.[173] This experience encompassed the classical Blalock–Taussig shunt, Potts and Waterston, all carried out before the introduction of prostanoid therapy. From 1950 to 1965, the surgical mortality was 78%, and the mortality between 1965 and 1972 had dropped to 34%, still very high, and again before the introduction of prostanoid therapy. Trusler and his colleagues also from the Toronto Hospital for Sick Children reviewed the outcomes of patients who had undergone the Potts or Waterston shunts between 1965 and 1979.[174] This experience was not limited only to patients with tetralogy of Fallot. While providing reasonable palliation the high incidence of surgically induced pulmonary artery stenosis and pulmonary hypertension led to the conclusion that when possible the use of these shunts should be discouraged.[174] Gladman and his colleagues from the Toronto Hospital for Sick Children extended these observations in 1997, studying the morbidity and mortality of the modified Blalock–Taussig shunt performed in 65 patients who were operated on between 1990 and 1994.[175] The median age at palliation was 58 days, and follow-up angiography showed that in 33% of the patients there was angiographic evidence of pulmonary artery distortion (Fig. 16-4). Overall survival was 90% in these patients. A similar experience was reported by Godart and colleagues in 1998.[176] A very extensive experience with the Blalock–Taussig shunt was reported by Al Jubair and colleagues in 1998, providing information about 546 shunts performed in 478 patients between 1983 and 1995.[177] At the time of surgery, 78 patients were < 1 week of age, 270 from 1 week to 12 months, and 198 patients were over 1 year of age. The overall hospital mortality was 2.9%, and early surgical mortality was higher in the younger patient, 6.4% in those under 1 week, 3.7% between 1 week and 1 year, and 0.5% in patients over 1 year of age. Shunt failure was more common in patients < 3.0 kg and in those patients not anticoagulated intraoperatively.[177] The Pediatric Cardiac Care Consortium has reported its experience with systemic–pulmonary arterial shunts, performing a total of 2450 shunts between 1984 and 1993, of which 1667 were performed in infants, 746 in children, and 37 in the adults.[177A] Not all of these were performed in patients with tetralogy of Fallot. Overall shunt mortality (30 days) was 15% in those < 1 month of age, and 4% in those from 10 to 21 years of age. The central and Waterston shunts had the highest 30-day mortality of 17%, while the modified Blalock–Taussig shunt had a 7% mortality. Their data also showed an inverse relationship between mortality and weight.

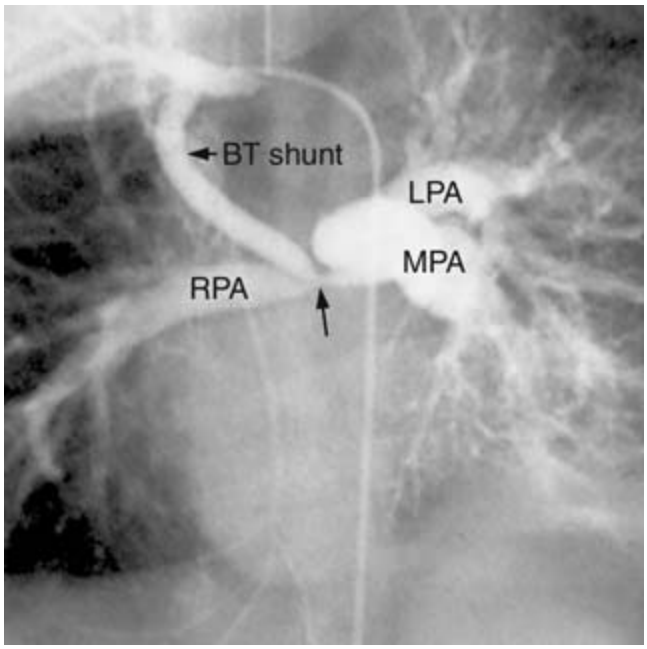


Fig. 16-4 Stenosis (arrow) of the right pulmonary artery (RPA) at the anastomosis site of right Blalock–Taussig (BT) shunt in a patient with tetralogy of Fallot. LPA, left pulmonary artery; MPA, main pulmonary artery.

Some patients were wonderfully palliated for many years by a single classical Blalock–Taussig shunt as in the patient reported by Taussig in 1972.[178] This patient had undergone a classic shunt at 23 months of age on January 23, 1947. This report documented his very good health 24 years later. Because his clinical status was so well, he did not wish to undergo cardiac catheterization and corrective surgery. Taussig and her colleagues have also published their observations on the 20- to 28-year follow-up on patients with tetralogy of Fallot operated on between 1945 and 1951.[179] This review focused on 432 patients known to be alive at the beginning of the 15th postoperative year. At the beginning of the 20th year, 376 patients were alive, 24 had died and 32 had been lost to follow-up. Review of the final status of the 432 patients showed that 169 patients had not undergone further surgery after their initial palliation; 36 underwent further palliation, and 227 had undergone complete repair. Only 37% of those who had undergone palliation were considered to be doing well compared with 79% of those who had been repaired. Thus as of January 1, 1974, 20–28 years after their first operation, 50.4% of the patients were alive. Slightly over 50% had married, and 319 children were born to parents with tetralogy of Fallot. Six women with tetralogy had 1 child with a cardiac malformation, and 2 men of the 128 married males had children with cardiac malformations, 1 child with tetralogy of Fallot (see section on recurrence). Taussig and her colleagues have reported extensively on the outcomes of the Blalock–Taussig shunts in her years at Johns Hopkins.[22,28,179–183] These papers document fully the earliest applications and outcomes of the classical Blalock–Taussig shunt in patients with tetralogy of Fallot and serve as part of the invaluable history of our specialty. Taussig also reviewed the outcomes of the Blalock–Taussig shunt in patients with single ventricle, dextrocardia, transposition of the great arteries with ventricular septal defect and pulmonary stenosis, and so-called type 4 truncus arteriosus, but these are not germane to the present discussion.

The Brock closed transventricular infundibulectomy

Other forms of palliation included the Brock pulmonary infundibulectomy and valvotomy, leaving the ventricular septal defect open.[184,184A] Brock (1903–80) had earlier performed a closed valvotomy for patients with pulmonary stenosis [185] and Brock and Campbell in 1950 had provided follow-up for the initial cohort of 33 patients with congenital pulmonary valvular stenosis showing the very gratifying results.[186] It was a natural extension to apply this technique for patients with tetralogy of

Fallot. They appreciated that the anatomy of tetralogy was considerably more complicated with the obstruction being primarily at infundibular level with secondary involvement of the pulmonary valve. The procedure extended to patients with Fallot's tetralogy consisting of a closed transventricular infundibulectomy to relieve pulmonary outflow tract obstruction. This procedure was suitable for older patients, and unlike a unilateral shunt, the Brock procedure provided symmetrical flow to both pulmonary arteries, clearly an advantage.[186] Conceptually the approach of dilating a narrowed infundibulum was a logical extension for the neonate and young infant with diminutive pulmonary arteries, whether surgically or using a transcatheter procedure. For at least some patients the Brock procedure provided excellent long-term palliation as in the patient reported by Gerlis *et al.* This patient born in 1949 underwent a Brock procedure in 1953, dying at 47 years of age.[186A]

Table 16-1 Status of procedures for treating tetralogy of Fallot

Procedure	Status
Classic and modified Blalock–Taussig shunt	Still used
Potts and Waterston shunt	Largely abandoned
Closed Brock infundibulectomy	Abandoned
Pleurectomy/pleurodesis/asbestos poudrage	Abandoned
Thoracic omentopexy	Abandoned
Formalin-infiltration of arterial duct	Abandoned
Right ventricular outflow tract reconstruction with pericardium or conduit; VSD not closed	Still used
Palliative balloon angioplasty of RVOT	Still used

RVOT, right ventricular outflow tract.

Other forms of palliation

One earlier form of palliation was the use of pleurectomy and pleurodesis.[187,187A,187B] This procedure was used to stimulate the growth of transpleural collateral vessels to improve crippling hypoxemia and symptomatology when standard forms of palliation or repair seemed impossible, or too risky. The pleurodesis was accomplished by the performance of a posterolateral thoracotomy with pleurectomy and then asbestos-poudrage was often used to further stimulate collateral growth. This approach obviously had limited applicability and made subsequent repair very difficult. Most of the patients subjected to pleurodesis did not survive long enough to develop the pulmonary complications of this procedure. A short-lived procedure to attempt to improve the circulation to the lungs was to bring the great omentum into the chest and into contact with the left lung.[187] There is little if any follow-up on this procedure. Another interesting maneuver to enhance or provide a seemingly stable source of pulmonary blood flow was to inject formalin into the wall of the arterial duct, a procedure designed to maintain ductal patency.[188–192] Unfortunately, all too often the duct still closed precipitously, and interest in this procedure waned. Furthermore, this procedure was not without its own complications to the recurrent laryngeal nerve.[193]

Thus in the surgical history of the palliation of tetralogy of Fallot, some procedures continue to be used, while others have been either largely or completely abandoned (see Table 16-1).

Total repair of tetralogy of Fallot

The era of corrective surgery was ushered in by Lillehei and his colleagues in 1955, just half a century ago, at first using the technique of cross-circulation,[194,194A,194B] and a number of these patients have survived, providing data for truly long-term follow-up.[195] Vincent Gott has provided an interesting historical vignette about CW Lillehei and the total correction of tetralogy of Fallot.[194B] The 1950s and 1960s were witness to tremendous numbers of patients with tetralogy of Fallot and many other forms of congenital heart malformations undergoing corrective surgery and staged repairs. In this era, surgical mortality and morbidity were high, but many patients benefited from the remarkable skills of these pioneering surgeons. The construction of systemic-to-pulmonary artery shunts in the era before prostaglandin also had mortality and morbidity. Distortion of the pulmonary artery with narrowing or acquired non-confluence was sadly not an uncommon finding.[79,83,173–177] The central shunts while technically easier to perform especially when the pulmonary artery was small were more prone to severely distort the shunted pulmonary artery, especially the Potts shunt.[79,83,174,196–207] These shunts tended to be large and pulmonary hypertension was not infrequent. Some of these patients went on to develop aneurysms of the pulmonary artery, which on occasion ruptured. The classical Blalock–Taussig shunt could also result in pulmonary hypertension, but this occurred much less frequently than with the central shunts.[200,201] The morbidity from these shunts could add substantially to the risk at repair, both from the aspect of a distorted pulmonary artery and the necessity of its reconstruction, the adverse effects of pulmonary hypertension, and in those patients with long-lasting shunts, the deleterious effect of chronic volume loading on left ventricular function. It soon became apparent that the Potts shunt while providing reasonable palliation proved difficult to take down from a midline sternotomy at the time of complete repair, and even more difficult to adequately expose and reconstruct a post-Potts stenotic left pulmonary artery. All kinds of complications were catalogued including phrenic nerve injury, damage to the recurrent laryngeal nerve, gangrene of the hand ipsilateral to the subclavian shunt, and a wide variety of orthopedic complications including limb length discrepancy, scoliosis, etc. Throughout the 1950s and 1960s symptomatic infants were palliated with a shunt, and medical maneuvers were used to optimize these patients' status. These maneuvers included the recognition that iron deficiency could result in hypoxic cerebral infarcts and that morphine and then later a beta blocker could be used to treat the hypercyanotic spells so characteristic of the patient with Fallot's tetralogy.[207A] Some indeed considered propanolol the preferred palliation for tetralogy of Fallot.[207A] During the 1950s and over the next 25 years, the pertinent angiographic features of typical Fallot anatomy and all its variations were described in luxurious detail.[83,208–210] There was particular emphasis placed on the right ventricle, the nature of the ventricular septal defect, the right ventricular outflow tract and the pulmonary artery circulation. The observation that an abnormal epicardial distribution of a major coronary artery could confound repair, or at least make standard repair hazardous or worse led to scrutiny of the coronary arteries, their origin and epicardial course, again in this era with angiographic techniques.[79,83–98,106] In this era the neonate, infant and small

child were palliated with a shunt, while the older child when symptomatic underwent primary repair. As with most of medicine in that era, advances were often based on retrospective analyses of outcome, both favorable and adverse. Those morphological features though to convey a favorable outcome for repair were widely exalted and those issues that might jeopardize outcome were discussed at length. It soon became clear that in that era small pulmonary arteries were a risk factor, but how small was too small? Adverse coronary artery anatomy, multiple ventricular septal defects, ventricular hypoplasia, low birth weight, severe extracardiac anomalies, etc., were correlated with poor outcome.[79] Left ventricular hypoplasia was considered in those years as causal for many operative deaths. This in fact was a myth and true left ventricular hypoplasia in tetralogy is uncommon.[211] It was more likely that death in these cases reflected myocardial failure, perhaps indicative of inadequate myocardial protection during the performance of cardiopulmonary bypass, or some other factor.

Primary repair in the neonate and young infant

It was Castaneda and his colleagues at the Children's Hospital in Boston who in the early 1970s advocated primary repair of tetralogy at any age,[162] believing that this approach should avoid the deleterious effects of a shunt procedure, reduce right ventricular hypertrophy and hypertension, ideally as a corollary reducing the risk of late ventricular arrhythmias. This approach of primary early repair should, according to Castaneda,[212,212A] also promote pulmonary angiogenesis and alveologenesis, supporting the observations of Johnson and Haworth in this regard.[213] Furthermore, he speculated that by eliminating chronic hypoxemia, cognitive and psychomotor development should be optimized. This approach of primary repair was advocated by the Boston group for virtually all forms of congenital heart disease previously treated by staged operative procedures.[214] The infrastructure or framework for neonatal repair and repair of the small infant was already in place with the pioneering work of Barratt-Boyes and others (see Chapter 3).[215,216] During the 1970s this approach was not readily assimilated and many continued to palliate the symptomatic neonate or young infant with a shunt, thus staging to later repair. The mid 1970s also saw the development and application of an E-type prostaglandin to maintain ductal patency, thus providing a medical maneuver to stabilize the fragile and deeply cyanotic infant whose circulation was in large part duct-dependent.[161] The administration of *n* E-type prostanoid allowed these patients to stabilize with correction of any base deficit, thus permitting surgery on a much more stable patient. It is of historical interest that in the era of palliation and before prostaglandin therapy, the Boston group routinely performed a shunt on babies in a hyperbaric chamber, using this approach to increase tissue oxygenation. In this regard, Lillehei (1918–99) has provided an interesting review of the milestones in the development of open heart surgery.[217]

This is not the appropriate forum to discuss the evolution in the surgical technique as applied to patients with tetralogy of Fallot. Those aspects are fully covered in Kirklin and Barratt-Boyes *Cardiac Surgery*.[79] Suffice it to say, however, in addition to advances in myocardial protection, some began to limit the extent of the right ventriculotomy and its obvious potential deleterious effect on the form and function of the right ventricle. They approached the right ventricular outflow tract and ventricular septal defect through the right atrium and the pulmonary artery. This approach allowed when required a more limited right ventriculotomy. The pulmonary annulus was often hypoplastic in tetralogy of Fallot and nomograms were devised to provide guidance as to when a transannular patch was required.[79] The combination of a pulmonary valvotomy often combined with the transannular patch resulted in pulmonary insufficiency of variable severity, and this issue clearly impacted on the well-being of many patients with tetralogy of Fallot as we shall see.

Throughout the 1970s and 1980s many large surgical series accumulated, and the results for tetralogy repair continued to improve. The data and surgical insights provided by Kirklin[79A] and his associates provided templates for excellence, and mortality for the repair of the usual form of tetralogy of Fallot fell to below 5%, and even less in some centers.[79] These issues are fully discussed in Kirklin and Barratt-Boyes and by Kirklin *et al.*[79,218] Pulmonary artery indices were derived, the McGoon and Nakata index (see Chapter 18) and outcomes were stratified by pulmonary artery index.[219,220] The correlation of outcome with pulmonary artery caliber was weak in most of the reported series.[79,218,221] There was still ongoing discussion as to whether primary repair of the neonate and young infant was preferred over a staged approach, and publications taking each position frequented the literature.[222–225] With the ever improving surgical results and the introduction of cross-sectional echocardiography in the 1980s and later color flow Doppler mapping, soon some advocated repair of tetralogy on the basis of echocardiographic imaging alone.[226–229] Even complex coronary artery anatomy can be sorted out using echocardiographic imaging.[107,230,231] What became readily apparent was that patients with straightforward tetralogy anatomy could be repaired at very low risk. The conundrum occurred in those patients with very small pulmonary arteries, 2–3 mm or less (Fig. 16-5). Castaneda and his group in advocating early primary repair felt that the pulmonary arteries were small because they were underfilled.[162,212,212A,214] By increasing flow the small compliant vessels would dilate accommodating right ventricular output. But there was clearly a lower limit for this strategy and this was the source of considerable discussion. Numerous ther-

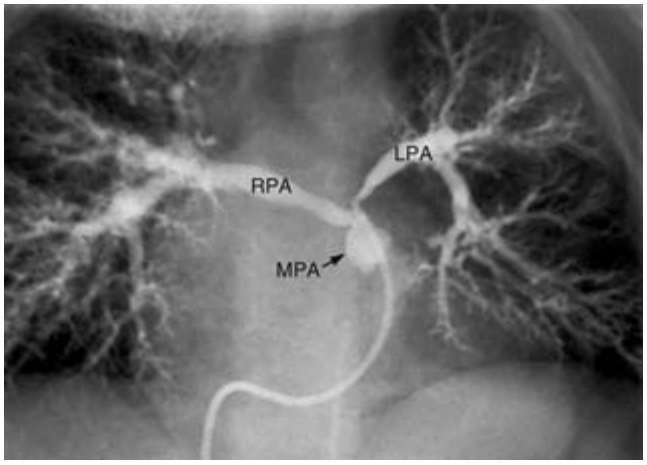


Fig. 16-5 Dysplastic pulmonary arterial anatomy with central stenosis in a patient with tetralogy of Fallot. LPA, left pulmonary artery; MPA, main pulmonary artery; RPA, right pulmonary artery.

apeutic strategies were employed for these challenging cases, including shunting; right ventricular outflow tract patch with the ventricular septal defect left open; interposition of a valved or nonvalved conduit between the right ventricle and pulmonary artery, again with the ventricular septal defect left unrepaired; repair with partial closure of the ventricular septal defect, or with a fenestrated patch, or patch with a one-way valve, etc. With the advent of the interventional cardiology, some advocated balloon dilatation of the right ventricular outflow tract or percutaneous transcatheter myectomy of subvalvar pulmonary stenosis in tetralogy of Fallot as a strategy to promote forward pulmonary blood flow thus stimulating pulmonary artery growth.[232–237] There is adequate clinical experience showing that these maneuvers did enhance oxygen saturation and did stimulate growth of the pulmonary arteries and in some patients growth of the pulmonary annulus.[233–235]

In 1991, Di Donato and colleagues from the Children's Hospital in Boston published their experience with neonatal repair of tetralogy with and without pulmonary atresia.[238] Twenty-seven symptomatic neonates underwent repair between 1973 and 1988 at a mean age of 8 ± 8.4 days with a mean weight of 3.0 ± 0.7 kg. Twenty-five transannular patches were used and two conduits. Five deaths occurred, 3 of these attributed to avoidable technical problems and all deaths occurred in patients with very small pulmonary arteries. The actuarial survival at 5 years was 76%. Pigula and his colleagues again from Boston reported on the outcomes of 99 neonates and young infants < 90 days with tetralogy ± pulmonary atresia repaired between 1988 and 1996.[239] Fifty-nine were prostaglandin E dependent at the time of repair and 91% were symptomatic at the time of repair. Early mortality was 3% (3 of 99) with actuarial survival rates of 94% at 1 year and 91.6% at 5 years (Fig. 16-6). The 1-, 2-, and 5-year freedom from reoperation for the tetralogy with pulmonary stenosis patients was 94%, 88%, and 81% respectively. For those with pulmonary atresia, 1-, 2-, and 5-year freedom from reoperation was 79%, 69%, and 50%, respectively.[239] The lower rate of freedom from reintervention in the pulmonary atresia group reflected the ongoing need to replace conduits and rehabilitate the pulmonary arteries (see also Chapter 18).

Hennein and colleagues from Ann Arbor reported in 1995 their experience with 30 neonates with symptomatic tetralogy of Fallot from July 1988 through September 1993 who underwent complete repair.[240] Sixteen patients had tetralogy and pulmonary stenosis, 9 had pulmonary atresia, 3 had nonconfluent pulmonary arteries, and 2 had both pulmonary atresia and nonconfluent pulmonary arteries. The median age at operation was 11 days with a mean weight of 3.1 ± 0.1 kg. Preoperatively, 14 patients were receiving an infusion of prostaglandin, 13 were mechanically ventilated, and 6 required inotropic support. Right ventricular outflow tract obstruction was managed by a limited transannular patch in 25 patients, infundibular muscle division with limited resection in 15, and insertion of a right ventricle–pulmonary artery valved aortic homograft conduit in 5 patients. There were no hospital deaths and 2 late deaths, for 1-month, 1-year, and 5-year actuarial survivals of 100%, 93%, and 93%, respectively. The hazard function for death had a rapidly declining single phase that approached zero by 6 months after the operation. Both late deaths occurred in patients with tetralogy of Fallot and pulmonary atresia who had undergone aortic homograft conduit reconstruction, so that the only independent risk factor for death was the use of a valved homograft conduit ($P <$ or $= 0.005$). Eight patients required reoperation, resulting in 1-month, 1-year, and 5-year freedom from reoperation rates of 100%, 93%, and 66%, respectively. Indications for reoperation were branch left pulmonary artery stenosis in 5 patients, residual right ventricular outflow tract obstruction in 2 patients, and severe pulmonary insufficiency in 1 patient. Independent risk factors for reoperation included an intraoperative pressure ratio between the right and left ventricles of 0.75 or greater ($P = 0.01$), Doppler residual left pulmonary artery stenosis of 15 mmHg or more, or Doppler right ventricular outflow tract obstruction gradient of 40 mmHg or more at hospital discharge ($P = 0.002$ and 0.02, respectively). Hirsch and colleagues extended this experience in their publication in the year 2000.[241] From August 1988 to November 1999 61 consecutive symptomatic neonates with tetralogy of Fallot underwent complete repair. Thirty-one patients had tetralogy of Fallot with pulmonary stenosis, 24 had tetralogy of Fallot with pulmonary atresia, and 6 had nonconfluent pulmonary arteries. The mean age at repair was 16 ± 13 days, and the mean weight was 3.2 ± 0.7 kg. Before surgery, 36 patients were receiving an infusion of prostaglandin, 26 were mechanically ventilated, and 11 required inotropic support. Right ventricular outflow tract obstruction was managed with a transannular patch in 49 patients and a right ventricle-to-pulmonary artery conduit in 12. Cardiopulmonary bypass time averaged 71 ± 26 minutes. There was 1 hospital death from postoperative necrotizing enterocolitis on postoperative day 71 and 4 late deaths, only 1 of which was cardiac-related. Actuarial survival was 93% at 5 years (Fig. 16-7). Follow-up was available for all 60 hospital survivors and averaged 62 months (range 1–141 months). Twenty-two patients required a total of 24 reoperations at an average interval of 26 months after repair. Indications for reoperation included right ventricular outflow tract obstruction,[19] branch pulmonary artery stenosis (Fig. 16-8),[11] severe pulmonary insufficiency,[4] and residual ventricular septal defect.[1] The 1-month, 1-year, and 5-year freedom from reoperation rates were 100%, 89%, and 58%, respectively. The groups from the Marie Lannelongue Hospital has had a similar experience, reporting their results in 1994,[242,243] and Reddy and his colleagues then in San Francisco in 1995.[244] Sousa Uva and colleagues reserved palliation for patients with a severe associated cardiac anomaly, very low weight, or severely hypoplastic pulmonary artery tree.[242,243] With results like this for tetralogy of Fallot and for many other

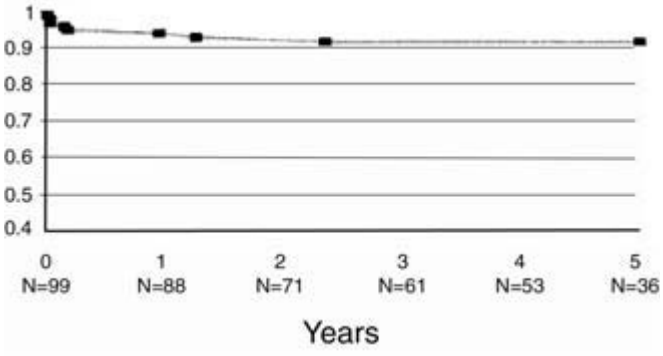


Fig. 16-6 Actuarial survival for 99 neonates and young infants undergoing repair of tetralogy of Fallot at the Children's Hospital in Boston between 1988 and 1996. There were 3 hospital deaths. (Reprinted from Pigula *et al.*,[239] Copyright (1999), with permission from Lippincott Williams & Wilkins.)

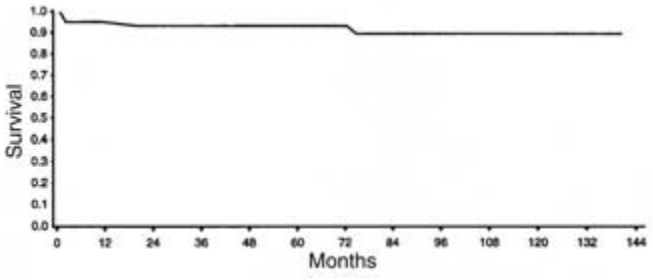


Fig. 16-7 Actuarial survival curve of 60 patients undergoing complete repair of tetralogy of Fallot as neonates. Survival was 93% at 5 years. (Reprinted from Hirsch *et al*.,[241] Copyright (2000), with permission from Lippincott Williams & Wilkins.)

conditions, it is not surprising that mortality associated with congenital heart defects in the United States continues to decline, a decline that is not explained by a decline in birth rate.[245] Knott-Craig and his colleagues have also reported their extensive and similarly gratifying experience.[246] Kaulitz and colleagues have reviewed the effect on the growth of the pulmonary arteries and the risk for late re-intervention following primary repair of tetralogy of Fallot in infancy.[247] They found that primary correction in infancy resulted in sustained increase in the diameters of the right and left pulmonary arteries, allowing for normal development of the proximal pulmonary arterial system in most patients regardless of their age and symptomatic status at operation.[247]

There remains discussion as to the timing of repair of the acyanotic infant with tetralogy of Fallot.[222–225] Parry and his colleagues reported on the overall outcome of 42 acyanotic infants operated between July 1992 and March 1999, with a median age of 62 days and median weight of 4.55 kg.[248] The pulmonary annular *Z*-value ranged from – 5.6 to + 3.0, with a median of –1.9. There were no deaths and only 24% required a transannular patch. Pulmonary insufficiency was assessed as trivial to mild. There were no late deaths, but 3 patients required re-intervention. This experience indicates that repair can be safely carried out in early infancy, with a low mortality and low rate for freedom from re-intervention.

The Toronto Hospital for Sick Children had for many years taken a cautious, indeed conservative approach to the surgical management of the patient with tetralogy of Fallot, preferring to shunt the neonate and small infant. Vebecky, when in Toronto and her colleagues, reviewed the outcomes of 270 children seen from 1978 to 1988 under 18 months of age at our institution.[249] Thirteen infants (4.8%) had major noncardiac lesions that precluded definitive care for their congenital heart disease. Twenty infants (7.4%) had major associated cardiac lesions (atrioventricular septal defect or absent pulmonary valve syndrome, or both). Survival in this group was poor, with only 58% reaching the age of 10 years. Four of the 7 deaths occurred before intracardiac repair was performed. The remaining 237 infants presented with isolated tetralogy of Fallot. Eighty-nine per cent survived to age 10 years. Sixty per cent of these infants required palliation, and survival in these infants did not differ from that in those who never required palliation (Figs 16-9, 16-10). However, 19 infants (8%) required palliation in the first month of life. In these children, survival to age 10 years was significantly lower (77%); secondary palliation was frequently required (n = 11), and a transannular patch or conduit at the time of repair (10 of 14 patients) was more likely needed than it was in children who had not undergone a palliative procedure during the neonatal period. We concluded that survival in infants with tetralogy of Fallot is unlikely to be different, regardless of whether primary repair or a staged repair is carried out.[249] This was certainly not the opinion of Castaneda in his comments to this paper.[250] More recently, Van Arsdell and his coworkers again from the Toronto Hospital for Sick Children reviewed the outcomes of 227 consecutive children with tetralogy of Fallot undergoing repair from 1993 to 1998.[225] There were 6 deaths (2.6%), with no mortality for primary repair in the past 6 years. The median age at repair was 17 months in 1993, falling to 8 months in 1998. Palliation decreased from 38% in 1993 to 0% in 1998. There was no change in the use of a transannular patch over time. With rare exception, we now prefer primary repair to palliation at any age. However, is this the wisest approach? Dodge-Khatami and colleagues wrote in 2001: "The optimal surgical approach and timing for repair of tetralogy of Fallot remains one of the more controversial issues in the treatment of congenital cardiac malformations." They go on to say: "But which approach, staged or complete early repair, leads to better quality of life, less health-related hazard, and what are the implications in decision-making for the physicians caring for these patients? If the overall outcome of a surgical modality is to be judged on the basis from continuous medical treatment, or the need for reoperation rather than operative mortality, does one or the other surgical strategy lead to an overall better outcome?" Sadly, there is no answer to this conundrum as they conclude: " The best approach to the repair of tetralogy of Fallot remains to be determined," advocating prospective randomized studies, including both strategic arms.[223]

Strategies to promote the growth of diminutive pulmonary arteries

Any number of procedures have been used to promote growth of diminutive pulmonary arteries. The type of procedure is of course influenced by the era of treatment, with some form of systemic-to-pulmonary artery shunt used from 1945 to the

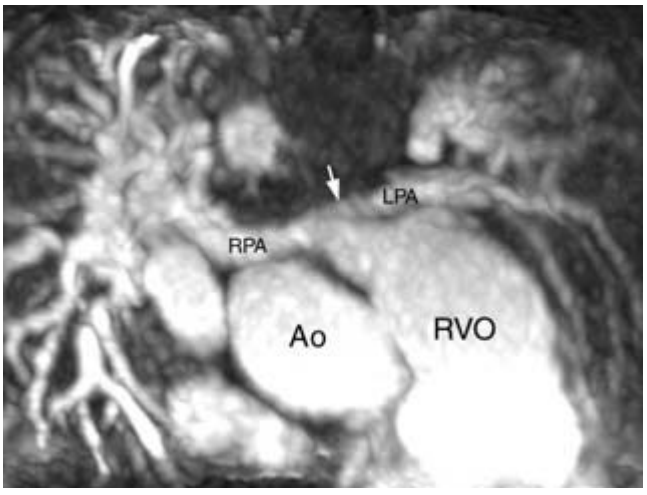


Fig. 16-8 MR angiography from a patient with repaired tetralogy of Fallot shows that both right (RPA) and left (LPA) pulmonary arteries are small. The left pulmonary artery shows focal stenosis of its origin (arrow). The right ventricular outflow tract (RVO) is aneurysmal. Ao, aorta.

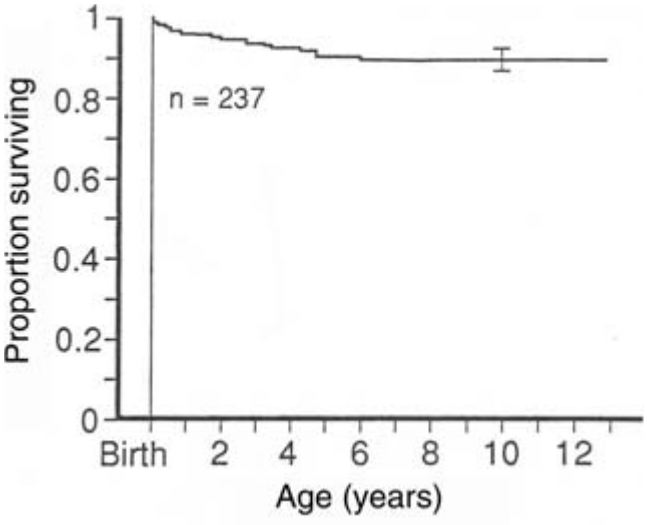


Fig. 16-9 Data from the Toronto Hospital for Sick Children. Kaplan–Meier estimate of survival of 237 infants presenting with isolated tetralogy of Fallot between 1979 and 1988. The survival rate to age 10 years is 89.5 ± 2.3%. (Reprinted from Vobecky *et al.*,[249] Copyright (1993), with permission from The Society of Thoracic Surgeons.)

present time. Then based on the Brock procedure,[184] some advocated a right ventricular outflow tract patch or conduit (valved or nonvalved) between the right ventricle and main pulmonary trunk.[79,80,239,241,243,251–253] These maneuvers were not without their own complications and we and others showed that a pericardial outflow tract patch tended to contract and narrow particularly the left pulmonary artery.[79,254] This can occur as well following transannular patch repair of tetralogy of Fallot (Fig. 16-5).[255] Others taking the lead from Castaneda advocated primary repair at any age and even with very small pulmonary arteries, supporting the position as stated earlier that the caliber of the pulmonary arteries reflects inadequate flow and that they will distend as pulmonary blood flow is augmented.[82,162,212,212A,214] Growth of the pulmonary arteries as shown by Rosenberg and his colleagues likely depended on the structural composition of the central arteries.[256] Such growth required elastin and a deficiency of elastin could negatively influence growth. Rosenberg *et al.* also suggested that elastin synthesis is greater in younger patients.[256] Over the past decade there has been considerable interest in catheter-based strategies to promote the growth of small pulmonary arteries.[257,258] Thus one advantage to connecting the right ventricle to the main pulmonary artery is catheter access to the branch pulmonary arteries for staged rehabilitation.

Tetralogy of Fallot with unilateral absence of pulmonary artery

Tetralogy of Fallot with congenital unilateral absence of a pulmonary artery occurs in about 1% of patients with tetralogy of Fallot (Fig. 16-11).[83] Unless there is associated congenital absence of the lung, there is a hilar pulmonary artery and intraparenchymal branches. The hilar pulmonary artery was originally connected to an arterial duct which on closing leads to isolation of the ipsilateral pulmonary artery and progressive hypoplasia of the involved lung.[259–265] In some patients with tetralogy of Fallot one pulmonary artery has been severely distorted by a previously constructed shunt, leading to either profound hypoplasia or acquired nonconfluence (Fig. 16-4).[262,263] Mortality for repair into a single pulmonary artery had been reported as high as 48%.[79] However more recently, repair with satisfactory outcome has been reported in single case reports and some modest series. Almost two decades ago, Mistrot and his colleagues reported the outcomes for 8 patients with either congenital absence or severe hypoplasia of one pulmonary artery.[262] Of these 8 patients 3 had congenital absence of the left pulmonary artery and 5 had an atrophic or occluded left pulmonary artery from a previous shunt. All 8 survived the reparative operation, but in none of the 5 patients with acquired loss of the left pulmonary artery could it be rehabilitated.[262] Mistrot and his colleagues attributed the excellent outcome in these 8 patients to the use of a valved conduit, preventing pulmonary regurgitation should the pulmonary vascular resistance be elevated after repair into the solitary lung.[262] More recently Zhang and colleagues reported a series of 24 patients, with tetralogy of Fallot with congenital unilateral absence of a pulmonary artery, who underwent repair.[266] These 24 patients accounted for nearly 1% of patients with tetralogy of Fallot (total cohort 2511) repaired in the same institution from May 1966 to February 1995. In 20 patients the left pulmonary artery was absent and in 4, the right. Two patients (8.3%) died within 2 hours of the operation, and both deaths were attributed to left ventricular hypoplasia, with preoperative left ventricular volume index (LVEDVI) of 23.5 mL/m^2 and 25 mL/m^2. Eight patients treated prior to 1983 were repaired with a homograft valved conduit, and of the 16 patients treated after 1984, only 1 with an anomalous coronary artery received a conduit. The others were repaired with a transannular patch with a monocusp, this being the surgical approach now advocated by this group.[266]

Tetralogy of Fallot with origin of pulmonary artery from ascending aorta

Tetralogy of Fallot with origin of one pulmonary artery, usually the left, from the ascending aorta, is also an uncommon situa-

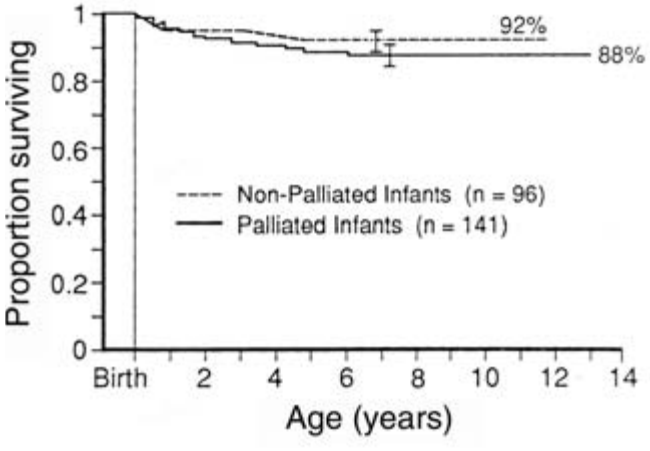
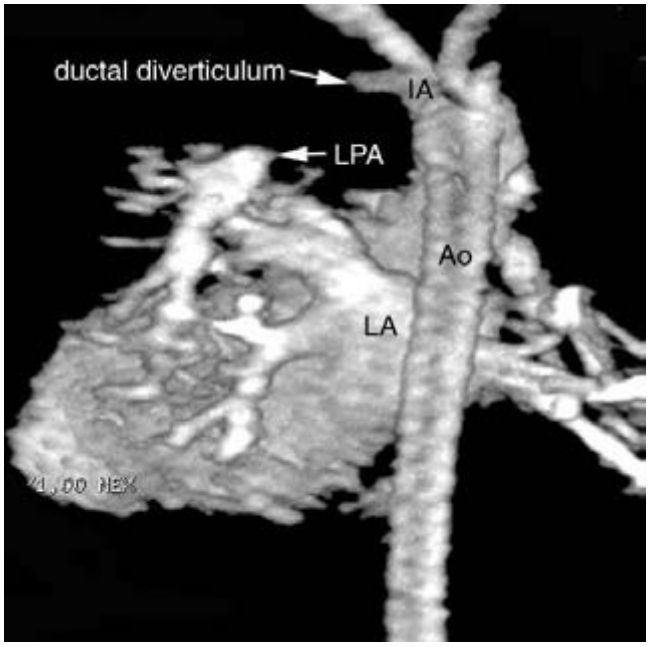


Fig. 16-10 Survival in the 141 infants with isolated tetralogy of Fallot requiring palliation is not significantly different from that seen in the 96 who never underwent palliation. (Reprinted from Vobecky *et al.*,[249] Copyright (1993), with permission from The Society of Thoracic Surgeons.)



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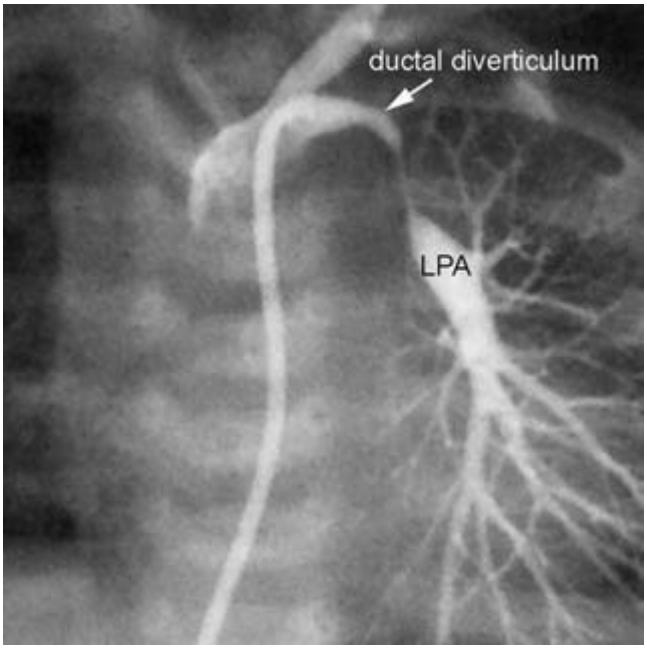

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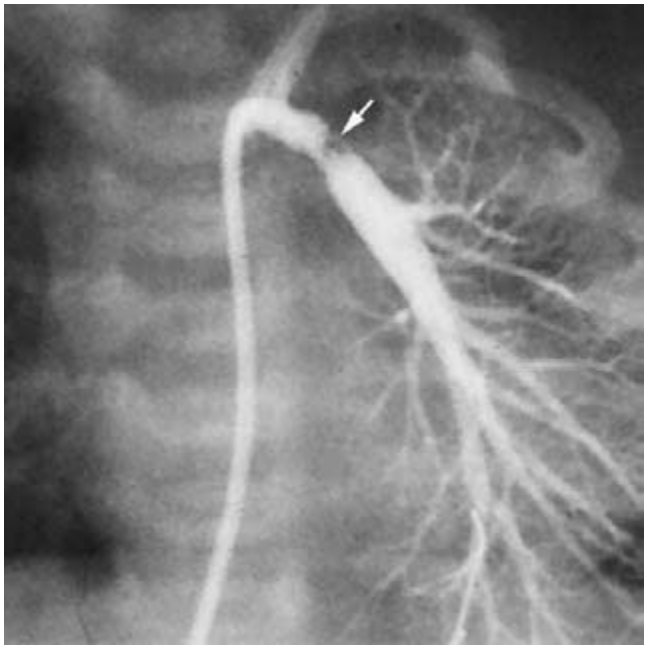


C

Fig. 16-11 Ligamentous origin of the left pulmonary artery in a patient with tetralogy of Fallot and right aortic arch. **A**. Three-dimensional contrast-enhanced MR angiogram of the thorax as seen from behind demonstrates small intraparenchymal left pulmonary artery (LPA). Note the ductal diverticulum in the base of the innominate artery (IA). **B**. The ligamentous ductus was probed. **C**. Angiogram shows that the ligamentous ductus was dilated with stent placement (arrow). Ao, descending aorta; LA, left atrium.

tion, occurring also in about 1% of patients with tetralogy of Fallot [81,83,267–275] (see also Chapter 7). This uncommon complicating anomaly may delay the typical presentation for the patient as pulmonary blood flow may be unilaterally excessive, thus allowing for maintenance of adequate arterial oxygenation. For some patients presenting late in infancy or beyond this "theoretical" advantage is outweighed by the reality of pulmonary vascular obstruction in the anomalously connected lung.[267–275] There are a number of reports of successful correction with re-anastomosis of the anomalously connected pulmonary artery. Patients surviving repair of this form of tetralogy of Fallot will require particular surveillance focused on the potential of unilateral pulmonary vascular disease and the possibility of anastomotic stenosis at the site of the re-implanted pulmonary artery.

Tetralogy of Fallot, low birth weight, and extracardiac anomalies

Data from the Baltimore–Washington Infant Study has shown that relative to controls, birth weights amongst all the infants with congenital heart disease are shifted toward the lower end of the scale, with 19% weighing < 2501 g vs. 7% for controls.[163,276] Low birth weight has been identified in about 25% of patients with tetralogy of Fallot and this can certainly impact on the outcome of palliative and reparative procedures.[276] Of 204 infants with tetralogy of Fallot enrolled in the Baltimore–Washington Infant study, the mean birth weight of this group was 2904 g, with 25.5% < 2500 g. The mean weight of the control group was 3351 g.[276] In a number of publications emanating from the University of Alabama amongst other centers and

summarized in Kirklin and Barratt-Boyes [79] low birth weight has been consistently identified as a risk factor for death at surgery for tetralogy of Fallot. Reddy and his colleagues amongst others have reported the results of complete repair of congenital heart defects in patients weighing 700 to 2500 g.[277,278] Clearly the risk of repair for the very low birth-weight baby is somewhat higher for the same condition in a baby whose weight is more appropriate.[277] In the report from Reddy and his colleagues, 20 patients had either tetralogy of Fallot or tetralogy with pulmonary atresia with 2 deaths in this group.[277]

Many studies have identified those noncardiac anomalies associated with tetralogy of Fallot.[37,79,163] The New England Regional Infant Cardiac Program enrolled 166 patients with tetralogy of Fallot and 46 with associated pulmonary atresia.[37] Sixty-six (31%) had associated extracardiac anomalies, and 26 (12%) were considered severe.[37] Francannet and colleagues studied 3 serious cardiac defects between five centers.[42] From a cohort of 1 740 159 live births, 295 patients were identified with tetralogy of Fallot in isolation and 84 patients had tetralogy of Fallot and an associated extracardiac defect.[42] Patients with tetralogy of Fallot tended in this study to have more associated extracardiac malformations than patients with transposition of the great arteries or the hypoplastic left heart syndrome.

Other specific complicating anatomic features

While the anterior displacement of the infundibular septum is the "hallmark" of tetralogy of Fallot, there are some variations that should be listed:

- a restrictive ventricular septal defect[279–286]
- multiple ventricular septal defects[79]
- nonconfluent pulmonary arteries with ascending aortic origin[267–275]
- nonconfluent pulmonary arteries with distal ductal origin[259–266]
- major aortopulmonary collateral arteries[112]
- right or left ventricular hypoplasia[83,211]
- unusual coronary artery anomalies including fistulae, origin of one coronary artery from the pulmonary trunk[84–109]
- aortopulmonary fenestration[287–295]
- scimitar syndrome.[296,297]

Each large series would be faced with patients with one or more of these unusual confounding features. They may or may not have increased the risk of repair, especially in the earlier eras of surgical experience.

Long-term follow-up

There are a number of issues that require careful surveillance in the patient surviving surgical repair of tetralogy of Fallot. These include:

- survival
- freedom from re-intervention
- impact of pulmonary regurgitation and requirement for pulmonary valve replacement
- ventricular arrhythmias and sudden death
- atrial arrhythmias
- complete heart block
- ventricular function
- quality of life issues
- bacterial endocarditis.

Survival

It is apparent that the era in which and the age at which the patient underwent repair would of course influence the outcome.[297A,297B] We have already indicated that in most centers today, > 95% of patients will survive staged or primary repair of tetralogy of Fallot, and in some centers surgical mortality approaches zero. This was not always the case, and in the early days of surgical repair, mortality in some series was 40–50%, or even more.[79,194] With increasing surgical experience and the neutralization of most of the important risk factors, surgical results continued to improve. Lillehei and his colleagues have reported the outcomes of the first 106 patients to survive repair at the University of Minnesota, with follow-up of 105 patients.[195] These patients reported on in 1986 were followed until death or for up to 26–31 years (mean 23.7 years) (Fig. 16-12). Twenty-one patients died during the follow-up, with 8 of these deaths during the first 10 years, 12 between 10 and 20 years, and 1 > 20 years. The causes of death were sudden in 5, accidental in 4, heart failure in 2, reoperation in 2, suicide in 2, and miscellaneous reasons in the remainder. Of the 21 deaths, 13 were clearly cardiac related. The actuarial survivals were 92.5% at 10 years, 80% at 20 years, and 77% at 30 years. The most common cause of late death was a sudden and unexpected event in patients who apparently appeared to be doing well.[195] These events all occurred after the first decade of the operation, and again suggested an arrhythmia as the primary etiology. For this group of early survivors of complete repair, freedom from reoperation/intervention at 30 years was 91%.[195] Reoperations were not uncommon in this era with requirements to close residual ventricular septal defects, relieve residual right ventricular outflow tract obstruction, close atrial septal defects, etc. Kirklin and his colleagues reported the early and late results of 337 patients with tetralogy of Fallot operated between 1960 and 1964.[298] Hospital mortality for all patients was 15%, 11%, 11%, 10%, and 7%, respectively, for each of the years from 1960 to 1964. Kirklin and his associates had also reported on the

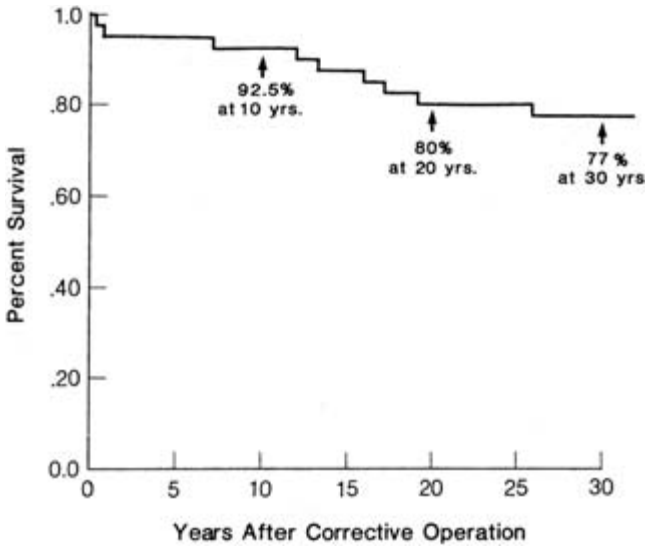


Fig. 16-12 Actuarial survival of 105 patients discharged from the hospital after repair of tetralogy of Fallot. (Reprinted from Lillehei *et al.*,[195] Copyright (1986), with permission from Lippincott Williams & Wilkins.)

mortality of patients operated from 1955 to 1959.[298] The operative mortality was 50%, 28%, 24%, 19% and 16%, respectively for these early years of tetralogy repair.[298] Four patients died late, 2 of whom died suddenly and in these 2 autopsy examination demonstrated an intact repair. One of the deaths occurred in a patient with a moderate-sized residual ventricular septal defect. Nollert and his colleagues have also reported on the long-term survival of 490 patients of a total cohort of 658 patients repaired between 1958 and 1977.[299] Operative ($n = 139$) and 1-year deaths ($n = 29$) were excluded from the analysis. Of the entire cohort, 39.7% had undergone a previous palliative operation. Actuarial 10-, 20-, 30-, and 36-year survival rates were 97%, 94%, 89%, and 85%, respectively (Fig. 16-13). Mortality increased 25 years postoperatively from 0.24% per year to 0.94% per year. The most common cause of death was a sudden unexpected event, followed by congestive heart failure. Multivariate correlations of reduced long-term survival were date of operation (before 1970), preoperative polycythemia, and use of a right ventricular outflow tract patch.[299] Patients without preoperative polycythemia and those not requiring a right ventricular outflow tract patch had a 36-year survival of 96%.[299] Data from the Mayo Clinic on long-term survival have also been provided for 163 patients surviving at least 30 days after complete repair of tetralogy of Fallot.[300] These patients had undergone repair at the Mayo Clinic between 1955 and 1960, with follow-up from 29 to 34 years. The overall 32-year actuarial survival rate was 86% as compared to an expected rate of 96% in a control population matched for age and sex (Fig. 16-14). Survival rates were also calculated for particular patient subgroups. The survival rates for those operated on < 5 years old, 5–7 years, and 8–11 years were 90%, 93% and 91%, respectively. Among patients operated at 12 years of age or older, the survival rate was 76%. Survival was also stratified by the type of palliative shunt. The performance of a palliative Blalock–Taussig shunt was not associated with reduced long-term survival, but the use of a previous Waterston or Potts shunt was associated with poorer long-term survival. Predictors of late mortality included older age at repair, previous heart failure, and a high RV/LV (≥ 0.5) postoperative systolic pressure ratio. There were 22 late deaths and the most common cause of a cardiac death was a sudden, unexpected event which occurred in 10 patients.[300] Nollert and his colleagues have also provided long-term follow-up of tetralogy of Fallot patients repaired as adults and followed for as long as 35 years.[301] Actuarial 10-, 20-, 30-, and 35-year survival rates for the 71 patients were 94%, 93%, 83%, and 72%, respectively, and not different from normal life expectancy. The most common cause of death was congestive heart failure ($n = 3$), followed by myocardial infarction ($n = 2$) and sudden death ($n = 2$). Sudden, unexpected deaths are a consistent finding in those many reports of long-term survivors of tetralogy repair[299,300] (see also section on ventricular tachycardia and sudden death). Norgaard and his colleagues have published their 20- to 37-year follow-up of patients operated between 1960 and 1977.[302] Of the 185 patients operated during this interval, 60 died in the hospital and 125 were discharged alive. Late survival was similar to other reports cited earlier, with the majority of late deaths sadly, sudden and unexpected. Rosenthal and his colleagues reported in 1984 on the 15- to 26-year prognosis after repair of 182 patients with tetralogy of Fallot operated before or during 1976.[303] They found that cumulative survival at 25 years postoperatively was 94.4%. They found that no significant relationship between survival and year of operation, age at operation, or presence of a prior shunt. They encountered 9 late deaths occurring between 6 and 23 years after operation, attributing these events to late-onset complete heart block in 2 patients, congestive heart failure in 4, suicide and accident in 1 each, and 1 unknown. Waien and colleagues reported the outcomes of 151 adult patients with repaired tetralogy of Fallot followed up for a mean of 3.2 years.[304] They entered follow-up at a mean age of 27.5 years, at a mean of 14 years after repair. This study now more than a decade old showed that overall late mortality was very low at 0.009 death/patient-year. Of the 4 patients who died during follow-up, only 2 can be attributed to congenital heart disease, and neither of these 2 deaths was sudden and unexpected. Exercise capacity assessed by serial exercise stress testing remained stable over the course of the admittedly small follow-up period. The presence of exercise-induced arrhythmia steadily decreased. One of the interesting findings of this study was that radionuclide angiography demonstrated a significant improvement in exercise right ventricular ejection fraction over time. The same patients demonstrated a progressive decrease in resting and exercise left ventricular function, although the left

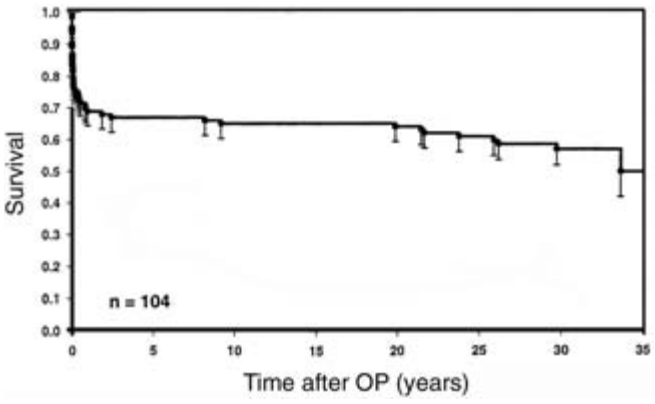


Fig. 16-13 Actuarial survival curve after repair of tetralogy of Fallot. The first, steep phase of the survival curve lasts *c.* 1 year. Each step in the curve denotes an event, and at each event, the standard error is indicated by vertical bars. Op, operation. (Reprinted from Nollert *et al.*,[299] Copyright (1997), with permission from The American College of Cardiology Foundation.)

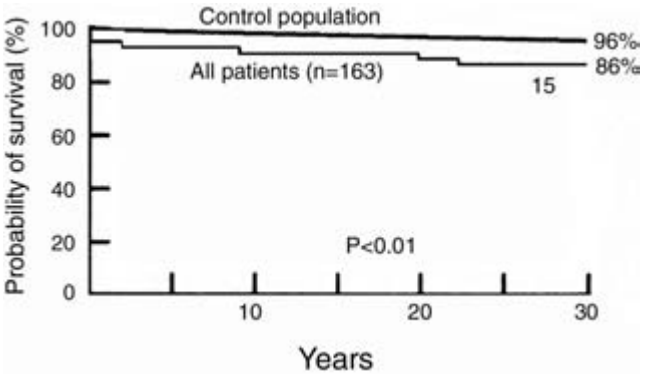


Fig. 16-14 Long-term survival of patients undergoing complete repair of tetralogy of Fallot surviving the immediate postoperative period. (Reprinted from Murphy *et al.*,[300] Copyright (1993), with permission from Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

ventricular ejection fraction still remained within the normal for their laboratory.[304] Bacha and his colleagues from the Children's Hospital in Boston have reported the long-term results after early primary repair of tetralogy of Fallot.[305] From January 1972 to December 1977, 57 patients < 2 years of age (median, 8 months) underwent primary repair with 8 early deaths and 1 death 2 years after repair [305] (Fig. 16-15). Freedom from re-intervention was 93% at 5 years and 79% at 20 years. This group did not find any difference in the survival or freedom from re-intervention between those with and without a transannular patch. Walsh and his colleagues extended these observations about late results in 220 infants operated between 1973 and 1985 at a mean age of 8 months.[306] Some of the patients had pulmonary atresia (see also Chapter 18). There were 17 early deaths (7.7%) in this experience. The mortality for uncomplicated tetralogy was 5%, and for complicated tetralogy 8%. The authors state that 89% of patients had some degree of pulmonary valve incompetence postoperatively.[306] Reoperation or catheter-based intervention was required in 17% of the survivors. Ninety-one per cent developed complete right bundle branch block; 6% right bundle branch block and left anterior hemiblock; but no patient sustained second or third degree AV block. Three late deaths occurred, but none was attributed to arrhythmia. This experience is clearly unusual in terms of the apparent absence of late sudden cardiac deaths. Hamada and colleagues have reported on the late survival and incidence of sudden death in 167 patients undergoing tetralogy repair by a single surgical team and followed for 27 years after a uniform surgical approach that did not include the use of an outflow tract patch.[304A] The patients were repaired at a mean age of 6 years. The 29-year actuarial survival was 86%, with 24 late deaths, 7 (4.2%) of which occurred suddenly. Three episodes of ventricular tachycardia and 2 episodes of atrial tachycardia were documented in follow-up. The survivors did not require reintervention and 89% were in New York Heart Association class I.[304A] Hokanson and Moller have also reviewed those issues that should be addressed in the long-term follow-up of adults with tetralogy of Fallot.[306A]

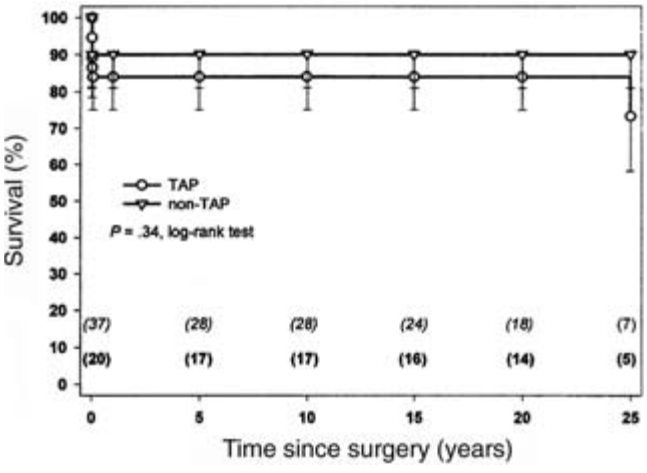


Fig. 16-15 Kaplan–Meier estimated survival according to type of repair ($P = 0.34$, log rank test). Error bars denote lower 95% confidence intervals. Numbers of patients in follow-up are shown in parentheses in italics (TAP, transannular patch) and boldface (non-TAP). (Reprinted from Bacha *et al.,*[305] Copyright (2001) Mosby Inc., with permission from Elsevier Inc.)

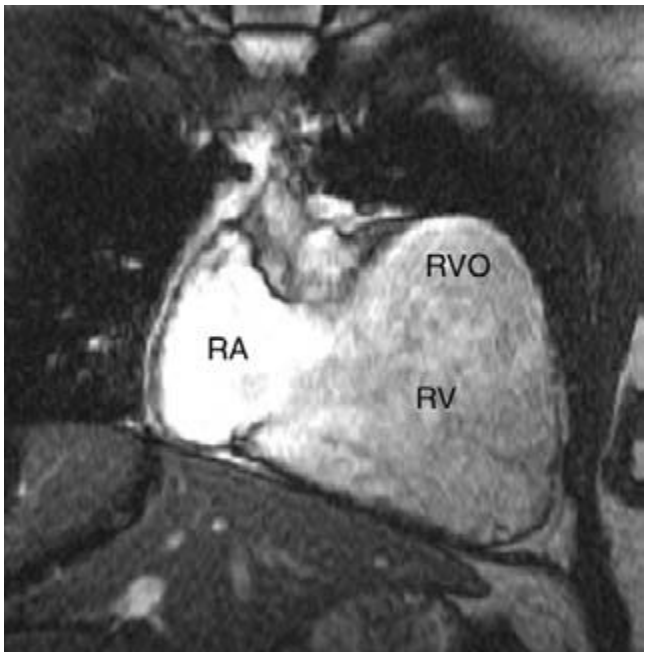
Freedom from re-intervention

Changing and evolving technologies would be anticipated to influence the incidence of certain complications.[79] For example, with the routine application of intraoperative transesophageal echocardiography, the requirement for reintervention for a residual ventricular septal defect, damage to the tricuspid or aortic valves, or important residual pressure gradients across the right ventricular outflow tract would be reduced. Recognition that juxtaductal stenosis of the involved pulmonary artery is not uncommon led to a reduced requirement for re-intervention. The advent of interventional cardiology has reduced the requirement for operative rehabilitation of stenotic pulmonary arteries, with balloon dilatation ± endovascular stenting as the treatment of choice. The requirement for re-intervention on the pulmonary arteries is certainly higher in patients with complex pulmonary atresia who have required unifocalization (see Chapter 18). Although there is less requirement for the use of a conduit in the patient with tetralogy of Fallot, those who did require a conduit will require ongoing surveillance for conduit failure (see Chapter 42). Thus there are a substantial number of residual anatomic/hemodynamic problems that must be assessed/excluded:

- ventricular septal defect
- right ventricular outflow and pulmonary arterial obstruction
- pulmonary regurgitation
- tricuspid regurgitation
- aortic regurgitation
- right ventricular dysfunction
- left ventricular dysfunction
- right ventricular outflow tract patch aneurysm
- pulmonary hypertension.

In the earlier eras of repair of tetralogy, an important residual ventricular septal defect was not uncommon.[79,194,195,298–303] This occurrence has been almost completely eliminated by the routine application of intraoperative transesophageal echocardiography. Today, most residual ventricular septal defects tend to be small and are important primarily in the context of endocarditis. The tricuspid valve can be distorted by the repair of the ventricular septal defect (see Chapter 3), but again important tricuspid regurgitation can be detected by intraoperative transesophageal echocardiography. Tricuspid regurgitation may also reflect chronic and severe volume loading of the right ventricle and the onset of tricuspid regurgitation would suggest the need for re-intervention on the right ventricular outflow tract ± tricuspid valve annuloplasty.[306B] In patients with longstanding unoperated tetralogy or tetralogy with pulmonary atresia (see also Chapter 18), progressive dilation of the aortic root can lead to aortic regurgitation, and of course infective endocarditis can also lead to hemodynamically important aortic regurgitation.[75–78,307–312] This reflects in part lack of muscular support for the aortic root and perhaps intrinsic properties of the aortic root.[306A] Niwa and colleagues found that progressive dilatation of the aortic root occurred more frequently in patients with previous longstanding dilatation of the aortic root; those with pulmonary atresia, a right aortic arch and a longer shunt-to-repair ratio.[310] Progressive aortic root dilatation was identified in 15% of the entire cohort of patients studied by this group. We are reminded by Warnes and Child[310A] that the earlier studies of Niwa and colleagues[310B] showed that underlining the tendency to aortic root dilation are histological changes of the media in the dilated aortic root of tetralogy patients resembling those

observed in patients with bicuspid aortic valves and the Marfan syndrome. Again in the editorial comment by Warnes and Child, with the tendency to earlier primary repair, this complication may be pathology from the past.[310A] Patients with tetralogy with a subpulmonary ventricular septal defect (although not strictly tetrads) may develop prolapse of the aortic valve with progressive aortic regurgitation. A lesser documented cause of postoperative aortic regurgitation is surgical injury to the aortic valve leaflet, usually the right cusp which is tethered or torn at the time of VSD repair.[79] The sequelae of such injury of the aortic valve may occur early or late as in the case of Bilfinger and colleagues.[311B] Fractional gradients at the level of the right ventricular infundibulum, pulmonary valve annulus and branch pulmonary arteries are well known,[312,313] but again most important residual obstructions can be assessed by intraoperative transesophageal echocardiography and eliminated by immediate reoperation if necessary. Kaushal and colleagues have also demonstrated that the pressure gradients observed in some patients in the right ventricular outflow tract are dynamic and that such dynamic gradients tend to decline significantly irrespective of their severity after transatrial repair of tetralogy.[314] Pulmonary arterial stenosis at the site of ductal insertion, adjacent to the site of arterioplasty or in the main pulmonary trunk just distal to transannular and main pulmonary artery patching are well known to require intervention,[313–318] but as stated earlier, operative intervention has evolved largely to catheter-based strategies. Aneurysmal bulging of a right ventricular outflow tract patch is not uncommon and in some patients progressive enlargement of the aneurysm in concert with worsening pulmonary regurgitation will lead to reoperation (Fig. 16-16).[315–318] Rarely a false aneurysm of the right ventricular outflow tract may develop following total repair and this obviously requires surgical revision.[319] Bulging of the patched right ventricular outflow tract is quite common, and while the term "aneurysm" has been used, this is not correct. The group from the Toronto Congenital Cardiac Center for Adults has also reviewed its experience with reoperation of adults with tetralogy of Fallot repaired earlier in childhood.[318A] This review focused on 60 consecutive adult patients who had undergone their primary repair at a mean age of 13.3 years and their subsequent re-repair at 33.3 years. Seventy-five per cent required reoperation because of long-



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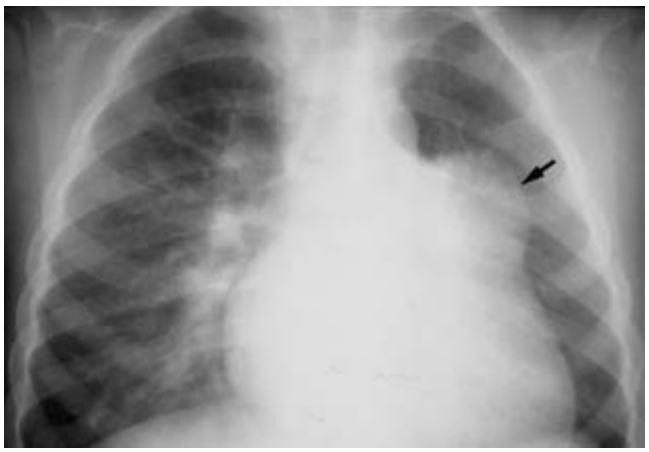

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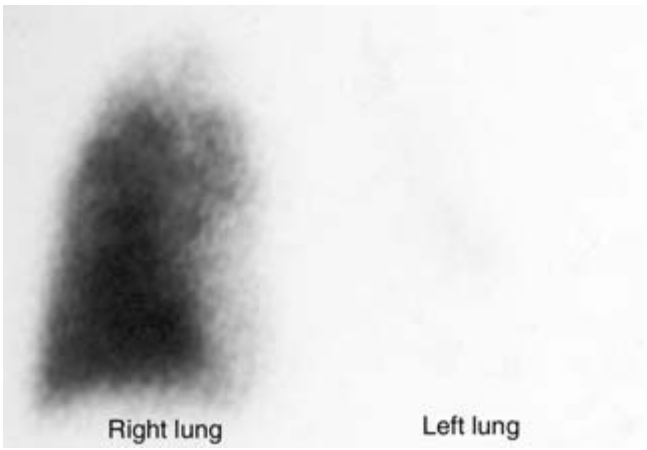

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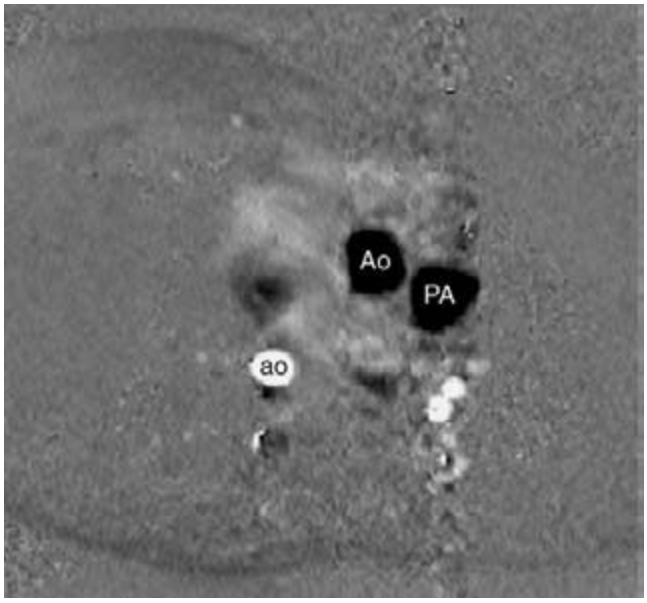
Fig. 16-16 Aneurysmal dilatation of the reconstructed right ventricular outflow tract (RVO). **A**. Cine MR image in right anterior oblique view shows an aneurysmal dilatation of the right ventricular outflow tract (RVO). **B**, **C**. Chest radiogram and radioisotope perfusion lung scan from another patient. The aneurysmal dilatation of the reconstructed right ventricular outflow tract and main pulmonary artery (arrow) is seen in the left upper heart border. There is very little perfusion to the left lung owing to severe compression of the left pulmonary artery by the aneurysmal sac. RA, right atrium; RV, right ventricle.

term complications of the right ventricular outflow tract. Severe pulmonary regurgitation or conduit failure was the most common cause in this group. A large residual ventricular septal defect was repaired in 6 patients and 3 required reoperation because of severe tricuspid regurgitation. A history of sustained ventricular tachycardia was present in 20 patients (33%) and supraventricular tachycardia occurred in 9 patients (15%). A bioprosthetic valve to reconstruct the right ventricular outflow tract was used in 42 patients. Additional procedures (n = 115) to correct other residual lesions were required in 46 patients (77%). There was no perioperative mortality. Actuarial 10-year survival is 92% ± 6%. At most recent follow-up, 93% of the patients are in New York Heart Association classification I or II.

Pulmonary regurgitation

Pulmonary regurgitation is an inevitable consequence of transannular patching and/or pulmonary valvotomy and will in some patients eventually compromise right ventricular function (Fig. 16-17).[79] Shinebourne and Anderson state that from 60% to 90% of repaired Fallot patients have some degree of pulmonary regurgitation.[320] With color flow mapping we would think the incidence of postoperative pulmonary regurgitation is likely 90% or more. One would hope that postoperative pulmonary regurgitation would be well tolerated. Unfortunately this does not seem to be the case. The data published by Shimizaki and coworkers indicate that isolated congenital pulmonary regurgitation is not well tolerated in the long term [321] (see Fig. 13A-7). They searched the literature for case reports of patients with isolated congenital pulmonary valve incompetence (admittedly an uncommon disorder) and produced an actuarial analysis for freedom from symptoms in the 72 patients identified. The actuarial freedom from symptoms was 77% at 37 years, 50% at 49 years, and 24% at 64 years. Clearly there are problems with this methodology, but the data still convey appropriate concerns about the effect of longstanding pulmonary regurgitation on right heart form and function. The outcome is likely worse in patients who underwent repair later in childhood or adolescence where chronic hypoxemia exacted its toll on right ventricular form and function. One would also anticipate that chronic pulmonary regurgitation would be less well tolerated by those patients who had undergone a large right ventriculotomy, excision of extensive muscular trabeculae and a large transannular patch. Even in the short term a monocusp valve placed in the pulmonary position does not, in our experience, prevent pulmonary insufficiency and did not seemingly improve the immediate postoperative outcome.[322] The late results of primary repair of 63 infants < 1 year of age reported by Cobanoglu and Schultz suggest an excellent outcome with 88% having good-to-excellent functional status and only 4 patients with more than moderate pulmonary regurgitation by echocardiography.[322A]

There is considerable discussion as to the indications and timing for pulmonary valve replacement,[79,320] and Shimazaki's data have been used to indicate that for many post-repair tetralogy patients, this may become a reality or necessity. One of the issues is how best to measure or quantitate pulmonary regurgitation and its impact on right ventricular function[320,323–339] (see also section on ventricular function). Indeed, right heart function has been measured in many ways, and whatever methodology is used most would accept progressive deterioration in right ventricular function as one indication for consideration of pulmonary valve replacement. Exercise performance after tetralogy repair has been found to be subnormal by many investigators, and related in large part to the severity of pulmonary regurgitation.[336–339] Other indications for pulmonary valve replacement include progressive cardiac enlargement, progressive aneurysmal dilation of an outflow tract patch, the onset and progression of tricuspid regurgitation, and the onset of important atrial or ventricular dysrhythmias.[79,320,331–346] In any of these situations it is important to exclude important pulmonary artery pathology that might worsen the severity of the pulmonary regurgitation. When important right heart or pulmonary arterial obstruction has been excluded, pulmonary valve replacement usually decreases right ventricular size and end diastolic volume, improves right ventricular ejection fraction and exercise capacity. The Mayo Clinic has reviewed its experience with late pulmonary valve replacement.[340] This review included 42 patients (16 female and 26 male) operated on between July 1, 1974, and January 1, 1998. The mean age was 22 years (range 2–65 years). The mean interval between tetralogy repair and pulmonary valve replacement was 10.8 years (range 1.6 months–33 years). Mean follow-up was 7.8 ± 6.0 years (maximum 23 years). Indications for pulmonary valve replacement included decreased exercise tolerance in 58%, right heart failure in 21%, arrhythmia in 14%, syncope in 10%, and progressive isolated right ventricular dilatation in 7%. One patient died early (2%) of multiorgan failure. There were 6 late deaths, 3 of whom were cardiac related. Survival was 95.1% ± 3.4% and 76.4% ± 8.9% at 5 and 10 years, respectively. The functional class of patients was improved significantly; preoperatively, 76% of patients were in New York Heart Association classes III–IV, and after pulmonary valve replacement, 97% of surviving patients were in classes I–II (P = 0.0001). Moderate to severe reduction in right ventricular function was noted on preoperative echocardiography in 59% and on late echocardiography in 18% (P = 0.03). Of the 5 patients who had supraventricular arrhythmias before pulmonary valve replacement, 1 had postoperative recurrence and the arrhythmia is controlled with antiarrhythmic therapy; the other 4 are in normal sinus rhythm at late follow-up. Eight patients subsequently underwent pulmonary valve re-replacement without early mortality at a mean interval of 9.0 years. Freedom from pulmonary valve re-replacement was 93.1% and 69.8% at 5 and 10 years, respectively. The only significant risk factor for re-replacement was young age at the time of the initial pulmonary valve replacement (P = 0.023). Hazekamp and his colleagues from Leiden have had a similar experience.[345] From 1993 to July 2000, 51 patients were reoperated for pulmonary insufficiency at a mean age of 25.7 ± 11.9 years. The mean age at initial repair was 6.4 ± 7.2 years. A cryopreserved pulmonary (96%) or aortic (4%) homograft was implanted in the orthotopic position with the use of cardiopulmonary bypass 19.3 ± 9.1 years (2.7–40.3 years) after initial correction. Preoperative symptoms (New York Heart Association, NYHA class), degree of PI (echo-Doppler, MRI), right ventricular dimensions (MRI) and QRS duration were compared to findings at last follow-up. The follow-up was complete and had a mean duration of 1.7 ± 1.4 years. The hospital mortality was 2%. No serious morbidity occurred. Severe pulmonary insufficiency was present preoperatively in all patients. At last follow-up echo-Doppler studies showed pulmonary insufficiency to be absent or trivial in 96% and mild in 4% of patients. In 13 patients MRI studies were performed both pre- and postoper-



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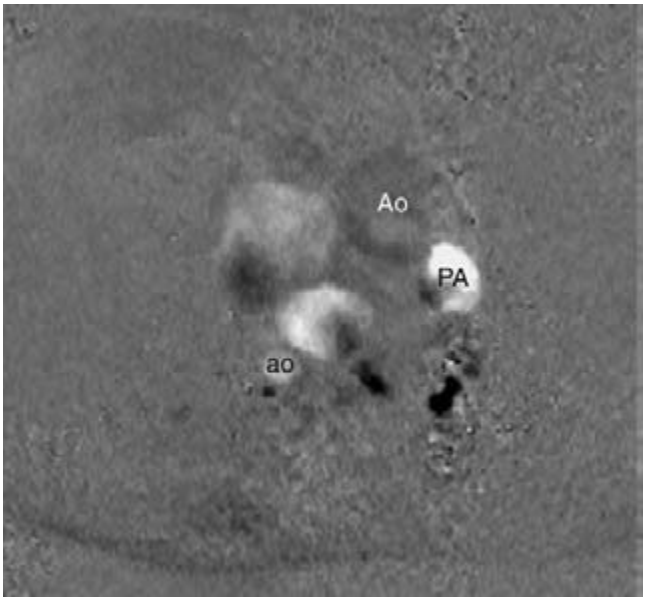

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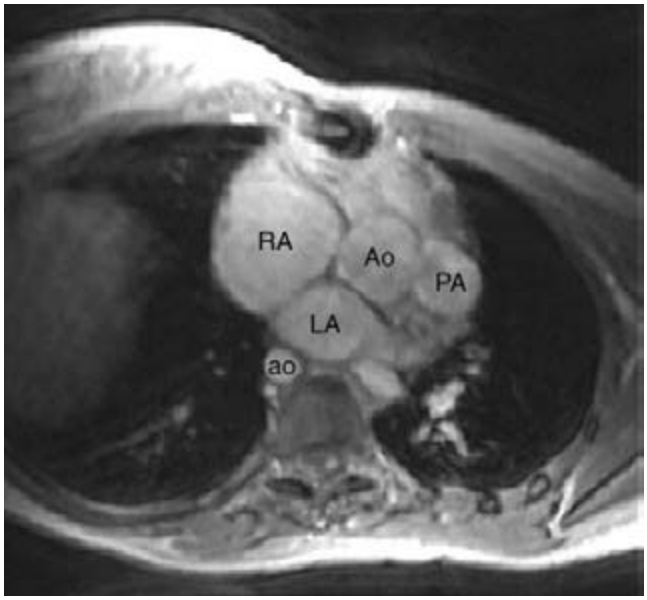

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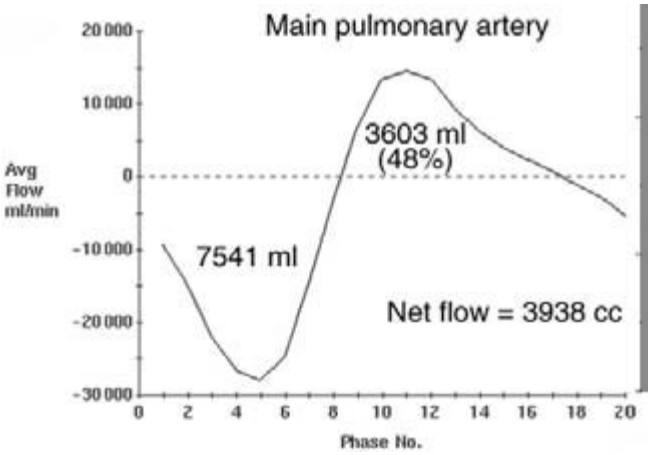

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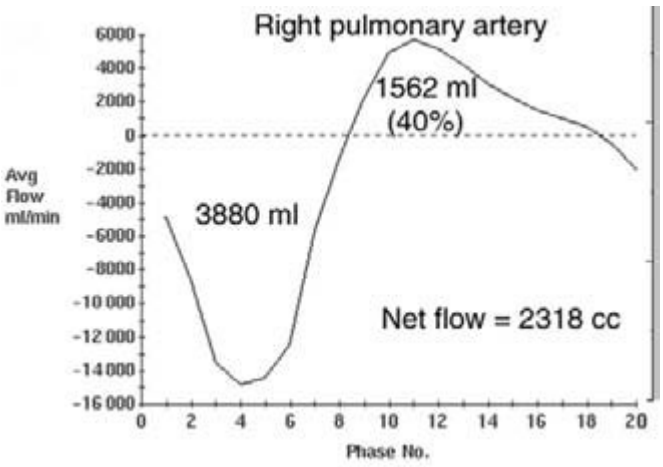

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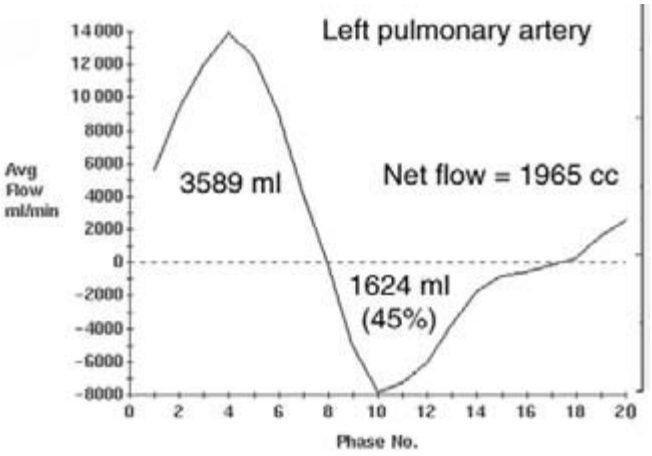

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Fig. 16-17 Pulmonary regurgitation after corrective surgery for tetralogy of Fallot shown by MR. **A**–**C**. Phase contrast (velocity-encoded) images obtained in systolic (**A**) and diastolic (**B**) phases and corresponding magnitude image (**C**). The images were obtained in a plane perpendicular to the main pulmonary artery (PA). In phase contrast images, the blood flow moving upward is coded as black, and the flow moving downward as white. Static regions are coded as gray. In systolic phase, both the ascending aorta (Ao) and the main pulmonary artery show black signals. In diastolic phase, there is no flow in the ascending aorta, while the main pulmonary artery contains white signals because of regurgitation. **D**–**F**. Time-flow curve of the flow through the main (**D**), right (**E**) and left (**F**) arteries show moderate degree of stenosis. Note that the regurgitation in the left pulmonary artery is severer than that in the right pulmonary artery. ao, descending aorta; LA, left atrium; RA, right atrium.

atively: in this group PI was reduced from a mean of 48% to 4%. After 6 months, NYHA capacity class had improved significantly from 2.3 ± 0.6 to 1.4 ± 0.5. After 1 year end-diastolic and end-systolic right ventricular volumes were reduced significantly. We have also reviewed our experience with pulmonary valve replacement late after repair of tetralogy of Fallot.[342] We identified 85 patients undergoing pulmonary valve replacement late (median 9.3 years) after repair of tetralogy (median age at repair 5.6 years). There was 1 early death and 3 late deaths, and of the late deaths 2 were likely noncardiac related. The actuarial survival was 95% ± 3% at 10 years and 87 ± 8% at 15 years (Fig. 16-18). Interestingly the age at the time of pulmonary valve replacement increased as the age of initial repair became younger. We estimated that about 1.2% of our cohort of patients who had undergone tetralogy repair had required late pulmonary valve replacement, an incidence likely to increase as this population ages even further. It is likely that the patient requiring a transannular patch for complete relief of pulmonary outflow tract obstruction will develop more important pulmonary regurgitation. The frequency of a transannular patch has varied considerably, depending on the era of surgery, surgical preference, etc. There is less evidence that the younger patient has a greater requirement for a transannular patch when compared to the older patient.[79] Redington and colleagues have provided data suggesting that the abnormalities in right ventricular systolic and diastolic function are found in most patients after repair of tetralogy of Fallot but that the reduction in ejection fraction is unrelated to pulmonary regurgitation, likely reflecting an impairment in contractile function related to intraoperative events.[329] Gatzoulis and his colleagues have studied right ventricular diastolic function 15 to 35 years after repair of tetralogy of Fallot.[347] They found that isolated right ventricular restriction was common late after tetralogy of Fallot repair, and that this both contributed to forward pulmonary arterial flow as well as shortening the duration of pulmonary regurgitation. These alterations result in less cardiomegaly and improved exercise performance.[347] It is of interest that Chaturvedi and colleagues also demonstrated acute right ventricular restrictive

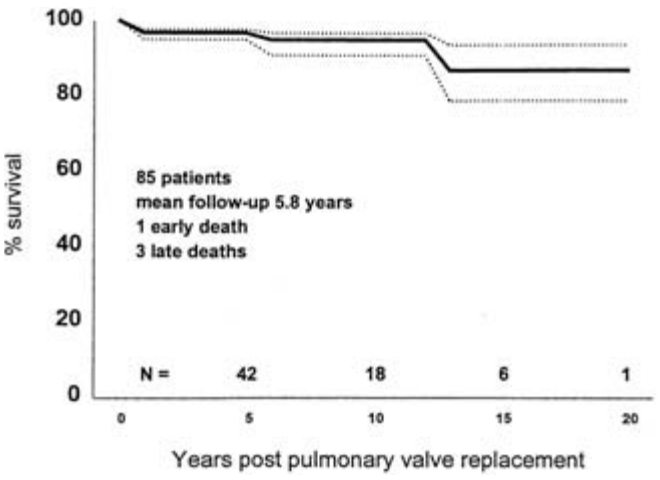

Fig. 16-18 Actuarial survival after pulmonary valve replacement in 85 patients with a mean follow-up of 5.8 years. The dotted lines indicate the 95% confidence intervals. The number of patients at risk entering each time period after valve replacement is indicated by N. (Reprinted from Yemets *et al.*,[342] Copyright (1997), with permission from The Society of Thoracic Surgeons.)

physiology after repair of tetralogy.[348] They found that this pattern of acute right ventricular restrictive physiology correlated with greater myocardial injury and postoperative myocardial stress with severe iron loading of transferrin.[348] Furthermore this prolonged hospital stay in part by virtue of reducing cardiac output. Therrien and her colleagues have provided some data indicating that pulmonary valve replacement in adults late after tetralogy surgery may not improve right ventricular function, supporting their position that in some patients operations are delayed too long.[341] They have shown, however, that pulmonary valve replacement late after tetralogy repair does reduce arrhythmia propensity, reducing the incidence of ventricular tachycardia from 22% to 9%.[343] The ability to percutaneously insert a pulmonary valve as performed by Bonhoeffer and coworkers may change our perspective as to the timing of re-intervention on these patients.[343A] Magnetic resonance imaging has been shown to be very effective in demonstrating right ventricular remodeling and improvement in function after pulmonary valve replacement.[347A] Finally, Kang and colleagues using phase-contrast cine magnetic resonance imaging have demonstrated differential regurgitation in branch pulmonary arteries, usually more from the left pulmonary artery.[347B] The etiology of this difference is uncertain.

What can we conclude about pulmonary regurgitation in the postoperative Fallot patient?

- Some degree of pulmonary regurgitation is inevitable after repair of tetralogy of Fallot.
- In the long term pulmonary regurgitation if not trivial-to-mild will not be tolerated and will impact on the form and function of the right ventricle.
- Numerous methodologies have been used to measure pulmonary regurgitation and right ventricular function.
- Important pulmonary regurgitation of long duration will cause right ventricular dilatation, impair right ventricular performance, lead to tricuspid regurgitation, and will predispose to atrial flutter/fibrillation, ventricular arrhythmias, and sudden cardiac death.
- Restrictive right ventricular diastolic physiology in some postrepair patients may delay/inhibit progressive right ventricular dilatation and dysfunction by reducing the amount of pulmonary regurgitation.
- There is a tendency to delay pulmonary valve replacement.
- The indications for pulmonary valve replacement are unclear, especially in asymptomatic patients.

Ventricular arrhythmias and sudden death

Silka and his colleagues write that the risk of late sudden death for patients surviving operation for common congenital heart defects is 25 to 100 times greater than an age-matched control population.[349] In their review, they found the incidence of sudden cardiac death in tetralogy of Fallot to be about 1.5 per 1000 patient-years.[349] For comparison, the incidence of sudden cardiac death in complete transposition was 4.9 per 1000 patient-years, and for aortic stenosis 5.4 per 1000 patient-years. There are now considerable data that ventricular arrhythmias and sudden death are irrevocably linked in the follow-up of the patient with tetralogy of Fallot, and that many factors contribute to that interface.[350–356] Ventricular arrhythmia is not just a concern for the operated patient with repaired tetralogy of Fallot.[357,358] Ventricular arrhythmia has been seen in the unrepaired, but usually older patient.[357] Deanfield and his colleagues

found that 12% of a cohort of unoperated patients had ventricular arrhythmia, with 0% in patients < 8 years to 58% in those > 16 years. In the corrected group of Fallot patients, 44% had a ventricular arrhythmia. This group found that the incidence of ventricular arrhythmia was associated with older age at repair, but not with era of surgery, duration of follow-up, or postoperative hemodynamic status.[358] It is unclear if any of the patients were repaired from the right atrial approach. The risk of sudden death late after tetralogy repair has been estimated to be as high as 5%, while some series have found no incidence of late sudden death. Kirklin and Barratt-Boyes have stated that the risk for sudden death is < 1% for children with tetralogy of Fallot operated under 5 years of age.[79] This finding is also supported by Joffe and colleagues who showed that late ventricular arrhythmia is rare after early repair of tetralogy of Fallot.[359] Jonsson and his colleagues identified 8 of 141 patients dying suddenly 6–23 years after tetralogy of Fallot repair.[358A] In this study the linearized rate of sudden death was 0.35%/year. When compared to the other 133 patients, those experiencing sudden death were older at operation, had disadvantageous postoperative hemodynamics, and several had a history of ventricular arrhythmia.[358A] The risk of sudden death is apparently higher in the patient repaired as an adult. There are a number of possible explanations for the increasing frequency of arrhythmias with increasing age of the patient. One possible explanation is the presence of increased fibrosis in the right ventricle compared to the left ventricle in the older patient as pointed out by Jones and Ferrans.[360] Also, more extensive surgery on the right ventricle and the extent of the ventriculotomy are both associated with an increase in ventricular arrhythmias, and these more extensive surgical interventions are required in older Fallot patients who have acquired more substantial hypertrophy.[79] Kobayashi and his colleagues showed that patients repaired without a ventriculotomy or with a minimal ventriculotomy had a lower rate of ventricular arrhythmia than those repaired with a substantial ventricular incision.[361] Nearly three decades ago Quattlebaum and his colleagues documented sudden death in 7 of 243 patients, 4 of these demonstrated complete right bundle branch block and three prolonged periods of ventricular ectopy.[362] Gatzoulis and colleagues studied the late follow-up of 178 adult survivors of tetralogy of Fallot repair.[363] These patients were followed for a mean duration since repair of 21.4 years. In this study of mechanoelectrical interaction they found that chronic right ventricular volume overload was related to diastolic function and this correlated with QRS prolongation.[363] They found that the risk of symptomatic arrhythmia was high in patients with marked right ventricular enlargement and QRS prolongation. Their data indicated that a QRS duration on the resting electrocardiogram of ≥ 180 ms was the most sensitive predictor of life-threatening ventricular arrhythmia.[363] This issue is not as simple as it seems. Sarubbi and colleagues have studied the accuracy and reproducibility of the measurement of QRS duration in right bundle branch block.[364] Their findings led them to conclude that the measurement of QRS duration is difficult, can be operator dependent and influenced by the presence of conduction abnormalities which reduce its accuracy and reproducibility. Kugler also urges caution in using QRS duration as a marker for predicting sudden death.[365] Yet others have also found that QRS prolongation is associated with inducible ventricular tachycardia after repair of tetralogy of Fallot.[366] In this study published by Balaji and colleagues, induced sustained monomorphic ventricular tachycardia was related to QRS duration, right ventricular dimension, H-V interval and symptoms. By multivariate analysis QRS duration was related to induced sustained monomorphic ventricular tachycardia. Furthermore, QRS duration ≥ 180 ms was 35% sensitive and 97% specific for induced sustained monomorphic ventricular tachycardia.[366] Extending their original observations that QRS prolongation is a risk marker for sustained ventricular tachycardia, Gatzoulis and coworkers have studied depolarisation–repolarization inhomogeneity after repair of tetralogy of Fallot.[367] They found that both depolarization and repolarization abnormalities were associated with post-repair ventricular tachycardia, and that increased QT, QRS and JT dispersion combined with a QRS ≥ 180 ms refined risk stratification in these patients.[367] Berul and his colleagues have found that the combination of both QRS prolongation and increased JT dispersion had very good positive and negative predictive values for sudden death.[368] These observations support the findings of Gatzoulis and coworkers that arrhythmogenesis in post-repair Fallot patients involves depolarization as well as repolarization abnormalities.[367] It is noteworthy that Hokanson and Moller studied the incidence of late sudden death in a large cohort of patients with tetralogy of Fallot operated at the University of Minnesota between 1954 and 1974.[369] The operative mortality during this period was 30%, and they defined an incidence of sudden death of 9%. Of the 288 patients followed up for this report, no patient with sudden death had documentation of a QRS duration > 180 ms. Ten patients had at least one electrocardiogram with a QRS duration > 180 ms, but none died suddenly.[369] Rather than QRS prolongation as a marker for late sudden death, Hokanson and Moller found that transient complete heart block persisting beyond the third postoperative day most strongly correlated with sudden death.[369] There are substantial clinical data that the electrophysiological and hemodynamic substrate for sudden death resembled that of sustained ventricular tachycardia with important pulmonary regurgitation being the predominant hemodynamic factor. The multicenter study reported on by Gatzoulis and his colleagues reviewed the course of 793 patients with repaired tetralogy of Fallot.[356] The mean age at repair was 8.2 years and the mean time from repair 21.1 years. Thirty-three patients developed sustained monomorphic ventricular tachycardia, 16 died suddenly and 29 had new onset of either atrial flutter or fibrillation.[356] The QRS duration and QRS rate of change between 1985 and 1995 were significantly greater in the ventricular tachycardia and sudden death groups. Older age at repair was associated with a higher risk of sudden death and atrial tachyarrhythmias. In both patients experiencing sudden death and ventricular tachycardia pulmonary regurgitation was the main hemodynamic condition and for those experiencing atrial flutter/fibrillation tricuspid regurgitation was the significant condition.[356] It is of interest that several years before the multi-institutional study of Gatzoulis and his colleagues,[356] Cullen and his colleagues concluded that nonsustained ventricular arrhythmia on ambulatory electrocardiographic recordings did not predict sudden death.[370] Others have asked about the prognostic significance of induced sustained ventricular tachycardia after repair of tetralogy of Fallot, and some have advised that a positive electrophysiologic study should be interpreted with caution as the rate of an arrhythmic event is so low.[351,351A] There is electrophysiological evidence that sustained ventricular tachycardia in this setting often results from a reentry circuit.[320,351] This reentry circuit requires areas of slow conduc-

tion. Right bundle branch block, whether central or peripheral, is common, occurring in as many as 90% of repaired Fallot patients. Fragmented electrograms indicative of focal areas of slow conduction have been recorded throughout the right ventricle as well as its inflow and outflow tracts. In addition the ventriculotomy scar, ventricular septal defect, and outflow tract patch have each been implicated as areas of potential block within the reentry circuit.[351] Daliento and his colleagues have studied the role of adrenergic nervous activity in patients after surgical repair of tetralogy of Fallot.[371] Their analysis of heart rate variation showed a reduction in vagal control and sympathetic dominance in repaired Fallot patients compared with a healthy control population. The MIBG and SPECT analyses were consistent with a reduction in nerve endings in the right and left ventricular walls, indicative as well with an inhomogeneous distribution of the adrenergic nervous system.[371] The uptake of MIBG was significantly reduced in patients at risk of ventricular tachycardia or fibrillation. Just about two decades ago, Garson and his colleagues suggested that vigorous pharmacological therapy of ventricular arrhythmias substantially reduced in their experience the risk of sudden death.[352] This experience has not been widely confirmed by others, as noted in Saul *et al.*s review.[351] Thus the literature seems to indicate, as pointed out by Gillette [372] that: (1) ventricular arrhythmias tend to increase with age following Fallot repair; (2) sustained ventricular tachycardia after Fallot repair in adult patients is found in those with outflow tract aneurysms, severe pulmonary regurgitation or both, and (3) the transatrial approach seemingly reduces the risk of life-threatening arrhythmias and right ventricular dysfunction.[373–375] One should not be reassured by those studies that did not observe any incidence of sudden or unexpected deaths during follow-up.[303,306,376] Many of the data have focused on ventricular arrhythmias developing late after Fallot repair, and the significance of these disturbances and relevance to sudden death. Giroud and colleagues have found no correlation between the presence of ventricular late potentials and the presence or complexity of spontaneous ventricular arrhythmias early after operation. Their data indicated that ventricular late potentials and spontaneous ventricular arrhythmias occurred frequently early after repair and were not predictive of sudden deaths.[377] More recently Davos and colleagues have shown global impairment of cardiac autonomic nervous activity late after repair of tetralogy of Fallot.[377A] This results in marked reduction of heart rate variability and baroflex sensitivity in these patients The reduced heart rate variabilty also related to markers of sustained ventricular tachycardia and sudden cardiac death.

Nonsustained ventricular arrhythmia has been documented in as many as 42% of patients after repair of tetralogy of Fallot, and it is problematic whether pharmacological therapy in these patients reduces the risk of sudden death.[351] Saul and his colleagues have suggested that inducible ventricular tachycardia is a poor predictor of sudden death.[351,351A] They furthermore speculate that malignant events are unlikely (but not impossible) in patients with good postoperative hemodynamics, normal ambulatory monitoring and negative electrophysiological evaluations.[351] Right ventricular wall motion abnormalities were found to be a common finding after repair of tetralogy of Fallot, and these are associated with repolarization–depolarization abnormalities.[378] Vogel and his coworkers infer that these findings support a mechanoelectrical interaction as fundamental to the pathogenesis of right ventricular disease in these patients.[378] Dietl and his colleagues have found that the right atrial approach to repair of tetralogy of Fallot significantly reduced the risk of life threatening arrhythmias without increasing the risk of supraventricular arrhythmias.[375] This approach is clearly important in the surgical management of tetralogy of Fallot in the presence of anomalous coronary arteries as shown by Brizard and his colleagues.[379] Ghai and colleagues have shown that moderate to severe left ventricular dysfunction in association with QRS prolongation > 180 ms has high positive and negative predictive value for sudden cardiac death in adults late after repair of tetralogy of Fallot.[354A] In their Kaplan–Meier analysis, moderate or severely impaired left ventricular systolic function was associated with a greater mortality ($P < 0.01$). This study is interesting because it focuses on the left ventricular substrate.

Walsh and his colleagues in 1988 presented in table form the reported incidence of sudden death and ventricular ectopic activity in published series dating from 1972 to 1985.[306] Saul and his colleagues have presented a thoughtful overview of those many factors to be considered when trying to prevent sudden death after repair of tetralogy of Fallot.[351] In 1999 they wrote there are no clinical parameters that can be used to accurately assess the risk for sudden death. They acknowledge that poor hemodynamics and ventricular ectopy on ambulatory recordings are reasonably sensitive indicators, they may still fail to identify patients at high risk. Furthermore as we stated earlier, the significance of inducible monomorphic ventricular tachycardia is uncertain.

So, what can one conclude about sudden death in the post-repair Fallot patient?

- Sudden, unexpected death is a reality with an incidence of from 0.5% to about 6%.
- This event is likely related to ventricular arrythmias and/or a history of complete heart block.
- Ventricular arrhythmias are seen in the older tetralogy patient before repair, and thus may be a consequence of the disease.
- Sudden, unexpected death is more common when the patient was repaired at an older vs. younger age.
- The right ventricle of the older patient is likely more hypertrophied, has more fibrous tissue and has required more extensive surgery, thus predisposing the patient to ventricular arrhythmias.
- Moderate or severe left ventricular dysfunction is more common in adult patients experiencing sudden cardiac death after repair of tetralogy of Fallot.
- The combination of QRS ≥ 180 ms and significant left ventricular dysfunction has high positive and negative predictive value for sudden cardiac death
- Abnormal adrenergic nervous system activity is found after tetralogy repair and may indicate patients at risk for ventricular arrhythmias.
- Postoperative disadvantageous hemodynamics including important residual right ventricular outflow tract obstruction or severe pulmonary regurgitation with their impact on the right ventricle seemingly predispose to ventricular arrhythmias.
- A QRS duration > 180 ms and rapid rate of change in QRS duration *may* be markers for patients at risk for sudden, unexpected death.
- The significance of inducible monomorphic ventricular tachycardia while worrisome is unclear.
- There is no single marker as yet absolutely predictive of late sudden death in the post-repair Fallot patient.

Atrial flutter and fibrillation

Atrial tachyarrhythmias have been well documented in the long-term follow-up of patients who have undergone repair of tetralogy of Fallot, and these contribute substantially to late morbidity and mortality.[195,246,299–302,304,320,340,341,343,356,380–382] For a number of years, however, serious atrial rhythm disturbances were seemingly underestimated or their importance not appreciated in the long-term follow-up of tetralogy patients as the focus was on serious ventricular rhythm disturbances.[380] Roos-Hesselink and colleagues in 1995 found atrial flutter/fibrillation in one-third of patients followed for a median duration of follow-up of 17.5 years, and these patients had been repaired at a mean age of 9.1 years.[381] Patients developing serious atrial rhythm disturbances were usually older at follow-up. In the multicenter study of 793 post-repair tetralogy patients published by Gatzoulis and colleagues, 29 patients had one or more episodes of sustained atrial flutter/fibrillation.[356] Their age at repair was significantly greater than that of the arrhythmia-free patients and these patients were older than those who developed ventricular tachycardia.[356] The percentage freedom from sustained ventricular tachycardia, sudden cardiac death, and atrial flutter/fibrillation at 35 years from repair was 88.1%, 91.7%, and 89.6%, respectively. Patients repaired with a transannular patch and thus free pulmonary regurgitation were more likely to develop sustained ventricular tachycardia and sudden death when compared to those who did not require a transannular patch. Pulmonary and tricuspid regurgitation were the main residual hemodynamic lesions relating to arrhythmia and sudden death in this survey.[356] Harrison and his colleagues from the Toronto Adult Center for Congenital Heart Defects performed a retrospective cohort study of 242 patients with repaired tetralogy of Fallot and identified 29 patients (prevalence of 12%) with sustained episodes of serious atrial arrhythmias.[382] Patients with repaired tetralogy of Fallot but without sustained arrhythmia ($n = 213$) constituted a comparison group. The development of atrial arrhythmias was associated with substantial morbidity including congestive heart failure, reoperation, subsequent ventricular tachycardia, stroke, and death (combined events, 20 of 29 patients; 69%). The rate of combined events (congestive heart failure, stroke, and deaths) in the 213 "arrhythmia-free" patients was 30% (64 of 213 patients). Event-free survival after repair was 18 ± 2 years for the atrial arrhythmias group and 28 ± 1 years for the arrhythmia-free group ($P < 0.001$). Patients with atrial arrhythmias were older at surgical repair (25 ± 16 vs. 10 ± 9 years, $P = 0.001$), and at most recent assessment were aged 48 ± 12 vs. 32 ± 10 years ($P = 0.001$). The atrial arrhythmias group had a higher mean right atrial volume and proportion of significant pulmonary regurgitation than matched controls. The development of atrial arrhythmias in the adult late after tetralogy of Fallot repair identifies patients at risk and is associated with older age at repair, a higher frequency of hemodynamic abnormalities, and increased morbidity. As Saul has stated atrial flutter/fibrillation in these patients post-tetralogy repair with normal atrioventricular node function may also precipitate sudden death events.[351] AV nodal function may be abnormal after tetralogy of Fallot repair as shown by Niederhauser and colleagues.[383]

Ventricular function

There is the understanding that after repair of tetralogy of Fallot, left ventricular function remains normal or nearly so, while there is the tendency for deterioration of right ventricular function. Both right and left ventricular function have been assessed in the pre- and postoperative patient with tetralogy of Fallot, using many different methodologies. As one might anticipate, the measurement of left ventricular function is technically easier to quantitate than right ventricular function. Ventricular performance is influenced by many factors including the age of the patient, the degree and duration of chronic hypoxemia to which they were exposed prior to repair, the duration and size of a systemic-to-arterial shunt if used, the adequacy of myocardial protection and thus likely the era in which repair was carried out, the size of the right ventriculotomy and the extent of muscle resection, and the duration and severity of postoperative pulmonary regurgitation. In the presence of a longstanding shunt, the left ventricle is volume loaded, and this may lead to its functional impairment. Gatzoulis and his colleagues have assessed right and left ventricular systolic function late after repair of tetralogy of Fallot using radionuclide angiography.[384] In patients with severe residual right ventricular outflow tract obstruction or regurgitation, reoperation led to improved right ventricular function. Overall in these patients repaired at a mean age of repair of 12.6 years and mean age at last follow-up of 37.7 years, the right and left ventricular systolic function remained stable at a mean interval of 5.7 years between the two radionuclide angiography studies.[384] The right ventricular ejection fraction at rest was 37.5% at the first study and 39.0% at the second, and with exercise 40.2% and 41.7%. Similarly left ventricular ejection fraction was 54.3% at rest at the first study and 55.9% at the second. At exercise, the left ventricular ejection fraction was 59.2% at the beginning of the study and 60.3% at the second study. Schamberger and Hurwitz have also studied the course of right and left ventricular function using radionuclide angiography in patients with pulmonary insufficiency after repair of tetralogy of Fallot.[385] Their data showed that long-standing pulmonary regurgitation had a deleterious effect on both right and left ventricular function. At the beginning of the study which took place about 1.2 years after repair, both right and left ventricular function were normal, decreasing to subnormal values at an average of 10.2 years after surgery. Niezen and coworkers assessed left ventricular function using MR imaging in adults with mild pulmonary insufficiency following tetralogy repair.[386,387] They found that despite mild-to-modest right ventricular enlargement, global left ventricular function was preserved, remaining in the normal range. This was not the finding of Kondo and coworkers who found that latent left ventricular dysfunction during exercise was related to pulmonary insufficiency-induced right ventricular diastolic overloading after repair of tetralogy of Fallot.[388] Abd El Rahman and colleagues have studied the relation between right ventricular enlargement, QRS duration, and right ventricular function in patients with tetralogy of Fallot and pulmonary regurgitation after surgical repair of Fallot's tetralogy.[389] They found a correlation between the right ventricular size obtained by three-dimensional echocardiography and QRS duration on the surface ECG, indicating mechanoelectrical interaction. They showed as well that the severity of pulmonary regurgitation had a negative influence on right ventricular ejection fraction and combined systolic and diastolic global function, as assessed by myocardial performance.[389] Thus, from the many reports in the literature, it is difficult to be dogmatic about the course of left ventricular systolic function in the long-term following tetralogy of Fallot repair. Certainly in some patients left ventricular function will remain normal or nearly so, many years after

repair. In other patients one might anticipate deterioration in function reflecting any number of factors, including unfavorable ventricular–ventricular interaction in the setting of postoperative pulmonary regurgitation and right ventricular outflow tract aneurysm and akinesia.[389A]

The right ventricle certainly bears the burden of tetralogy repair, at least in some respects as discussed earlier. Free pulmonary regurgitation will ultimately impact on the form and function of the right ventricle, with chronic volume loading and this may ultimately lead to tricuspid regurgitation and egregious atrial and ventricular arrhythmias. In the acute term, immediately after repair of tetralogy of Fallot, right ventricular diastolic function is characterized by a pattern of restrictive physiology.[390] This pattern as shown by Cullen and his colleagues is responsible for a slow postoperative recovery.[390] Helbing and his colleagues have also studied right ventricular diastolic function in children with pulmonary regurgitation after tetralogy repair using the technique of magnetic resonance velocity mapping.[335] They found in this group of 19 children operated on at a mean age of 1.5 years and studied at a mean age of 12 years that right ventricular diastolic function is characterized by impaired relaxation and restriction to filling.[335] This is associated with reduced exercise function. Norgard and his colleagues have studied the relationship between right ventricular diastolic function and the type of outflow tract repair.[391] The finding of restrictive diastolic right ventricular function was identified independent of the type of outflow tract repair (transannular patch vs. nontransannular patch).[391] This group also showed that restrictive right ventricular physiology is inversely related to the age at repair,[391] a finding conformed by Munkhammar and colleagues.[392] Not all studies showed that restrictive diastolic right ventricular function was associated with poor exercise performance. Gatzoulis and his colleagues showed that this pattern of right ventricular diastolic function was associated with less cardiomegaly and improved exercise performance.[347] Yet any number of investigations have found that impaired exercise capacity after repair of tetralogy of Fallot is directly related to the severity of the postoperative pulmonary regurgitation.[326,335–346] It is also of interest that transannular patching and right ventricular patching equally affect late functional status.

Impairment of exercise performance or tolerance is not uncommon after repair of tetralogy of Fallot and has been attributed to any of a number of factors including residual right ventricular outflow tract obstruction, pulmonary regurgitation, pulmonary arterial stenosis, chronotropic incompetence, and pulmonary pathology.[326,335–346,393–403] Yetman and her colleagues showed that patients with tetralogy repaired during infancy have impaired exercise capacity, and while this is multifactorial in origin, chronic pulmonary insufficiency producing a dilated and dysfunctional right ventricle is clearly important.[393] This reduced exercise tolerance is based on maximum endurance time, maximal VO2, VAT, and maximal workload.[393] Pulmonary valve replacement for severe pulmonary regurgitation after tetralogy repair has been shown to dramatically improve aerobic exercise capacity. Jonsson and his colleagues have shown that work capacity is moderately reduced 13 to 26 years after repair of tetralogy of Fallot, a finding they attributed to either right ventricular hypertension or pulmonary regurgitation.[394] Those pulmonary abnormalities limiting exercise capacity after tetralogy repair have been associated with a decreased vital capacity, a lower breathing reserve capacity and an inadequate decrease in physiologic dead space which results in an excessive ventilatory response during exercise.[394–403] Furthermore decreased lung compliance has been attributed to an increase in lung blood volume and interstitial water.[397–403] Eyskens and colleagues could not demonstrate a correlation between right ventricular function and aerobic exercise capacity.[337] Abnormal postexercise cardiovascular recovery has been examined by Ohuchi and colleagues, reflecting metabolic and autonomic recovery and surgery-related abnormal cardiac autonomic activity and impaired hemodynamics.[401A]

Complete heart block

There have been many studies of the specialized conduction system after repair of tetralogy of Fallot.[383,404–413] Some of these studies have focused on the mechanism for the development of right bundle branch block after repair of Fallot's tetralogy, and other studies on the mechanism and significance of right bundle branch block with left anterior hemiblock. Lillehei and his colleagues stated that the incidence of surgically acquired heart block occurred in about 10% of patients with congenital heart disease operated in the years 1954 and 1955.[195] These operations took place before pacemaker therapy and most before the introduction of isoproterenol in August 1955. There were no survivors in this experience in the era before pacemaker therapy (January 30, 1957) and the routine use of isoproterenol. Surgically induced complete heart block is today rarely encountered. Knowledge about the course of the specialized conduction tissue and its relationship to the ventricular septal defect (see Chapter 3) was crucial to reducing this complication. Kirklin and Barratt-Boyes stated in 1993 the incidence of surgically induced complete heart block is now very low following repair of tetralogy of Fallot.[79] They cited an incidence of complete heart block in 1.3% of patients operated at Green Lane Hospital from 1963 to 1978; in 0.9% in patients operated at the University of Alabama from 1967 to May 1986; and in 0.6% of the patients in the University of Alabama-Boston Children's Hospital experience. Rarely, late onset unprecedented complete heart block will occur many years after tetralogy repair as documented in the report of Karpawich and colleagues.[414] Transient complete heart block following cardiac catheterization as well as surgery has been well documented.[369,415]

Wolff and her colleagues reported some years ago that left anterior hemiblock and complete right bundle branch block was predictive of late onset complete heart block and sudden death.[416] That these findings and conclusions could not be reproduced should not be surprising considering the potential anatomic origins for the genesis of complete right bundle branch block.[320,404–406,409,411,413] The incidence of postoperative left anterior hemiblock is estimated to be about 6% to nearly 25%, but is more likely < 10%.[320,409] These sites include the inferior border of the ventricular septal defect, within the moderator band, or distally where peripheral fibers could be disrupted by the ventriculotomy.[320] As mentioned elsewhere in this chapter, Hokanson and Moller found that transient complete heart block persisting beyond the third postoperative day most strongly correlated with sudden death.[369] For those rare patients who do develop complete heart block after a catheter study or surgery, pacemaker therapy can be easily extended to the neonate.

Infective endocarditis

Infective endocarditis is a well-known complication occurring in the repaired Fallot.[306A,308,311,417–421] The endocarditis may

affect the aortic valve, tricuspid valve, pulmonary artery, residual ventricular septal defect, and may sometimes affect the anterior mitral leaflet in its area contiguous with the aortic valve.[308,311] Of all patients with congenital heart disease and infective endocarditis, in one series, tetralogy of Fallot accounted for 16%.[418] Morris and colleagues have reported on a 30-year incidence of infective endocarditis after surgery for a congenital heart defect.[422] They found that only 1.3% of patients with repaired tetralogy of Fallot and followed up to 30 years developed endocarditis.[422] Hokanson and Moller found 1 case per 998 patient years (8 cases in 7982 patient years), noting that 3 of these proved fatal.[306A] Patients who have undergone surgical repair of tetralogy of Fallot require life-long endocarditis prophylaxis.

Quality of life issues

Data published by Taussig and her colleagues on some of the earliest and longest survivors of the Blalock–Taussig shunt showed that these patients led active and productive lives.[178–182] Many went to college and obtained baccalaureate degrees, held responsible jobs, married, had children, etc. The majority of reports discussing long-term results indicate that the overwhelming number of repaired Fallot patients are in New York Heart Association classification I or II, lead normal and active lives, and seek medical follow-up only when symptomatic. Concerns have been raised over the years of the cognitive function of the chronically hypoxemic patient, and some will have sustained the infirmities posed by cerebrovascular strokes and/or brain abscess. These adverse events were considerably more common in the era of palliation or before and in those years when repair was routinely deferred until the patients was 5 years of age, or older. We have discussed earlier in this chapter the risk of recurrence when one of the parents has had tetralogy of Fallot. Those patients with 22q11 deletion may have a variety of difficulties impacting on schooling including learning difficulties, behaviour disorders, and speech and language deficits. Physicians caring for these patients must be aware of the risks inherent to adenoidectomy, because of the positional abnormalities of the internal carotid arteries associated with the velocardiofacial syndrome.[423–429] Internal carotid arteries of unusual size and tortuosity were found before or at the time of pharyngeal flap surgery in 3 children who had the velocardiofacial syndrome with velopharyngeal insufficiency. In 2 cases, medial displacement of the arteries prevented surgery, and in the other, hypernasality persisted because only a narrow, asymmetrical flap could be raised. Thus to prevent damage to the medially displaced internal carotid arteries, some advocate nasendoscopy or other investigations in the preoperative assessment of children for palatopharyngoplasty, although some consider these of limited value.[428,429] Aberrant brain morphology has been found in some patients with velocardiofacial syndrome. These changes are potentially related to the language and learning deficits associated with the syndrome.[430,431] Extracardiac anomalies are not uncommon in patients with tetralogy of Fallot, and the more common of these include omphalocele, tracheoesophageal fistula, VATER and CHARGE syndrome.[163,432–434] Trisomy 21 is probably the most frequent chromosomal abnormality encountered in these patients. In a population-based study of the epidemiology of tetralogy of Fallot, associated malformations and survival in western Denmark 1984–92,[432] Down syndrome, cleft palate, cleft lip and palate and combined skeletal, gastrointestinal and renal lesions (VACTERL association) were prevalent. Twenty-four infants died (26% of total), 13 (54%) of the deaths occurring during the first year of life. Mortality was significantly increased in infants with extracardiac malformations (50% vs. 19%, $P < 0.05$). Eighteen deaths (75% of total deaths) occurred before corrective surgery and 7 of these deaths were sudden. Walker and his colleagues have shown that those who have undergone surgical correction of tetralogy of Fallot have a normal quality of life, with few differences compared to controls.[434A]

Unusual complications

A variety of coronary–right ventricular or pulmonary artery fistulae have been observed to develop subsequent to repair of tetralogy of Fallot.[435–437] The most common setting for this complication is that following a right ventriculotomy, a small coronary–cameral fistula will appear. It is likely that this fistula results from trauma to a small coronary artery branch, usually infundibular,[437] although it is conceivable that reduction in right ventricular pressure from systemic to normal or near-normal could unmask a trivial congenital communication. Kadokami and colleagues have documented the spontaneous closure of a coronary–cameral fistula following repair of a patient with tetralogy of Fallot.[438] Moran and colleagues have also reported the development of a divided right ventricle occurring subsequent to tetralogy repair.[439] They suggest a minimum incidence for this occurrence of 3.1%.[439] We are not entirely persuaded that this is always a *de novo* development because anomalous muscle bundles are known to complicate the typical infundibular morphology of tetralogy of Fallot.[83,440] In this regard, Zuberbuhler in his recent review of tetralogy of Fallot suggests that anomalous right ventricle muscles contribute to right ventricular outflow muscular obstruction, a finding recognized in 11% of operated tetralogy patients in the Pittsburgh series.[441] Large aortopulmonary collateral arteries, both direct or indirect, are common to those patients with tetralogy and pulmonary atresia (see Chapter 18), and small collateral arteries and enlarged bronchial arteries are known to develop after thoracotomy for palliation of these patients. Lund has reported the development of large systemic collateral arteries originating from the right subclavian and internal mammary arteries after repair of tetralogy of Fallot.[442] The angiographic findings of this patient are similar to those seen after the construction of cavopulmonary anastomosis in the palliation of one-ventricle hearts, and "beg" the question of whether they should be interrupted before Fontan palliation (see Chapters 35 and 36).

In the cascade of unusual developments after repair of tetralogy is the development of subaortic stenosis or aortic value stenosis.[443–450] Subaortic obstruction is a very uncommon finding, both in the unoperated as well as in the repaired Fallot patient (excluding the patient with an associated type C complete form of atrioventricular septal defect). Following repair of tetralogy of Fallot, subaortic stenosis may be recognized early[448] or late.[449] Other uncommon complications include aneurysmal degeneration of the subclavian artery used in a Blalock–Taussig shunt or the formation of a pseudoaneurysm after a staged repair of tetralogy of Fallot.[451–454] This latter aneurysm has been found at the systemic end of a ligated shunt. A fatal esophageal–arterial fistula 17 years following tetralogy of Fallot repair has also been reported in a patient in whom the Blalock–Taussig shunt had been apparently ligated at the time of repair.[455] The

use of polytetrafluoroethylene tubular grafts in the construction of a modified Blalock–Taussig shunt has been complicated by seroma formation, related likely to the porous nature of the synthetic material.[456–460] Serous fluid will drain through the interstices of the fabric.[456–60] This results in excessive and prolonged chest tube drainage and/or localized seroma formation around the graft. We documented this complication in 18.8% (26 of 138) of patients.[456] The subclavian and vertebral steal has been observed following the classical Blalock–Taussig shunt, and while there is the potential for symptomatology, vascular collateralization about the base of the brain usually prevents or minimizes symptoms.[461–464] We have mentioned earlier those non-cardiac complications related to the performance of a classical Blalock–Taussig shunt. One of the more serious is limb ischemia on the side of the shunt. This ischemia may result in gangrene,[465] incipient gangrene requiring revascularization;[466] or some patients may experience claudication many years after the shunt.[467] Another manifestation, indeed a subtle one, is a weaker handgrip ipsilateral to the shunt, implicating both vascular supply and muscularization.[468] Other unusual complications, in this case iatrogenic, are those instances where the Blalock–Taussig shunt has been inadvertently connected to the pulmonary vein.[469,470] Patients who develop acute-onset shunt related occlusion may benefit from anti-thrombotic therapy delivered either systemically or by direct infusion into the blocked shunt. Stenosis of the shunt can be treated by either balloon dilatation or in some cases transcatheter-placement of an endovascular stent.[471–475] A number of catheter-delivered devises can be used to close residual classical or modified Blalock–Taussig shunts.[476–478]

In summary, the fortunes have dramatically changed for the patient with tetralogy of Fallot over the past six decades. Operative repair can usually be achieved with little mortality and morbidity, and with the trend to earlier repair, perhaps some of the complications intrinsic to repair of the older patient will be avoided. There is evidence that right ventricular hypertrophy can, to some extent, regress after repair,[479–481] but again this is less of a concern for the patient repaired in early infancy. Pulmonary regurgitation is an almost inevitable consequence of tetralogy repair, and when more than trivial or mild, this will eventually exact its toll on the form and function of the right ventricle. Sudden and unexpected cardiac death has been and to this date continues to be a tragic end for patients considered to be doing well. Many of these sad events have been identified in patients with unsatisfactory hemodynamics or in those where the right ventricle may have been compromised by late operation, extensive ventriculotomy and wide excision of hypertrophied muscle. While QRS duration and rate of QRS duration widening may be helpful in identifying patients at risk for sudden death, this issue is far from clear. While many patients with tetralogy of Fallot and indeed other complex conditions may have made the journey from "the blue and into the pink" Somerville has, in her prescient way, questioned the rosy outlook for the repaired Fallot patient.[482] Perhaps Amnon Rosenthal has best placed these issues into perspective, when he wrote "Adults with tetralogy of Fallot – repaired yes, cured no."[483]

All references can be found at the end of the book. See pp. 682–94 for Chapter 16.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom and Shi-Joon Yoo

Tetralogy of Fallot with Absent Pulmonary Valve

I (RMF) can still remember Dr Alexander S. Nadas describing the murmur of the baby with tetralogy of Fallot and absent pulmonary valve: like the sound of walking and crunching on freshly packed snow – how right he was! Indeed, the presence of a loud to-and-fro murmur in a cyanotic neonate with associated respiratory distress is usually indicative of tetralogy of Fallot with an absent pulmonary valve.[1] This infrequent variant of tetralogy of Fallot also shows malalignment of the infundibular septum producing right ventricular outflow tract obstruction with a ventricular septal defect.[2–9] As in the usual expression of tetralogy of Fallot, the pulmonary valve annulus is often hypoplastic and the aortic arch is right-sided in about 25% of the patients. Those coronary artery abnormalities well known to confound early repair of the usual form of tetralogy are also well represented in this tetralogy variant.[2–9] Similarly, the pulmonary arteries may be non-confluent with a distal ductal origin of the pulmonary artery, usually the left, or origin of the pulmonary artery, again usually the left, from the ascending aorta.[2–17] But what is so peculiar to the syndrome of tetralogy of Fallot with absent pulmonary valve is: 1. absence or rudimentary formation of the pulmonary valve leaflets; 2. aneurysmal dilatation of one or both pulmonary arteries with the propensity to bronchial compression; and 3. congenital absence of the arterial duct in those with confluent pulmonary arteries (Fig 17-1).[2–9]

Incidence and associated conditions

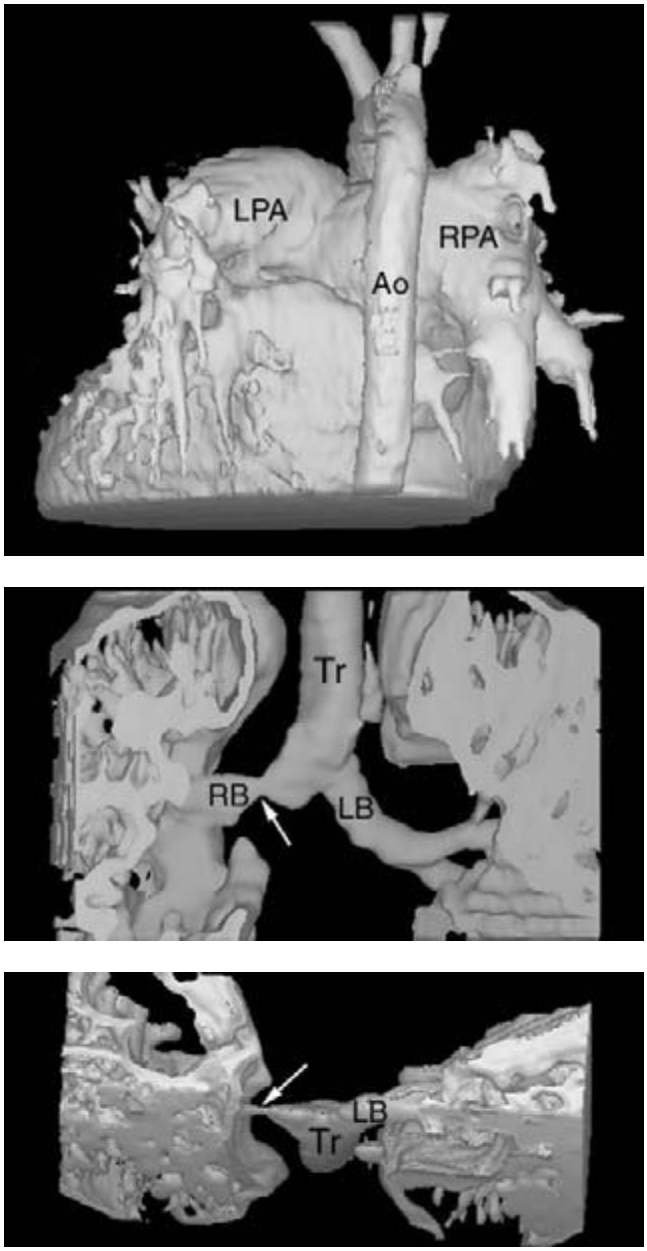
This condition is uncommon, and has been estimated to occur in 2–6% of patients with tetralogy of Fallot.[1–4,7–9] Data from the New England Regional Infant Cardiac Program suggest a prevalence of *c*. 0.0065 per 1000 live births.[18] Fyler states that at The Children's Hospital in Boston, tetralogy with absent pulmonary valve was encountered in only 22 patients from 1973 to 1987.[19]

Deletions and microdeletions of chromosome 22 have been demonstrated in patients with the DiGeorge syndrome, velocardiofacial syndrome, conotruncal anomaly face syndrome, and conotruncal anomalies.[20–33] It is not surprising that deletion within chromosome 22 is common in patients with the absent pulmonary valve syndrome. Such deletions were found in 6 of 8 patients reported by Johnson and his colleagues.[20] The frequency of this deletion was reported to be *c*. 15% in the study of Goldmuntz and her colleagues.[30,31] Because of the presence of deletions in most of the absent pulmonary valve syndrome patients examined by Johnson and his colleagues, they suggest this supports a specific genetic and embryologic mechanism involving the interaction of the neural crest and primitive aortic arches as the cause of the absent pulmonary valve syndrome.[20] Interestingly, siblings with tetralogy and absent pulmonary valve have been reported, but without the microdeletion.[34]

Morphology of the syndrome

The pulmonary valve leaflets may be virtually absent in some patients with this syndrome, while in others the pulmonary valve is represented by small vestigial remnants of dysplastic tissue.[2–8] The ventricular septal defect is usually large and non-restrictive as in the usual patient with tetralogy and anterosuperior displacement of the infundibular septum is also present. One of the recurrent themes in patients with this disorder from the newborn to the older patient is compression of the larger airways by the massively dilated pulmonary arteries (Fig. 17-1B), and the impact of a disordered airway on morbidity and mortality. Rabinovitch and her colleagues demonstrated that not only were the larger bronchi compressed by the often huge mediastinal pulmonary arteries, but that abnormally branching pulmonary arteries associated with an absent pulmonary valve resulted in compression of intrapulmonary bronchi.[35] This finding could possibly explain why some patients do not demonstrate airway improvement after "successful" surgical repair of the cardiac malformation. Others have corroborated the abnormal branching pattern with its typical tufting pattern, but have not been able to document compression of intrapulmonary bronchi.[36]

In the patient with tetralogy of Fallot with absent pulmonary valve, one branch pulmonary artery may exhibit more dilatation than the other. It has been suggested that the orientation of the right ventricular outflow tract towards the right pulmonary artery will produce greater dilatation of the right pulmonary artery, and vice-versa.[9] Not infrequently, the dilatation of both branch pulmonary arteries will be impressive. Coarctation, stenosis, or hypoplasia of one pulmonary artery may also occur in the patient with tetralogy and absent pulmonary valve.[2–4,11] The pulmonary arteries in this condition, like the usual form of tetralogy of Fallot, may be non-confluent. One pulmonary artery, usually the left, may be "isolated," originating from a left-sided arterial duct.[2–4,12] The pulmonary artery with a ductal origin does not demonstrate the aneursymal dilatation of the contralateral pulmonary artery with its right ventricular origin. Calder and her colleagues and others have also reported non-confluent pulmonary arteries in this condition, but with one pulmonary artery originating from the ascending aorta.[2–4,10,14–17] In



A

B

C

Fig. 17-1 Tetralogy of Fallot with absent pulmonary valve. **A**. Three-dimensional CT angiogram of the thorax seen from behind demonstrates aneurysmally dilated branch pulmonary arteries. **B**. Three-dimensional display of the airway as seen from front shows narrowing (arrow) of the right main bronchus (RB). **C**. Three-dimensional display of the airway as seen from below shows that narrowing is severe in the anteroposterior direction (arrow). Ao, descending aorta; LPA, left pulmonary artery; RB, right main bronchus; RPA, right pulmonary artery; Tr, trachea.

the 3 patients in Calder's report with tetralogy of Fallot and absent pulmonary valve leaflets, the left pulmonary artery originated from the ascending aorta in 2 and the right pulmonary artery originated from the ascending aorta in the third.[10] We have studied several patients in whom the left pulmonary artery had a distal ductal origin, and 2 patients with origin of the left pulmonary artery from the ascending aorta.[2–4] Aortopulmonary collaterals of variable size may coexist in the patient with tetralogy of Fallot and absent pulmonary valve.[2–4,37,38] Often the collaterals are small and indirect. Less frequently, they are large, direct and thus originating from the descending thoracic aorta entering the lung at the hilum, clearly complicating surgical management unless they are dealt with before repair.

Other associated cardiac conditions include aortic stenosis, coarctation of the aorta, complete and partial atrioventricular septal defect, total anomalous pulmonary venous connections, azygos continuation of the inferior vena cava, etc.[2–5,39–42]

Outcome analysis

There is considerable experience with the prenatal diagnosis of conotruncal anomalies,[43] and indeed tetralogy of Fallot is readily diagnosed in the fetus and many families have opted for termination of pregnancy once the fetal diagnosis is made.[43–51] Hornberger has recently commented on the outcome of 18 fetal cases of tetralogy of Fallot with absent pulmonary valve.[50] Seven families opted for termination of pregnancy; there were 4 spontaneous intrauterine deaths, 3 neonatal deaths and 2 deaths in infancy. Thus there were only 2 survivors (18%) in the continuing pregnancies. Fetal hydrops and polyhydramnios has been diagnosed in some of these patients.[51] Razavi and colleagues have just reported on the prenatal diagnosis and outcome of 20 cases of absent pulmonary valve syndrome, this group accounting for 1% of prenataly diagnosed congenital heart defects.[50A] Of this cohort there were 6 terminations of pregnancy, 3 intrauterine deaths, 5 neonatal deaths, 3 infant deaths and 3 patients who did not die. Ten of the 11 "liveborn" infants required early ventilation.

It is unusual for a patient with tetralogy of Fallot with absent pulmonary valve to present in adulthood.[52,52A] While some patients with this syndrome have a clinical course similar to those with the usual form of tetralogy of Fallot, many present as neonates or young infants with the clinical presentation precipitated by respiratory distress.[2–5] Others present in heart failure. Bronchial compression may result in profound hyperinflation, and relapsing neonatal pneumothorax may occur, further aggravating the situation (Fig. 17-2). Most patients with this condition require surgical intervention when neonates or young infants.[1–9] Why some patients do not is unclear. Donofrio and her colleagues have studied patients with this syndrome dividing them into those with and those without respiratory symptoms.[53] No difference was noted in branch pulmonary artery diameters between groups; however, the pulmonary valve/aortic valve ratio, reflecting the dimension of the narrowest pathway from the right ventricle, was larger in those with respiratory symptoms (0.74 ± 0.15 vs. 0.60 ± 0.07, $P < 0.05$). Pulmonary valve diameter correlated with main and right pulmonary artery diameters. They concluded that patients with tetralogy of Fallot with absent pulmonary valve and respiratory compromise have a greater pulmonary valve/aortic valve ratio but do not have greater dilatation of proximal branch pulmonary arteries. This suggested that the pathophysiology of the airway dysfunction is not due solely to compression of the bronchi but may be related to the blood flow dynamics in the pulmonary vessels. Moon-Grady and colleagues found no correlation between postnatal measurements of pulmonary arteries and outcome.[49A] It should be remembered that an occasional patient with absent pulmonary valve, but with an intact ventricular septum and a patent arterial duct may present with neonatal respiratory distress.[53A]

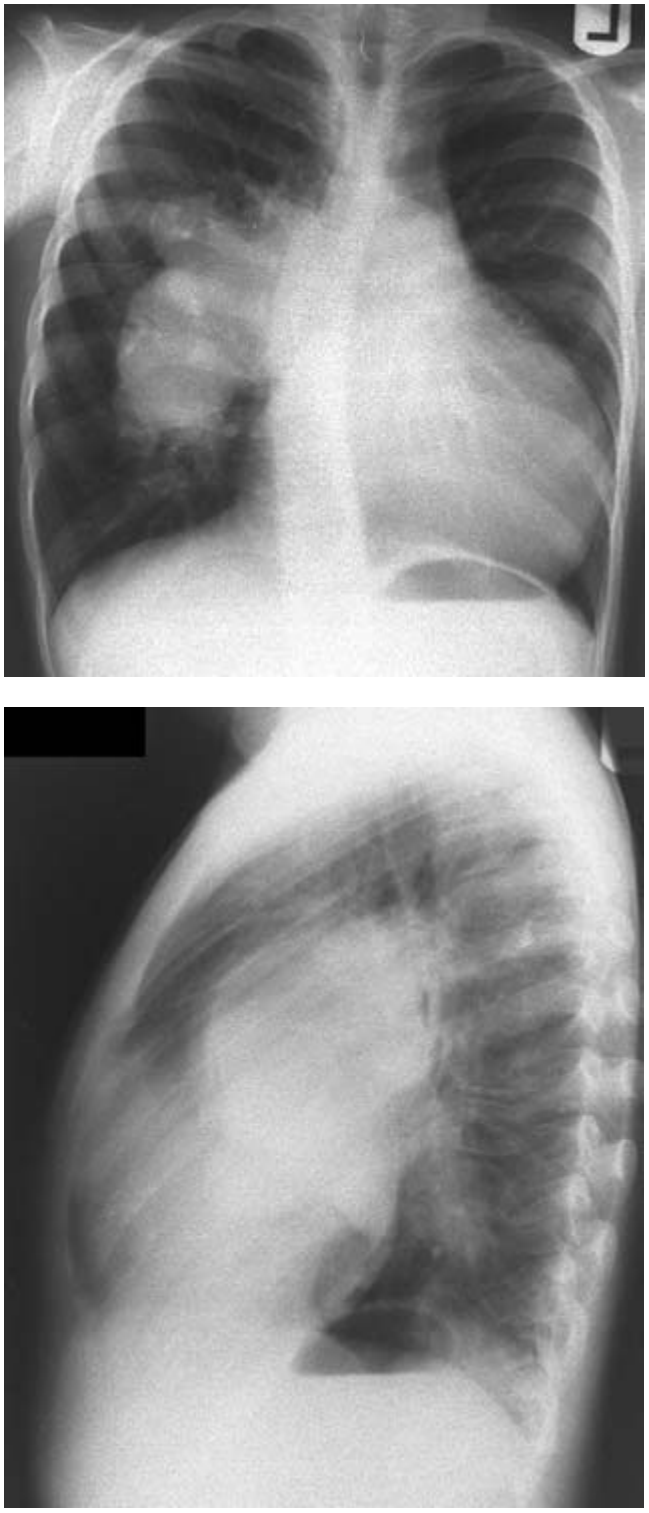


Fig. 17-2 Frontal (**A**) and lateral (**B**) chest radiograms from a patient with tetralogy of Fallot, absent pulmonary valve and respiratory distress demonstrate markedly dilated central pulmonary arteries and hyperinflation.

A conservative "wait and see" posture is likely to be unsuccessful for the sickest infant requiring ventilatory support. Heinemann and Hanley have advocated ventilating these babies while they are supine on their stomachs, hoping to alleviate some of the bronchial compression.[54] Historically, surgical management has focused primarily on dealing with the pulsatile and aneurysmally dilated pulmonary arteries, and for many years there was no consistent approach to the surgical management of these patients.[15,55–66] Because tracheobronchial cartilage matures over the first 6–9 months of life, some patients with relatively modest airway obstruction may demonstrate spontaneous improvement with time.[67–70] Some have advocated pulmonary artery banding as a maneuver to reduce the profound pulsatility of the pulmonary arteries, and others ligation of the main pulmonary trunk and construction of a systemic-to-pulmonary artery shunt.[55,56,61,62] Banding of the main pulmonary trunk was thought to reduce the striking pulsatility of the branch pulmonary arteries.[56] Litwin and his colleagues treated the severely symptomatic infant by translocating a pulmonary artery from the posterior mediastinum to an anterior position and interposing a graft in place of the artery.[61] None of these palliative maneuvers was very attractive. During the past decade or so, with increasing experience of neonatal repair for a wide range of congenitally malformed hearts, most now favor a one-stage repair. This may be combined with positioning of a homograft valve, conduit or pericardial cusp in the pulmonary position, patch closure of the ventricular septal defect, and plication of one or both pulmonary arteries.[71–81] Stenting of the major bronchi may be necessary in some because of the severe narrowing of the airway by the aneurysmal pulmonary arteries. In addition, lobar air-trapping may be so severe as to necessitate partial or total lobectomy. Corno and his colleagues have treated post-repair bronchial compression by division of the aneurysmal left pulmonary artery and its prolongation with interposition of a conduit.[74A]

The Pediatric Cardiac Care Consortium has reported the outcomes of 41 patients with tetralogy of Fallot and absent pulmonary valve.[81] Twenty of their patients (48.8%) died, and the majority of these were neonates or young infants weighing < 5 kg. McDonnell and his colleagues of the Children's Hospital of Philadelphia published in 1999 their surgical experience with this condition.[74] From January 1, 1984 to August 1998, 28 patients with have undergone complete repair (median age 11 days, range 1 day to 16 years). Thirteen patients required ventilation for respiratory failure preoperatively and extracorporeal membrane oxygenation was used in 3. Twenty-six patients underwent pulmonary artery plication (11 anterior, 15 anterior/posterior). The right ventricular outflow tract was reconstructed with a patch in 19, valved conduit in 5, and monocusp valve in 4. The early mortality was 21.4% (6/28), with 1 late death. All early deaths occurred in infants intubated preoperatively. Survival was 77% (95% confidence limit [CL], 56%, 89%) at 1 year and 72% (95% CL, 50%, 86%) at 10 years. After surgery, 3 patients underwent reoperation for persistent respiratory symptoms, which resolved after repeat plication and placement of a valved conduit. Freedom from death or reoperation was 68% (95% CL, 46%, 83%) at 1 year and 52% (95% CL, 29%, 71%) at 10 years. In a multivariable analysis, only preoperative intubation was associated with a worse outcome as shown clearly by their Kaplan–Meier estimates of freedom from death or reoperation when those requiring preoperative intubation were compared to the group not requiring ventilation ($P = 0.04$). On the basis of this experience they concluded that long-term outcome for patients with tetralogy of Fallot and absent pulmonary valve who survive the initial repair is good. They further suggest that repeat plication and pulmonary valve implantation

may improve outcome in some patients with persistent airway compression. Some have advocated translocation of the pulmonary artery anterior to the aorta and away from the tracheobronchial tree (the Lecompte maneuver (see Chapter 25B) as an adjunct to complete repair, in order to enhance airway mechanics.[67] The "Lecompte" approach with the use of a right ventricle-to-pulmonary artery conduit is the current approach used by the group at the University of California at San Francisco (A Azakie, personal communication). Choudhury and colleagues reported in 2000 their surgical experience with 46 consecutive patients including 5 infants, aged 2 months to 43 years, undergoing primary surgical correction during the past 8.5 years.[72] All the patients underwent two-dimensional echocardiography and cardiac catheterization. Nine patients had mild and 10 moderate pulmonary artery hypertension. The repair consisted of patch closure of the ventricular septal defect and reconstruction of the right ventricular outflow tract. A valve was incorporated in the pulmonary position in 19 patients. Pulmonary arterioplasty was performed only in infants. Overall hospital mortality was 4 out of 46 patients (8.6%). Two out of 5 infants died accounting for 40% mortality. Forty-two survivors were followed up from 4 to 101 months; 40 patients are in functional class I and two in class II. Actuarial survival at 8.5 years was 91%.

Seventy-six patients with tetralogy of Fallot and absent pulmonary valve, age 1 day to 41 years at repair (median age at repair 3.5 years, mean age 5.4 years) were operated on at the Toronto Hospital for Sick Children including a few adults at the Toronto Hospital's Cardiac Centre for Adults (Figs 17-3, 17-4). There were 7 early deaths and 3 late deaths, although there have been no early deaths in the past 5 years. Thirty-five patients thus far have required reoperations, 2 of whom had 2 and 1 a third reoperation. The Kaplan–Meier curve for survival is 85% ± 6.3% at 15 years and freedom from reoperation is 45% ± 7% at 10 years. The majority of the reoperations were required because of stenosis and/or regurgitation of the prosthesis in the pulmonary position. Some required secondary operations to plicate the aneurysmal pulmonary arteries and a few reintervention to address significant post-repair pulmonary arterial stenoses following aneurysm resection/plication. With most repairs utilizing some form of prosthetic valve in the pulmonary position, reoperation and reintervention are inevitable. Some have used the 99mTechnigas ventilation lung scan to assess the pulmonary obstructive lesions in the patient with postoperative respiratory failure.[72A] The more recent summaries of surgical experiences show that while surgical mortality in this group of patients, particularly in symptomatic infants, has always been substantially higher than typical tetralogy of Fallot, contemporary surgical results are improving.[72B,72C] Indeed Hew and colleagues report that since 1990 operative mortality decreased to 11% (P = 0.04) and respiratory distress was the only time-related predictor of survival in multivariate analysis (P = 0.004).[72B] Their experience with this disorder included 54 consecutive patients operated between 1960 and 1998. The median age and weight were 4 months and 4.8 kg. Respiratory distress was present in 23 patients (10 neonates, 16 required ventilation). A variety of surgical procedures was utilized, although aggressive homograft replacement of the central pulmonary arteries has been associated with improved survival in patients with tetralogy and absent pulmonary valve, especially in neonates with severe respiratory distress. Operative, 1-, 5-, and 10-year survivals were 83%, 80%, 78%, and 78%, respectively.[72B]

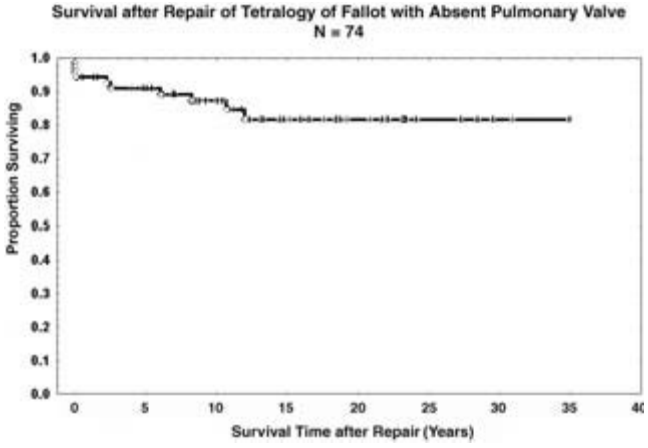


Fig. 17-3 Kaplan–Meier survival curve of Toronto Hospital for Sick Children's experience with tetralogy of Fallot and absent pulmonary valve.

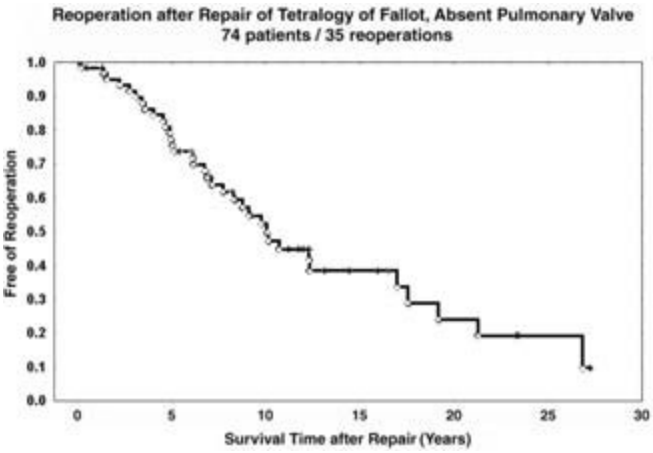


Fig. 17-4 Also from Toronto, this Kaplan–Meier curve depicts freedom from reintervention. Reintervention was necessary for plication of aneurysmal pulmonary arteries, replacement of conduit, and porcine valve in the pulmonary position, etc.

Miscellaneous complications

Other complications may also be related to the aneurysmal dilatation of the pulmonary arteries. One patient was described with mechanical compression of the left anterior descending coronary artery by the aneurysmal pulmonary trunk.[82] Massive hemoptysis has been recorded in another patient.[83] Complete opacification of one newborn's lung has been attributed to pulmonary venous obstruction by the aneurysmally dilated branch pulmonary artery.[83A]

Cardiopulmonary function following repair of tetralogy of Fallot with absent pulmonary valve has largely been undocumented. A single report exists in the literature concerning a small cohort of patients following repair of tetralogy of Fallot with absent pulmonary valve and compared to a similar cohort of patients with tetralogy of Fallot repaired with a transannular patch.[43] Heart rate, maximal oxygen consumption, oxygen consumption at anaerobic threshold, and maximal respiratory

exchange ratio were similar for the two groups. There was no significant difference for ventilation and gas exchange parameters at rest or at maximal exercise, and values for both groups were below the predicted normal for healthy subjects. Breathing reserve, however, did tend to be somewhat lower in the group with tetralogy of Fallot with absent pulmonary valve. This appeared to correlate with the presence of a higher ratio of deadspace to tidal ventilation at maximal exercise. These patients may require use of a higher minute ventilation to achieve adequate alveolar ventilation. Limited data from our own institution demonstrate the same pattern of results on exercise testing in a cohort of patients with tetralogy and absent pulmonary valve repaired beyond infancy. It is important to realize that this cohort of absent pulmonary valve patients in the literature ranged from 3 to 11 years of age at the time of repair and thus certainly do not reflect the more severe spectrum of this entity in which preoperative ventilation and repair in infancy is the rule. It remains unclear how earlier repair and possibly the more frequent use of a valved homograft might impact on the exercise performance of more recent cohorts of patients.

In our experience the survivors of repair of the infantile group often have reactive airways with some chronic obstruction and many require long-term bronchodilator therapy. We have also had the experience that in some infants requiring pulmonary artery aneurysm resection/plication that the pulmonary arteries do not grow satisfactorily (Fig. 17-5), and balloon angioplasty and/or endovascular stenting has been necessary to rehabilitate the pulmonary artery(s). For those who undergo an elective repair, the follow-up considerations are similar to the regular tetralogy postoperative patient (see Chapter 18). The postoperative management of the most severely affected neonate may require extracorporeal membrane oxygenation.

Thus what are the issues of the variant of tetralogy of Fallot with an absent pulmonary valve?

- Aneurysmal pulmonary arteries frequently result in bronchial compression and profound airway obstruction.
- Unless the pulmonary arteries are non-confluent, the arterial duct is congenitally absent.
- There is a predilection amongst patients with this syndrome for microdeletion 22q11, and for survivors of surgical intervention with the stigmata of the velocardiofacial syndrome.
- Surgical techniques have evolved from palliation to primary repair. Most repairs now utilize some prosthesis to maintain pulmonary valvular competence. There is a recent bias towards the use of a conduit. This will necessitate the requirement for reintervention. Surgical mortality in this group of patients, particularly in symptomatic infants, has always been substantially higher than typical tetralogy of Fallot, but results are improving. Pulmonary artery reduction plasty is a helpful and important surgical adjunct.
- Some patients may require endobronchial stents to maintain airway patency postoperatively.
- Pulmonary arteries requiring plication/reduction plasty must be studied for anatomic residua.

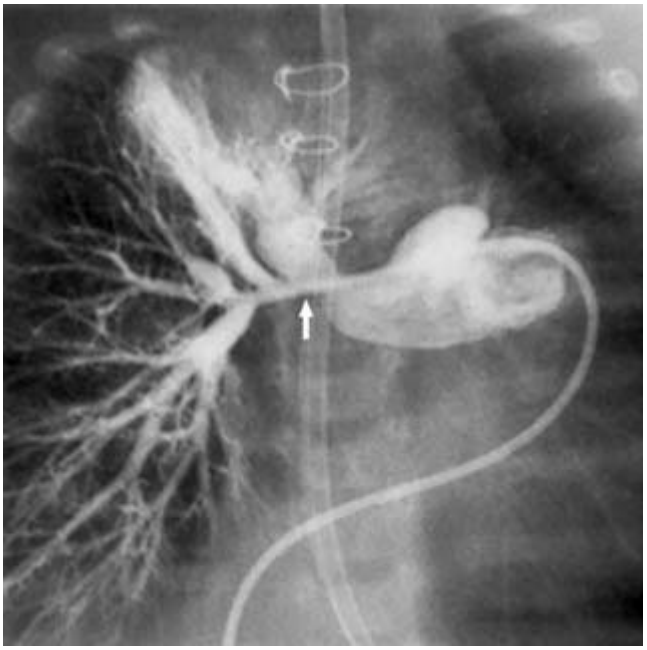


Fig. 17-5 Right pulmonary arteriogram from a patient who underwent repair of absent pulmonary valve with plication shows development of severe stenosis (arrow) of the right pulmonary artery at the hilum.

- Pulmonary function tests may remain abnormal with findings consistent with obstruction.
- Many of the late issues in follow-up of this variant are those of the usual form of tetralogy of Fallot.

Finally, an absent pulmonary valve may complicate other conditions, and in those situations massive dilatation of the pulmonary arteries and its sequelae may not dominate the clinical picture.[3,4] One of the more peculiar conditions is that of the absent pulmonary valve with defective regional myocardial development.[3,4,84–91] The tricuspid valve is abnormal in this situation, being either stenotic or more commonly imperforate as we first described in 1979. In this regard, the morphology of the tricuspid valve departs from the usual expression of tricuspid atresia, namely an absent right atrioventricular connection with sulcus tissue interposed between the floor of the right atrium and the rudimentary right ventricle (see Chapter 29). The arterial duct is usually present in newborns with this condition, unlike the tetralogy variant with absent pulmonary valve. Myocardial non-compaction is also a conspicuous feature of this combination of anomalies and the ventricular septum may appear disproportionately enlarged resembling asymmetric septal hypertrophy (see Chapter 41G). Litovsky and colleagues in 2000 reported 3 new cases of absent pulmonary valve with tricuspid atresia or severe tricuspid stenosis and reviewed the other 24 cases reported at that time.[91] The outcomes of these patients was very poor and only a few survived, either palliated with some form of shunt or with Fontan palliation.[91]

All references can be found at the end of the book. See pp. 694–7 for Chapter 17.

The Natural and Modified History of Congenital Heart Disease
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Kerstin Amark, Robert M. Freedom, and Shi-Joon Yoo

Tetralogy of Fallot with Pulmonary Atresia (Pulmonary Atresia and Ventricular Septal Defect)

The designation *tetralogy with pulmonary atresia* has been used interchangeably with *pulmonary atresia and ventricular septal defect*.[1–8] Some have eschewed the use of "tetralogy" when it is difficult to discern clinically evidence of infundibular septation.[1–3] The designation "pulmonary atresia and ventricular septal defect" is not synonymous with tetralogy and pulmonary atresia because pulmonary atresia and ventricular septal defect can be found in the patient with atrioventricular discordance, single-outlet aorta, and pulmonary atresia. This chapter will concern itself with the outcome of patients with tetralogy of Fallot with pulmonary atresia. Other designations that have historically been used to describe the morphological and clinical characteristics of some of these patients include truncus arteriosus type IV, and pseudotruncus arteriosus, but these have fallen into disfavor.[5] Patients with pulmonary atresia and atrioventricular discordance will be considered in Chapter 26A. The necessity to characterize fully the pulmonary circulation is not confined just to the patient with tetralogy and pulmonary atresia.[1–8] The same considerations apply to patients with any form of "single" ventricle malformation, tricuspid atresia, patients with right or left atrial isomerism, atrioventricular discordance, etc.

Incidence and extracardiac malformations

Data from Denmark published in 1971 indicate a prevalence for tetralogy of Fallot as 0.4 per 1000 live births.[9] A number of other studies indicate that congenital pulmonary atresia occurs in from 27% to 42% of these patients,[10,11] and using 33%, Bertranou and his colleagues give an incidence for tetralogy with pulmonary atresia of 0.013 per 1000 live births.[12] Data from the New England Regional Infant Cardiac Program provided a frequency of 0.042 per 1000 live births for tetralogy with pulmonary atresia,[13] while that of the more recently completed Baltimore–Washington Infant Study did not specifically mention pulmonary atresia with ventricular septal defect.[14] Amongst neonates presenting with cyanosis and cardiac hypoxemia, pulmonary atresia with ventricular septal defect is a frequent diagnosis, included with transposition of the great arteries and pulmonary atresia and intact ventricular septum.[8,11] The Prospective Bohemia Survival study identified 55 patients with pulmonary atresia and ventricular septal defect amongst 815 569 children born between 1980 and 1990 in Bohemia.[15] These accounted for a prevalence of 0.07 per 1000 live births and 1.09% of all heart malformations surveyed during this study.[15] In the Northern Health Region of England, Leonard and colleagues identified 60 patients with pulmonary atresia and ventricular septal defect from 601 635 live births for a prevalence of 0.100 per 1000 live births.[16]

A wide range of extracardiac malformations have been identified in the patient with pulmonary atresia and ventricular septal defect. One of the more consistent findings in any cohort of patients with conotruncal anomalies is chromosome 22q11 deletion.[17–29] This is often manifested as the velocardiofacial syndrome or conotruncal anomaly facies syndrome, CATCH-22, etc. Patients with pulmonary atresia and ventricular septal defect have been reported to have 22q11 hemizygosity in 23–40%.[17–29] In patients with tetralogy of Fallot and pulmonary atresia, additional anomalies of the aortic arch, ductus arteriosus and pulmonary arteries are more common in patients with than in those without the 22q11 deletion. Indeed, cardiovascular abnormalities have been found in about 83% with this deletion. There seems to be a predilection between those with multiple aortopulmonary collaterals and small central pulmonary arteries and chromosome 22q11 deletion.[20,21,26]

Other chromosomal abnormalities are not uncommon in pulmonary atresia and ventricular septal defect, just as in any complex cardiac defect. Trisomies 13–15, 21 and 18 have been described in 5%, 4% and 3% of cases respectively.[13] Syndromes as CHARGE have been sometimes reported, but more often there are constellations of more or less severe malformations involving other organ systems than the cardiovascular, but with no syndrome name. In the Toronto review 41% of the total population of 206 patients with pulmonary atresia and ventricular septal defect had significant extracardiac disease or malformations and 11% had at least two other organ systems involved apart from the cardiovascular.[30] Familial occurrences of pulmonary atresia and ventricular septal defect are uncommon, but have been reported in siblings and in a father and son.[31,32] The authors of these papers suggest a multifactorial pattern of inheritance.

Cardiac morphology in pulmonary atresia with ventricular septal defect

The morphology of the heart with tetralogy of Fallot with or without pulmonary atresia has been described in detail in many publications.[1–8] The essence of tetralogy of Fallot with or without pulmonary atresia is cephalad malalignment of the infundibular septum (Fig. 18-1).[33] This results in anatomic obstruction of the right ventricular outflow tract and a malalignment-type of ventricular septal defect.[33] The aorta overrides the ventricular septal defect and is rotated in a counter-clockwise direction.[34] Right ventricular hypertrophy is an inevitable consequence of this mal-

formation as is dilatation of the aortic root. This latter feature is more conspicuous in the patient with associated pulmonary atresia and dilatation of the aortic root and progresses over time. The presence or absence of infundibular septation is not predictive of the type of pulmonary circulation.[1–3,35–38] The complicating anomalies of systemic and pulmonary venous connections, the variability in origin and epicardial distribution of the coronary arteries and the types of aortic arch (left, right, cervical, double) have been dealt with elsewhere.[36,37] One complicating feature of the intracardiac anatomy that warrants comment is that situation where the ventricular septal defect is or becomes restrictive, usually from obstructing atrioventricular valve tissue or rarely from muscular obstruction.[36,37,39,40] Another uncommon complicating feature in these patients is aortic valve stenosis.[41,42] But it is the understanding of the often complex pulmonary circulation that is so critically important to the treatment and outcome of these patients.

Embryologic origin of the main, right and left pulmonary arteries, and the intrapulmonary arteries

To understand the complex nature of the pulmonary circulation in these patients it is helpful to understand the origins of the main and central intrapericardial pulmonary arteries (Fig. 18-1).[43–46] The main pulmonary trunk likely originates from the process of septation of the truncus and aortic sac.[43–50] Several hearts demonstrating normal truncal septation, but with the branch pulmonary arteries originating from the aorta have been described.[47–50] These very unusual hearts are characterized by a main pulmonary trunk originating normally above a right ventricular infundibulum and connected to the descending aorta through a patent arterial duct. No branch pulmonary arteries originate from the main pulmonary trunk. The right and left pulmonary arteries in these extremely rare cases can arise from the ascending aorta, or from the descending thoracic aorta (representing persistence of primitive intersegmental arteries). The intrapericardial right and left pulmonary arteries arise from the proximal sixth aortic arches. Indeed, the definitive branch pulmonary arteries originate from the aortic sac, often before the sixth aortic arches are completely formed.[43–45] The intrapulmonary arteries, the arteries within the lung parenchyma, are derived from the vascular plexus of the embryologic lung buds arising from the foregut.[43–45] There is also abnormal development of fourth aortic arch derivatives in the pathogenesis of tetralogy of Fallot with or without pulmonary atresia.[51]

The pulmonary circulation

The right and left pulmonary arteries are often confluent with or without a blind main pulmonary trunk, sometimes fibrous, connecting with the ventricular mass (Fig. 18-2).[1–4,6–8,34,36–38,52–95] Sometimes, the site of conjunction between the right and left pulmonary arteries is imperforate, or virtually so, presumably secondary to constriction of the arterial duct.[34,36,37,59–61,96] Confluent pulmonary arteries may be supplied by a patent arterial duct; direct aortopulmonary collaterals originating from the descending thoracic aorta; less commonly indirect aortopulmonary collateral from the head and neck branches of the aortic arch or rarely from the abdominal aortic branches; by a coronary artery–pulmonary artery connection; from an aortopulmonary fenestration; or from a fifth aortic arch.[1–4,6–8,34,36–38,52–95,97–116] The solitary arterial duct may be right- or left-sided, or bilateral arterial ducts may be present.[92] Only a few examples of a fifth aortic arch supporting the pulmonary circulation have been reported.[111–113,116] Hashimoto and his colleagues considered the possibility that their unusual aortopulmonary collateral artery was a fifth aortic arch, but they dismissed this possibility.[116] From their drawing, I think this peculiar vessel is indeed a fifth aortic arch. Rarely, bilateral ducts and non-confluent pulmonary arteries occur without intracardiac defects.[117]

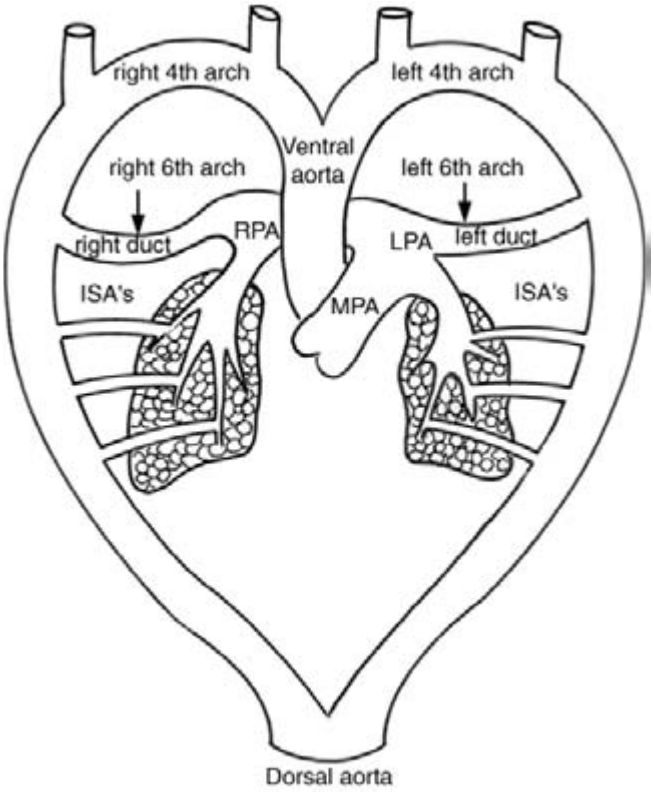


Fig. 18-1 Embryologic origins of the pulmonary arteries. The main pulmonary artery (MPA) is formed by the septation of the truncus and aortic sac. Intrapericardial right (RPA) and left (LPA) pulmonary arteries arise from the sixth aortic arches with some contribution from the aortic sac. The intraparenchymal pulmonary arteries are derived from the vascular plexuses of the lung buds. These vascular plexuses are supplied by the intersegmental arteries (ISAs) in the early embryonic period. The intersegmental arteries lose their vascular connections as the vascular plexuses are connected to the sixth aortic arches. The distal parts of the sixth aortic arches become arterial ducts.

The pulmonary arterial supply in patients with pulmonary atresia and ventricular septal defect is for the most part via the arterial duct or from collateral arteries originating directly or indirectly from the aorta or its branches. The surgical challenges in these patients are many, but much of the challenge rests with the ability to define, recruit, and rehabilitate the pulmonary arteries. However, for those patients with pulmonary atresia, diminutive pulmonary arteries, multiple large and small aortopulmonary collaterals, definition of the source or sources of blood supply to each of the bronchopulmonary segments may prove difficult.[2–4,6–8,34,36–38,71,72,88] One of the important considerations is whether the patient with a complex pulmonary circulation will be substantially improved by surgery, or whether

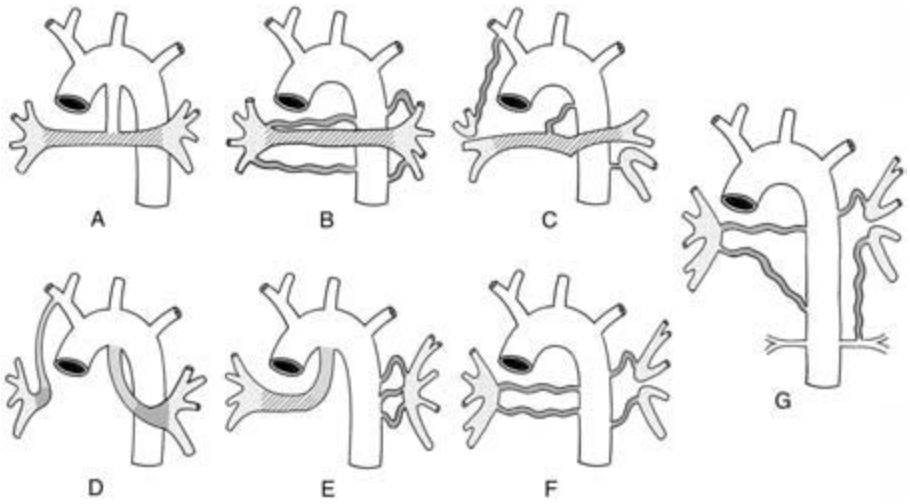


Fig. 18-2 Various patterns of pulmonary arterial anatomy and source(s) of blood supply in pulmonary atresia and ventricular septal defect. The right and left pulmonary arteries can be confluent in the mediastinum as in **A**–**C**, or nonconfluent as in **D**–**G**. The confluent pulmonary arteries can supply the entire lungs (**A**, **B**). In this situation, the source of blood supply is more commonly a patent ductus arteriosus (**A**) and less commonly multiple major aortopulmonary collateral arteries (**B**). There can be a compartmentalized segment in the presence of confluent pulmonary arteries as in **C**. In this occasion, the source of blood supply is almost always major aortopulmonary collateral arteries. The nonconfluent pulmonary arteries can be supplied by bilateral ductus arteriosus (**D**), a patent ductus arteriosus to one lung and major aortopulmonary collateral arteries to the other lung (**E**), or by multiple major aortopulmonary collateral arteries to both lungs (**F**, **G**). The collateral arteries arise usually from the aorta or its branches in the thorax (**B**, **C**, **E**, **F**) but rarely from the abdominal aorta or its branches (**G**).

such intervention should be avoided because of the potential and reality for jeopardizing the often fragile pulmonary circulation, thus further compromising the patient.[12,118]

Nonconfluent pulmonary arteries usually implies a congenital abnormality.[4,6–8,36,37,52–54,62,66,72,79,80] However, nonconfluence may be acquired following surgical palliation, either purposefully (as after a classical Glenn anastomosis), through scarring and distortion of a pulmonary artery from a systemic-to-pulmonary artery surgical anastomosis, or from ductal constriction.[59–61,96] When the pulmonary arteries are congenitally non-confluent, this indicates a completely separate origin for the right and left pulmonary arteries. Either the right or left pulmonary artery may originate from the ascending aorta; from an arterial duct; from direct or indirect aortopulmonary collaterals; or in some patients mediastinal pulmonary arteries cannot be identified by any methodology (Fig. 18-2). It is important to remember that in most cases the two blood sources (i.e. the arterial duct and aortopulmonary collateral arteries) usually do not coexist in supplying the same bronchopulmonary segment.[95] Thus in some patients nonconfluent pulmonary arteries will be supported by bilateral arterial ducts; by an arterial duct on one side and aortopulmonary collaterals to the other; or by different aortopulmonary collaterals, etc.[36,37] The collateral circulation may involve in the older patient the aortic vasa vasorum[119] and connections between the coronary arteries and bronchial arteries are well described as well.[120–123] Connections between the root of the aorta (i.e. aortopulmonary fenestration) or coronary artery and pulmonary trunk may support some or the entirety of the pulmonary blood supply.[97–110] Amin and coworkers found coronary artery-to-pulmonary artery collaterals in about 10% of their patients with pulmonary atresia and ventricular septal defect, with the majority of these involving the left coronary artery.[104] In this series of 9 patients with the coronary artery-to-pulmonary artery collaterals, no patient had evidence of myocardial ischemia.[104]

Two per cent of patients with pulmonary atresia and ventricular septal defect are found to have bilateral patent arterial ducts, and bilateral patent arterial ducts are identified in 5% of patients with either complete or corrected transposition of the great arteries.[62,80] The highest prevalence of bilateral patent arterial ducts is found in patients with asplenia syndrome (25%). It is of interest that bilateral arterial ducts may support the entirety of the pulmonary circulation but may also support the entirety of the systemic circulation in those rare patients with aortic atresia and interruption of the aortic arch[124] (see also Chapter 35).

The designation of those systemic arterial vessels considered collateral circulation to the lungs has changed commensurate with increased understanding of the origin and distribution of these vessels. For many years all collateral arteries to the lungs regardless of their sites of origin were considered bronchial arteries. This is incorrect, as many of these vessels did not have the appropriate anatomy, nor origin, nor did they follow the course of the major bronchi (Fig. 18-3).[63,123] In some patients with reasonably well-developed pulmonary arteries, one can define a group of small and tortuous systemic-to-pulmonary artery collateral arteries with a multifocal origin from the aorta and its branches (Fig. 18-4). These vessels are probably acquired and contribute to total pulmonary blood flow.[74] The other major type of systemic-to-pulmonary collateral artery are rather large arteries frequently associated with absent or hypoplastic central or mediastinal pulmonary arteries, considered congenital, and representing persistent embryonic ventral splanchnic arteries.[44,45,74,125] Rabinovitch and her colleagues have categorized those collateral vessels into three major types, both by their site of origin as well as from the way in which they connect to the lung.[4,65,126] These three types are: (1) direct aortopulmonary collateral; (2) indirect aortopulmonary collateral; (3) true bronchial arteries. Direct aortopulmonary collaterals probably represent persistence of primitive intersegmental arteries which

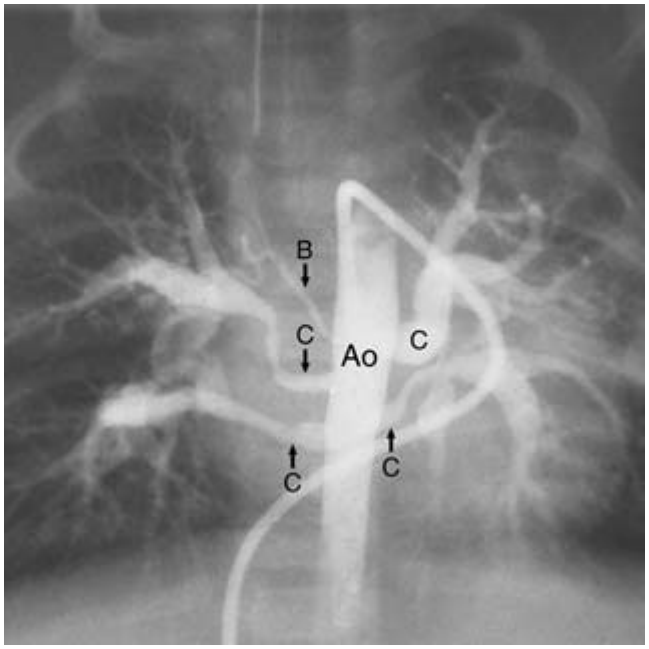


Fig. 18-3 Multiple aortopulmonary collateral arteries (C) of congenital origin. The collateral artery supplying the left upper lung is unobstructive, but the others show long segment narrowing. Notice that a mildly dilated right bronchial artery (B) is seen to follow the course of the bronchus.

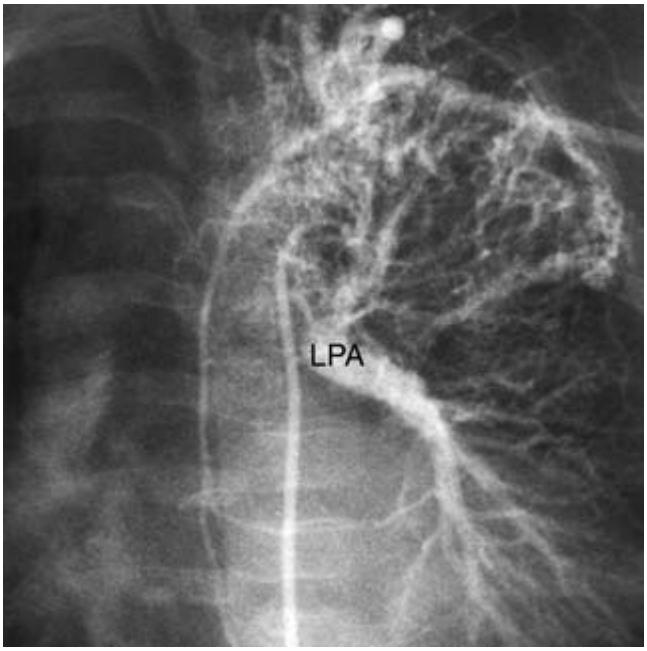


Fig. 18-4 Acquired collateral blood supply to the left upper lung. The suppliers are the normal vessels that are dilated. The anastomoses are to the far peripheral parts of the pulmonary arteries with retrograde filling of the pulmonary circulation. LPA, left pulmonary artery.

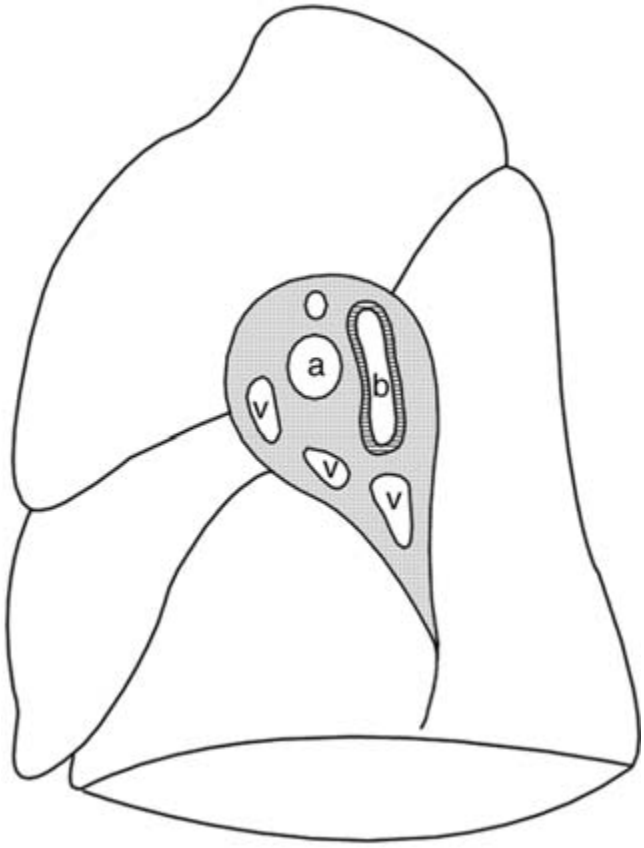
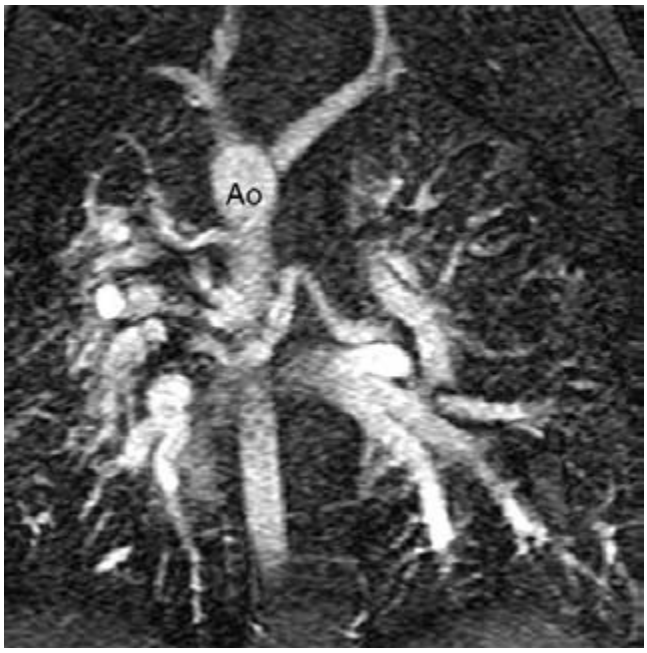


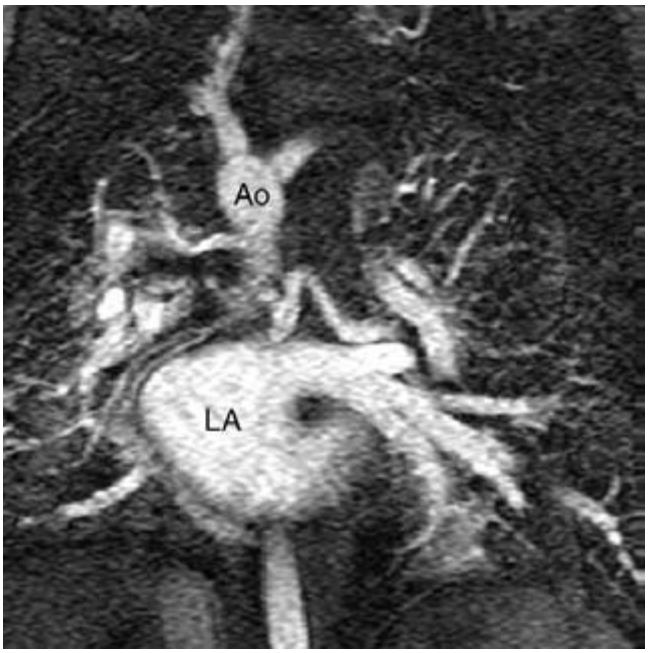
Fig. 18-5 Medial view of the right lung showing the hilum and inferior pulmonary ligament, which together form a "comma"-shaped opening in the visceral pleura. The direct and indirect major aortopulmonary collateral arteries get access to the lung through this natural opening. a, right pulmonary artery; b, right main bronchus; v, pulmonary veins.

originate from the descending thoracic aorta and which have not involuted. The direct and indirect collaterals get access to the lung through the natural opening and cleavage in the visceral pleural envelope; the hilum and inferior pulmonary ligament (Fig. 18-5). They usually number from two to six in any patient. They connect with the central or true pulmonary artery in the mediastinum or with the intrapulmonary artery at its lobar or segmental branch level. They should be differentiated from the acquired collateral arteries that have interconnections with the minute peripheral tributaries of the intrapulmonary arteries. These acquired collaterals may be either the preexisting bronchial arteries that enter the lung through the hilum or the newly formed transpleural systemic–pulmonary communications (Fig. 18-4). Rarely, indirect collateral arteries can be identified originating from or adjacent to the renal arteries as well.[36,37] The majority of direct aortopulmonary collateral arteries are narrow with stenoses, and the pathologic basis for this anatomic obstruction is related to the prominence of intimal cushions as well as the resistance to flow imposed by their length and caliber (Fig. 18-3).[36,37,90] With ongoing turbulent flow through the point of stenosis or narrowing within the collateral vessel and with increasing polycythemia and hyperviscosity, it is common for the obstruction within the aortopulmonary collateral to worsen, eventuating in virtual acquired absence of flow through that particular vessel. For this reason such collateral circulation is appropriately considered precarious. Some major direct aortopulmonary collaterals with no evidence of obstruction will perfuse its bronchopulmonary segment(s) at systemic pressure, and thus it is possible within a given lung to have some bronchopulmonary segments with and without pulmonary vascular obstructive disease (Fig. 18-3).[36,37,90] The development of fixed pulmonary vascular obstructive disease is usually a consideration beyond the neonatal period. Indeed, the combinations for source of pulmonary blood flow and differential areas

of pulmonary vascular disease are very complex, as are the sources of collateral supply, from below the diaphragm to cervical collateral arteries. Once one has identified the sources of blood flow to each lung, two questions must be clarified (Fig. 18-6). How many bronchopulmonary segments are connected to the true pulmonary arteries? And then, what are the various sources of arterial blood supply to each bronchopulmonary segment?[1–4,6–8,36–38,45,54,56,58,68,70–79,81,88,90,92,93] Those pulmonary arteries supported wholly by a patent arterial duct usually have a normal segmental supply within the lung.[34,36,37] This is far from the situation in those patients with systemic-to-pulmonary collateral arteries. Usually as pointed out by Yen Ho, these collateral arteries coexist with so-called central pulmonary arteries.[81] The collateral vessels, having their origin from the systemic circulation, course to the lungs and feed the pulmonary circulation in one of two ways. The collateral artery may continue directly into the pulmonary parenchyma and support and supply a number of bronchopulmonary segments. In other situations, the collateral runs towards the hilum of the lung, anastomosing with branches of the central pulmonary artery. In this situation, the particular collateral artery supplies the segmental area distal to its entrance to the pulmonary parenchyma, supporting all the bronchopulmonary segments fed by the central pulmonary artery. One must define for each of the bronchopulmonary segments whether it is connected to a true or central pulmonary artery, to a collateral, or both. If one identifies an aorto-pulmonary collateral supplying one or more bronchopulmonary segments, is it safe to interrupt this particular collateral as part of staged surgical or pre-surgical(i.e. catheter intervention) management? Or must that collateral be connected in some



A



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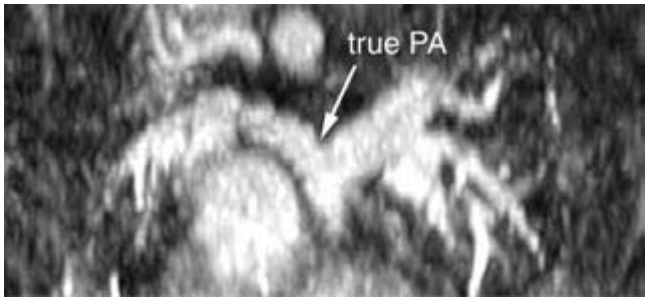

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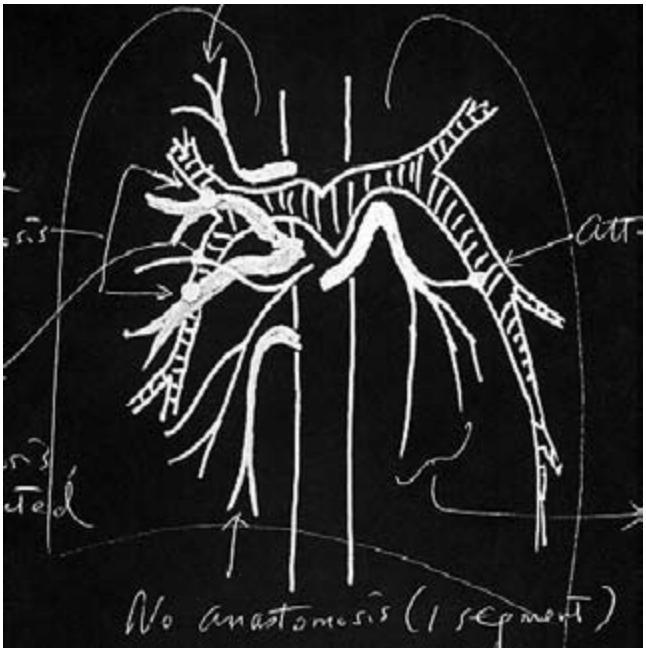


D

Fig. 18-6 An example of pulmonary vascular anatomy and sources of blood supply. **A**–**C**. Contrast-enhanced magnetic resonance angiograms showing complex vascular anatomy. **D**. Composite drawing from magnetic resonance angiograms and subsequent x-ray angiograms. The information regarding the sources of blood supply, the courses of the vessels in the mediastinum, the lung segments supplied by each collateral and vascular communications between the lung territories should be provided. Ao, aorta; LA, left atrium; PA, pulmonary artery.

way, so-called unifocalized, directly or indirectly, to the true right or left pulmonary artery?[1–4,6–8,36–38,45,54,56,58,68,70–79,81,88,90,92,93] The answer rests in the nature of the blood supply to each bronchopulmonary segment. If the specific bronchopulmonary segment has a connection to the true pulmonary artery as well as arterial supply from an aortopulmonary collateral (clearly a dually supplied segment), or are clearly connected within the lung by arterial channels to other bronchopulmonary segments which are connected to the true pulmonary arteries, then it would be prudent to interrupt the collateral. If the collateral artery is the only source of arterial supply to the given segment of lung, then interruption could lead to infarction of those segments supplied by the collateral. The impact of the appreciation of any segment that is supplied only from an aortopulmonary collateral is that this segment of lung would have to be surgically connected or unifocalized to prevent infarction. Iyer and Mee have reported their extensive experience in the repair of pulmonary atresia and ventricular septal defect and major aortopulmonary collaterals, specifically focusing on the criteria for ligation of these collateral arteries.[127] Their first criterion for ligation of a major aortopulmonary collateral was that the collateral artery unequivocally duplicated supply to a segment from a central pulmonary artery. The second criteria for ligation of a collateral was the presence of wide connections between the collateral and central pulmonary arteries. Finally, duality of supply does not necessarily mean that one source of supply may be more or less precarious than the other. The arborization anomalies of the intraparenchymal pulmonary arteries are another of the complex features of the pulmonary circulation in patients with pulmonary atresia and ventricular septal defect.[34,73,128,129] These anomalies are characterized by abnormal distribution of arterial supply to various segments of the lung and often there are stenoses within some of the intraparenchymal arteries.[34,36,37,128,129] These may be recognized by caliber changes as well as by differing density of distribution of vessels to given segments of lung when compared to a normal pattern of distribution.

The application and role of an E-type prostaglandin has been amply described in the management of the patient with pulmonary atresia and a duct-dependent pulmonary circulation.[130–131] Prostaglandin administered intravenously or orally has dramatically altered the potential for surgical intervention by preventing anatomic constriction and closure of the arterial duct in those patients whose pulmonary blood flow is in large part duct dependent and thus stabilizing the patient. There is considerable literature addressing the effect of prostaglandin on the histologic integrity of the arterial duct.[132–137] However, there is not a consensus as to those changes in the wall of the arterial duct subsequent to prostaglandin therapy, and whether these histological changes may potentially disadvantage the patient.[132–137] Silver and her colleagues from the Toronto Hospital for Sick Children[135] and Teixeira and his colleagues[136] examined the morphology of the arterial duct with special reference to prostaglandin therapy, and could not delineate specific changes attributable to its use.[135] None the less, aneurysmal change of the ductus arteriosus after prostaglandin E_1 administration for pulmonary atresia has been documented.[137] These alterations in the morphology of the arterial duct after prostaglandin administration may have some influence when one considers manipulation and stenting of the arterial duct.[138,139] One should also be aware of the effect of prostaglandin E_1 on the pulmonary circulation itself. Data from Haworth have shown that the most striking effect of prostaglandin E_1 administration was to reduce pulmonary arterial smooth muscle, with the inference that the pulmonary vascular bed would become more compliant.[140,141] There are those occasional newborn patients with pulmonary atresia who seemingly do not benefit from prostaglandin E_1 administration. In this context, there are those patients with absent ductus arteriosus and absent collateral pulmonary circulation where any effect would be on the integrity of the pulmonary vascular bed.[142,142A]

A right-sided aortic arch is identified in *c*. 20% of patients with pulmonary atresia and ventricular septal defect, similar to that in patients with tetralogy of Fallot.[1,5,36,37,51] The anatomy of the aberrant left subclavian artery in a right-sided aortic arch in a patient with tetralogy of Fallot/pulmonary atresia differs from that in persons with a normal heart. As pointed out by Velasquez and colleagues, the aberrant left subclavian artery originates directly from the aortic arch when tetralogy anatomy is present.[143] However, when the heart is normal, the aberrant left subclavian artery and arterial duct originate from a diverticulum. A double aortic arch and cervical aorta are well recognised in the patient with complex pulmonary atresia.[36,37,144] Coarctation of the aorta and interruption of the aortic arch have all been described in patients with tetralogy of Fallot, despite the usual reciprocal relationship between obstruction to pulmonary blood flow and obstruction to systemic blood flow.[144A] Such obstructive anomalies are very uncommon in the patient with tetralogy of Fallot and are even less common in the patient with pulmonary atresia. We described one of the very few cases of coarctation of the aorta in a patient with tricuspid and pulmonary atresia whose pulmonary blood flow was mediated by a fifth aortic arch.[113]

Airway compromise from a vascular ring has been described in the patient with tetralogy of Fallot, and double-aortic arch, left aortic arch, aberrant right subclavian artery, and a right-sided arterial duct, and a right aortic arch with aberrant left subclavian artery have been described as causal.[144–149] A so-called pulmonary vascular sling has also been reported in the patient with tetralogy of Fallot and severe airway compromise.[149] Other mechanisms compromising the airway in the patient with complex pulmonary atresia include aneurysmal dilatation of the ascending aorta compressing the right bronchus. An aneurysm of a large direct aortopulmonary collateral compressed the trachea, promoting respiratory distress in a patient with pulmonary atresia and ventricular septal defect.[150–152] The airway can be compromised by the aneurysm from the divided major aortopulmonary collateral artery after unifocalization as well.[153]

Outcome analysis

Although there is now considerable experience with the prenatal recognition and outcomes of fetuses with conotruncal anomalies[154,155] (see Chapters 16, 17 and 25A), there is substantially less information about the outcome of fetuses recognized to have tetralogy of Fallot with pulmonary atresia. Hornberger commented on the fate of 32 cases of fetal-diagnosed tetralogy of Fallot with pulmonary atresia.[156] Of these 32, twelve families (37.5%) chose termination of pregnancy; there were 2 spontaneous intrauterine deaths, 5 neonatal deaths, and 3 deaths in infancy with 1 patient lost to follow-up. The 9 survivors make up 28% of the entire cohort and 45% of the continuing preg-

nancies.[156] Boudjemline and coworkers have studied the prevalence of 22q11 deletions in fetuses with conotruncal cardiac defects.[154A] Of 61 fetuses with pulmonary atresia and ventricular septal defect, 11 (18%) had this microdeletion. In this study, more families opted for termination of pregnancy in those with 22q11 microdeletion when compared to those without the deletion.[154A] Boudjemline and colleagues have asked: "Can we predict 22q11 status of fetuses with tetralogy of Fallot?"[154B] One hundred and fifty-one consecutive fetuses with tetralogy of Fallot without or with pulmonary atresia were screened for 22q11 deletion. Additional echographic features were assessed including increased nuchal translucency (NT), intrauterine growth retardation (IUGR), polyhydramnios, extracardiac malformations, pulmonary arteries abnormalities. Twenty-five fetuses had a 22q11 deletion (16.6%). Increased NT, polyhydramnios and IUGR were more frequent in fetuses with 22q11 deletion as well as pulmonary arterial abnormalities. When these different features were present in the same fetus with tetralogy of Fallot, 22q11 deletion can be predicted with a sensitivity of 88%.[154B]

Survival of patients with tetralogy of Fallot and pulmonary atresia depends on the adequacy of pulmonary blood flow derived from the arterial duct, direct and/or indirect aortopulmonary collateral arteries, or less commonly from the coronary arteries, aortopulmonary window or fifth aortic arch.[6–8] For those patients with a duct-mediated pulmonary circulation, one would anticipate an early demise coincident with ductal constriction and closure. Kirklin and Barratt-Boyes suggest that in those patients whose pulmonary circulation is duct-dependent, the arterial duct has its usual tendency to close, albeit more slowly than normally.[34] They go on to state that in this group of patients with tetralogy and pulmonary atresia that without treatment, half this group are probably dead by 6 months of age and 90% have died by 1 year of age.[34] Conversely, for those patients with a stable and adequate pulmonary blood flow from whatever source(s), a greater longevity would be anticipated. Thus survival in to the sixth decade of life (admittedly uncommon) has been recorded in the unoperated patient with pulmonary atresia, ventricular septal defect, and multiple aortopulmonary collaterals.[157,157A,158,158A] Rygg and colleagues have reviewed the life history of the patient with tetralogy of Fallot in Denmark, commenting on the patients reported in Abbott's *Atlas* and other case series in the literature, with a particular focus on longevity. From Abbott's compilation the median age at death for the 85 patients with tetralogy of Fallot was 9 years, ranging from 11 days to 60 years. For those 30 patients with pulmonary atresia, the median age at death was 11 months, ranging from 9 days to 30 years. Rygg and colleagues also comment on the observations of Burke who found that the median age of death of patients with untreated tetralogy with pulmonary atresia was 11 months, similar to that in Abbott's series.[9]

Palliation of patients with severe tetralogy of Fallot was achieved beginning in 1945 with the Blalock–Taussig shunt,[159] and later the Potts and Waterston anastomoses[160,161] amongst others. Lillehei and his colleagues first successfully reported repair of a patient with tetralogy and pulmonary atresia in 1955,[162] and Rastelli and his colleagues reported the first use of an extracardiac conduit to repair this malformation in 1965.[163] In 1966 Ross and Somerville reported repair using a pulmonary homograft conduit to connect the right ventricle to the pulmonary artery.[164] The past three decades are witness to a variety of surgical techniques employed to promote the growth of diminutive pulmonary arteries or to "correct" the patient with complex pulmonary atresia.[34] These innovative approaches include a staged approach to unifocalization and more recently complete repair with unifocalization has been achieved in young infants with dramatic results. As pointed out by McElhinney and his colleagues amongst others, the aortopulmonary collaterals of these patients are highly variable in terms of number, size, origin course, arborization and they may constitute the sole source of pulmonary blood flow or they may supply only a single bronchopulmonary segment.[165] It is because of the profound heterogeneity of the pulmonary circulation in these patients that there is a broad continuum of the severity of the disease, and thus the timing of the clinical presentation. One end of the spectrum includes those neonates, infants and children who are severely hypoxemic because of grossly inadequate pulmonary blood supply and as well those babies in profound and intractable congestive heart failure reflecting excessive pulmonary blood flow.[8] At the other end of the continuum are those patients who have survived into late childhood, adolescence, and adulthood with adequate, but usually changing pulmonary blood flow.[157,158,166] In this latter group, the nature of the pulmonary blood supply continues to change or evolve because of the precarious nature of the collateral vessels in some patients, pulmonary vascular obstructive disease in unprotected collaterals, and the secondary, but very important changes reflecting hyperviscosity and *in situ* thrombosis. Thus any analysis of outcome in patients with pulmonary atresia and ventricular septal defect will be importantly influenced by the era during which the analysis takes place, by the nature and complexity of the pulmonary blood supply, and by the philosophy of the institution (conservative or aggressive) providing care to these challenging patients.

Bertranou and his colleagues in 1978,[12] using the 1949 Danish study published in 1971[9] and a survey of autopsied cases of tetralogy of Fallot with pulmonary atresia suggests, using a parametric analysis that only 66% of the patients are alive at age 6 months, 50% by 1 year, 33% at 2 years, 25% at 3 years, and 8% at age 10 years. The Danish data were used by this group because no patient had as yet undergone corrective surgery for tetralogy of Fallot, The Bohemia Survival Study identified 55 children at birth with tetralogy of Fallot from 1980 to 1990.[15] By 6 months of age, 61.8% were alive; between the first and fifth years of life, survival had dropped to 54.5%, and at 10 years to 45.2% and remained at this level to 15 years of age.[15] Obviously the survival will depend on the era captured and the surgical approach and expertise of the group involved. Leonard and coworkers have reported the natural and unnatural history of pulmonary atresia[16] (see also Chapter 34). Reviewing 601 635 live births from 1980 to 1995 in the Northern Health Region of England, they identified 129 patients with congenital pulmonary atresia.[16] Sixty of these 129 (46.5%) had pulmonary atresia with ventricular septal defect; 29 (22.5%) had pulmonary atresia and intact ventricular septum; and 40 (31%) presented with complex forms of pulmonary atresia.[16] The total mortality of the group was 72 of 129 (56%). The first week mortality for the entire group was 38%, and 15 of the 60 patients (25%) with pulmonary atresia and ventricular septal defect died in the first week of life. Interestingly, for those patients with pulmonary atresia with ventricular septal defect, neither the presence nor the absence of major aortopulmonary collaterals, nor pulmonary artery size or confluence could be shown to have any influence on survival.[16] Surgical deaths occurred in 7 of the patients with pul-

monary atresia with ventricular septal defect; hospital deaths not related to surgery occurred in 14 of these patients, and sudden deaths in 7 patients with pulmonary atresia with ventricular septal defect. Five of these 7 sudden deaths were unexplained at necropsy; 1 child had severe gastroenteritis, and 1 had a large pulmonary hemorrhage.[16]

It is of some historical interest to review our early experience (1950–72) of survival after a systemic-to-pulmonary shunt in infants < 30 days old with obstructive lesions of the right heart chambers.[167] This experience at the Toronto Hospital for Sick Children concluded just a few years before the era of prostaglandin therapy.[130] Thirty-six patients were palliated with a variety of systemic-to-pulmonary shunts from 1950 to 1965, and 61 in the era from 1966 to 1972.[130] The most common condition was severe tetralogy of Fallot with or without pulmonary atresia. In the earlier era, the overall mortality was 78%, and in the period from 1966 to 1972, the mortality was 34%. The mortality for those operated in the first week of life was double that of those operated in the second to fourth week of life. These results seem incomprehensible today! But in the era before routine administration of an E-type prostaglandin, many of these babies were moribund, indeed agonal, at the time of their surgery. The Children's Hospital in Boston used a hyperbaric chamber to increase tissue oxygenation in this early era.[130A] In this regard, Miller and his colleagues reviewed the clinical course in 50 patients with congenital pulmonary atresia and ventricular septal defect seen at the Boston Children's Hospital from 1955 to 1967.[130B] Fifteen patients with adequate or increased pulmonary blood flow did not require surgery (at that time). Of those 22 patients presenting in infancy with inadequate pulmonary blood flow, all 6 who did not undergo surgery died, and 7 of 16 shunted patients died. Of 13 patients requiring palliation in childhood, 3 died. They found that the Waterston anastomosis was the most favorable form of shunt, providing the best palliation.[130B]

How prostaglandin changed the fortunes of these babies! The ability to pharmacologically manipulate the arterial duct with prostaglandin is one of the signal contributions and innovations to the care of these babies that took place during the last 50 years of the 20th century.[130,168] For those babies surviving a palliative arterial shunt operation, there was the reality of distortion of the pulmonary artery, pulmonary hypertension and pulmonary vascular obstruction, and/or chronic congestive heart failure, and death. While pulmonary hypertension and pulmonary vascular obstruction were more common to the Potts or Waterston anastomosis, such pathophysiological changes were seen occasionally in patients after a Blalock–Taussig shunt as well.[169,169A,170] There is no doubt that these palliative systemic-to-pulmonary artery shunts enhanced the prognosis for patients with inadequate pulmonary blood flow. But these patients were still at risk for cerebrovascular accidents, brain abscess, general somatic complications of palliative surgery, limb length discrepancy, even gangrene of the ipsilateral limb in the era of the classic Blalock–Taussig shunt. In those patients with too large a surgically constructed shunt, morbidity and death could be attributed to chronic volume overloading and congestive heart failure or to the often insidious development of pulmonary vascular disease. Several years ago we reviewed the clinical impact and morbidity of the modified Blalock–Taussig shunts performed on 65 patients with tetralogy of Fallot in our institution from 1990 to 1994.[171] The evolution from the classical Blalock–Taussig shunt to the modified form of the shunt took place in the mid 1970s,[172,173] and most centers adopted the use of the modified Blalock–Taussig shunt using polytetrafluoroethylene.[34] Others used the subclavian arterioplasty so that a classical Blalock–Tausig shunt could be performed ipsilateral to the aortic arch without kinking and distorting the subclavian artery.[174,175] It is interesting to compare these results with those of Aziz and his colleagues also from Toronto cited earlier.[167] Excluding noncardiac causes of death, overall survival was 90% in the shunted patients, and self-limited morbidity complicated 11% of shunt operations.[171] In a similar but larger study extending between 1983 and 1995, Al Jubair and coworkers reviewed the results of 546 Blalock–Taussig shunts performed in 478 patients with a variety of cardiac conditions.[176] Early mortality was significantly increased in patients weighing 3.0 kg or less at 8/156 (5.1%) vs. 3/303 (1.0%). There was also a significant relationship between patient age and early mortality. The mortality in those patients 1 week or less was 6.4%, from 1 week to 1 year 3.7%, and > 1 year 0.5%. The late mortality in the same age groups was 3.8%, 2.4%, and 2.0%, respectively.[176] They also found that the use of intraoperative heparinization reduced mortality in this substantial series. There are many factors contributing to these excellent results, including earlier referral, more precise diagnosis, improved neonatal, surgical and anaesthetic care and expertise.[176] The preoperative use of prostaglandin and better postoperative care also both contribute to these excellent result. However, Al Jubair and coworkers conclude that the single most important predictor of mortality is the patients' preoperative condition, including metabolic acidosis, renal failure, septicemia, etc.[176] This shunt did stimulate growth of both the ipsilateral and contralateral pulmonary arteries, but had the potential for severe distortion as well.[8,36–38,177]

Just over a decade ago we reviewed our institutional experience with 104 consecutive patients with tetralogy of Fallot with pulmonary atresia who were diagnosed in the first year of life between January 1, 1976 and December 31, 1988 at the Toronto Hospital for Sick Children.[178] We chose this time period because it encompassed the era in which prostaglandin was introduced into our therapeutic algorithm.[130] This time period obviously eliminated those patients seen in the previous 25 years, many of whom had been treated with a variety of systemic-to-pulmonary artery shunts, with a few corrective operations as well. These data, had they been incorporated into our study, would likely have substantially altered our findings. For the entire cohort, the estimate of the probability of survival was 69%. We were surprised that we could find no difference in survival between those patients with a duct-mediated pulmonary circulation compared with those in whom the majority of the pulmonary circulation was collateral based. Thirty-three of the 72 patients with a duct-mediated pulmonary circulation underwent complete repair compared with only 5 of 32 patients in whom the pulmonary circulation was primarily collateral-mediated. Sixteen of these patients had a ductal stenosis in the pulmonary artery (Fig. 18-7). In the definition of the complex circulation in the second group, 97 collateral vessels were identified in the 32 patients (range 1–8, mean 3.06 per patient). Of these 97 collaterals, 90 originated as direct aortic branches from the descending aorta and 7 as indirect branches. At the initial angiographic investigation, stenoses were evident in 54% of the systemic collateral arteries. At the conclusion of the study 28% of the patients with a duct-mediated pulmonary circulation had died; 30 patients were alive (42%) after corrective surgery;

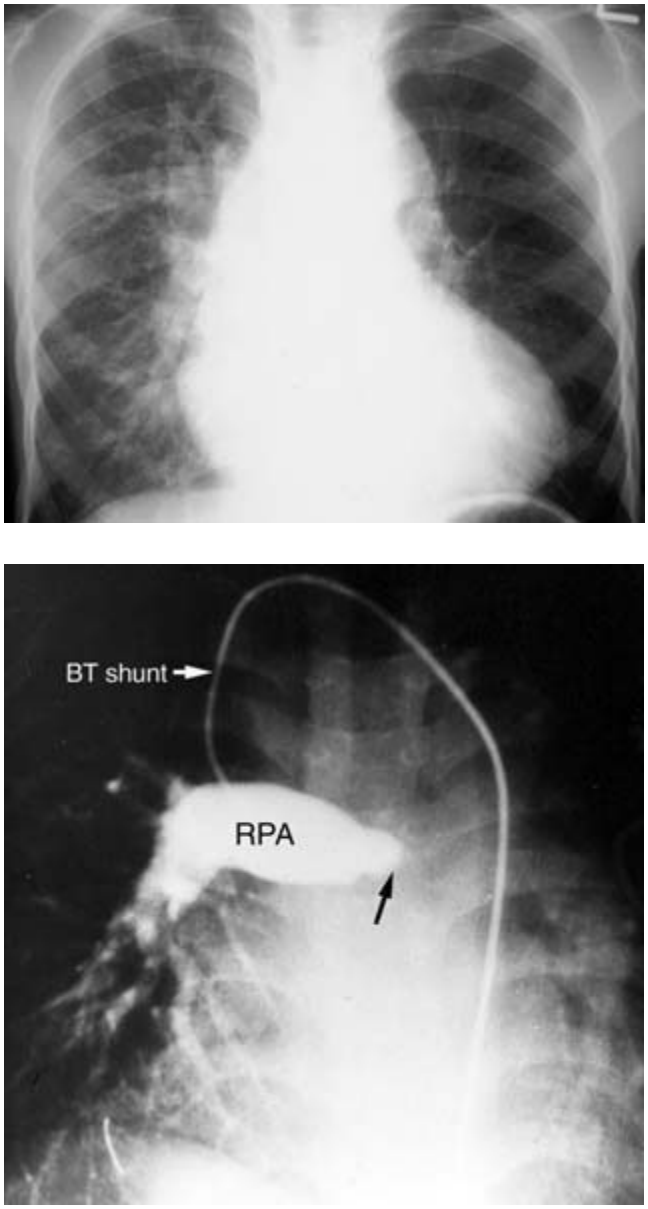


Fig. 18-7 Juxtaductal stenosis of the left pulmonary artery in a patient with pulmonary atresia, ventricular septal defect, left aortic arch and left ductus arteriosus. **A**. Frontal chest radiogram shows asymmetric pulmonary blood flow with oligemic left lung and plethoric right lung. **B**. Pulmonary arteriogram shows complete occlusion (arrow) of the left pulmonary artery origin. The catheter was introduced through the right Blalock–Taussig (BT) shunt.

19 patients (11%) were awaiting corrective surgery, and 3 patients (4%) were considered inoperable. Eleven of the 32 patients in the collateral-mediated circulation group did not undergo any surgery. The median age at death of the 5 patients who died was 14 days (range 6–128 days). The other 6 patients range in age from 1.3 to 7.71 years (mean 4.99) at the conclusion of the study. From this cohort of 32 patients, 9 (28%) died, 4 (13%) had undergone corrective procedures and survived and most of the remaining survivors were not considered candidates for repair.

A similar study has been carried out by Dinarevic and colleagues who reviewed the course of 54 infants seen between January 1972 and December 1992 at the Brompton Hospital in London, UK.[179] These authors also divided the patients into two groups: group 1, 30 patients with a duct-mediated pulmonary circulation; group 2, 24 patients with a collateral-mediated pulmonary circulation. Despite a variety of surgical procedures carried out in both groups, the calculated survival for the two groups was similar at 56% and 58%, respectively. More patients in group 1 had been repaired when compared to group 2, and as in our study, more patients in group 2 had stenoses within the pulmonary vascular bed and arborization anomalies. Both studies provide only survival data and unfortunately no data were provided or available on cardiopulmonary function or ability index. Bull and her colleagues have studied the mode of presentation and attrition of 218 patients with "complex" pulmonary atresia seen at either the Great Ormond Street Hospital for Sick Children or the National Heart Hospital from 1965 to 1991, acknowledging their conservative approach to management.[180] All of these patients had pulmonary atresia, ventricular septal defect, and their pulmonary blood supply exclusively from aortopulmonary collateral vessels. Sixty-five patients were first seen in infancy: 50% of these presented with severe cyanosis, 25% with heart failure, and 25% were been considered "well-balanced," referred for evaluation of a heart murmur, mild cyanosis or failure to thrive. The 16 deaths in this age range corresponded to a probability of survival to 1 year of age of 60%. One hundred and twenty-seven patients were followed up at some stage from their first to 10th birthday. There were 24 deaths in this age range, 19 within 1 month of 145 cardiac operations in 88 patients. For patients alive on their first birthday, their estimates provided a probability of survival to their 10th birthday of 65%. For patients alive on their 10th birthday, their estimates of probability of survival to age 35 was 16%. For those alive at age 20 years, their estimates of probability of survival to age 35 was 50.6%. Forty patients older than 10 years of age died, 28 within 1 month of 134 operations. Forty-three patients did not undergo operations, primarily because of the absence of intrapericardial pulmonary arteries and 29 had less than two collateral vessels. Because of the "conservative" approach to these patients in general, most did not undergo operation because they were considered too well to justify surgery that had the potential to worsen their condition.[118] Thirty-two patients without operation were alive at follow-up, with 10 over 20 years of age, and the oldest aged 45 years. As one surveyed cardiovascular complications in these 218 patients, endocarditis occurred at 1.2 events/100 patient-years. Aortic regurgitation was recognized in these patients, and actuarially, 91% were free of aortic regurgitation at age 10 years, 62% at age 20, and 38% at age 30. There were 15 adverse cerebrovascular events (median patient age 10 years, 1 event/100 patient-years). Fifty-eight definitive repairs were carried out with 18 deaths (31%) within 30 days of operation and another 4 within 3 months. Marelli and her colleagues have addressed the outcome of 26 cyanotic patients 18 years of age or older with pulmonary atresia and ventricular septal defect seen at the University of Calfornia in Los Angeles between 1978 and 1992.[166] The ages ranged from 18 years to 55 years with a mean ± SD of 28 ± 8.7. The mean oxygen saturation was 85% (± 3.2 SD), and the mean hematocrit was 57% (± 8.2 SD). Five of 11 patients who did undergo any surgery died. The mean age at the time of death for unoperated adult survivors was 33 years (± 1.5 SD). Ten cyanotic adults had undergone some form of palliation before age 18 years. The mean oxygen saturation was 85%

(± 4.8 SD), and the mean hematocrit was 52% (± 10.9 SD). The majority of these patients were in New York Heart Association class II. Six of these 10 patients subsequently underwent repair and all survived. In addition to quality of life issues, there is now some evidence that adults who are persistently cyanosed are depressed, but that should not be surprising.[181]

The repair of tetralogy of Fallot was accomplished in the mid 1950s[162] and the next decade was witness to numerous reports of surgical series of tetralogy patients, their early and mid-term outcomes. In 1966, tetralogy with pulmonary atresia was repaired using a pulmonary homograft,[164] and this stimulated interest in the salvage of those patients with complex pulmonary circulations. Some urged caution in the surgical treatment of those babies or older patients with complex pulmonary atresia, warning that aggressive intervention might worsen not improve.[118] Surgical ingenuity was put to the test and many procedures were used to stimulate growth of the small thin-walled pulmonary arteries. Some were challenged by the experience of Castaneda and his colleagues at the Children's Hospital in Boston who advocated primary and early repair of tetralogy of Fallot, demonstrating with clinical clarity that the pulmonary arteries in severe tetralogy were small because they were underfilled and that with surgery to restore outflow tract patency, the pulmonary arteries would quickly normalize in caliber.[182–185] The patient with confluent pulmonary arteries mediated by a solitary arterial duct was challenging, but certainly less so than the patient with a complex and multisourced pulmonary circulation. The former patient was managed with a systemic-to-pulmonary arterial shunt and then later in infancy or childhood, complete repair could be carried out, sometimes just with a transannular patch, but more frequently with a valved conduit.[184] There was no doubt that even in this group of patients there was ongoing morbidity and attrition, with many sustaining shunt-related complications. Thus many now repair this group of patients at the initial presentation, again because of shunt related mortality and morbidity and attrition between palliation and repair.

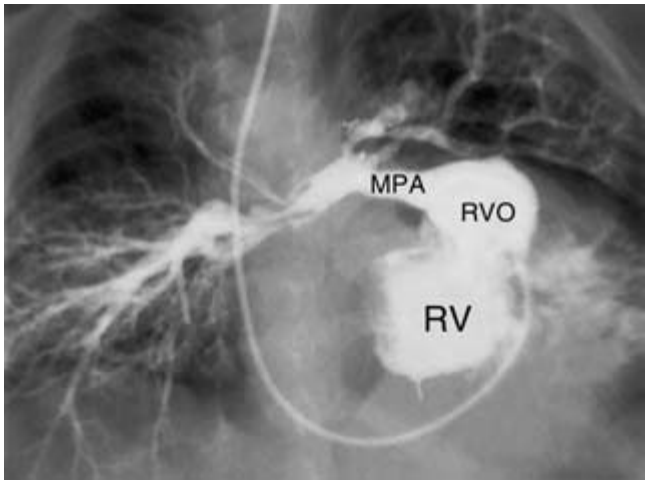


Fig. 18-8 Result of surgery in a patient with very precarious pulmonary circulation with multiple stenotic collaterals. Multiple interventional procedures were necessary after the surgery. MPA, main pulmonary artery; RV, right ventricle; RVO, right ventricular outflow tract.

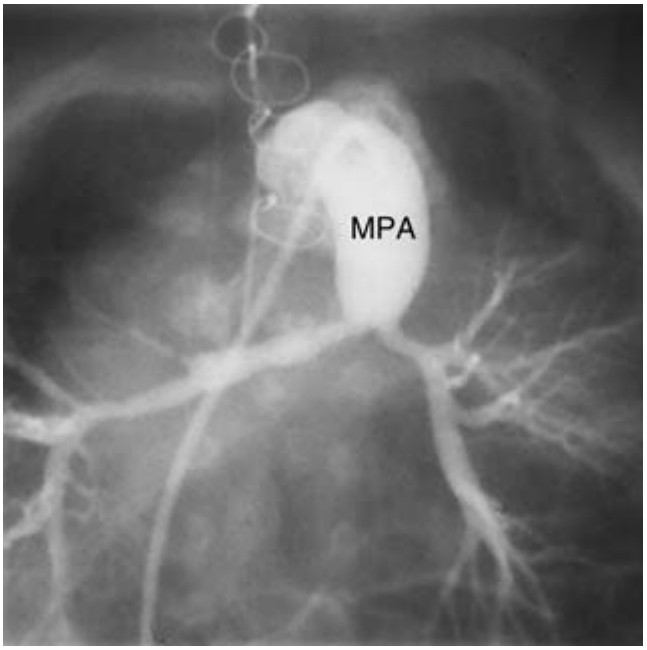


Fig. 18-9 Persistent hypoplasia of the pulmonary arteries after right ventricular outflow tract reconstruction. MPA, main pulmonary artery.

But what about the other group of patients, those with multiple aortopulmonary collateral arteries and important anomalies of arborization? How does one unifocalize, recruit and rehabilitate the diminutive pulmonary arteries in the patient with tetralogy of Fallot, pulmonary atresia, and multiple aortopulmonary collaterals? Initially, this wasn't necessarily the issue: it was to save a dying, hypoxic baby's life by augmenting pulmonary blood flow. Certainly some diminutive pulmonary arteries increased in caliber in response to these shunts. Some advocated dividing the small main pulmonary trunk and anastomosing it in an end-to-side fashion with the ascending aorta,[186,187] followed by repair if subsequent growth seemed adequate using guidelines published by Kirklin and his colleagues.[34] Others advocated placing a patch across the atretic distal infundibulum on to the main pulmonary trunk, leaving the ventricular septal defect open. While this could promote growth of the pulmonary arteries, not infrequently as we showed, this maneuver resulted in a proximal left pulmonary artery stenosis.[188] Others used a valved or non-valved conduit. Whether employing a transannular patch, a valved or non-valved conduit, these procedures provided access from the heart to the pulmonary arteries. This access permitted further and repeated rehabilitation of the pulmonary arteries using balloon angioplasty, a procedure begun in the early 1980s.[188–193] But the patient with small pulmonary arteries and multiple aortopulmonary collaterals provided a considerable challenge (Figs 18-8, 18-9). The surgical maneuvers and the timing used to promote growth of the small pulmonary arteries and to unifocalize the collaterals were diverse. Some asked if unifocalization was a realistic goal.[194] Benson and his colleagues working with Laks at the University of Calfornia in Los Angeles implemented a two-staged surgical procedure to unifocalize and promote the growth of small pulmonary arteries in the patient with pul-

monary atresia and a ventricular septal defect.[195] Initially a Dacron Y graft was anastomosed between the ascending aorta and the collaterals and a graft to the pulmonary artery. At the second operation, continuity was established between the right ventricle and the Y graft by using a valved Dacron conduit and the ventricular septal defect was closed. Many of these varied staged surgical procedures on an individual basis afforded reasonable palliation, and several series of staged unifocalization with eventual repair were reported in the literature. Others mobilized the segment of descending thoracic aorta with its collaterals to be incorporated into the pulmonary circulation.[196] These were just some of many surgical strategies employed to recruit and rehabilitate the multisourced pulmonary circulation of these patients.[34] There were other patients with pulmonary atresia, poorly developed aortopulmonary collaterals and hypoplastic pulmonary arteries not considered candidates for unifocalization and repair. These patients have benefited from a variety of palliative shunt procedures, including the classical and modified Blalock–Taussig shunts as well as in the 1950s and 1960s the Potts and Waterston shunts (see Chapter 16). Rodefeld and his colleagues have reported their results of a staged process beginning with creation of an end-to-side aortopulmonary window.[196A] This surgical anastomosis is constructed either just above the sinotubular junction or less commonly to the undersurface of the aortic arch. Their experience with 18 patients has been gratifying and 73% have undergone complete repair. The criteria for this approach include: (1) presence of centrally confluent true pulmonary arteries 1.0–2.5 mm diameter, with minimal arborization anomalies; (2) multiple small aortopulmonary collateral vessels, the majority connecting with the true pulmonary arteries; (3) marked cynaosis.[196A]

In this earlier era, Kirklin and his colleagues provided a number of guidelines to consider in contemplating the complete repair of tetralogy of Fallot, pulmonary atresia, and multiple aortopulmonary collaterals. These considerations included the presence or absence of multiple aortopulmonary collaterals, the size of the true central pulmonary arteries, the number of pulmonary segments supplied by the true pulmonary arteries and from the collateral circulation, the degree of arborization anomalies, etc.[34] In the earlier era (before 1992) unifocalization was almost always staged with later closure of the ventricular septal defect and thus one had the luxury of assessing the status of the pulmonary vascular bed after unifocalization. The decision to close the ventricular septal defect was frequently a difficult one, and the wrong decision was often unforgiving. But just as surgical methodologies were evolving so were those imaging techniques. The anatomy of the pulmonary circulation has been imaged by several modalities, both invasive and non-invasive. Flush biplane aortograms evolved to selective injection into collaterals ± digital subtraction technique, pulmonary vein wedge angiography, and balloon occlusion techniques. All helped to define with increasing clarity the nature of the pulmonary circulation in these very complex patients.[4–8,36–38,88] Increasing information was obtained from echocardiography [197,197A,197B,198] and there is more experience with CT and MR imaging of the pulmonary circulation as well (Fig. 18-6).[199–206] In those patients with duct-mediated confluent pulmonary arteries, cross-sectional echocardiography is probably adequate for preoperative management, with the caveat that small or otherwise significant collateral arteries can be excluded. While at this time, cross-sectional echocardiography and magnetic resonance imaging may provide helpful information in planning surgical management, we continue *c*. 2003 to image selectively the collateral circulation by cardiac catheterization, and to record pressures with an end-hole catheter in those collaterals without obvious stenosis.[36,37]

Kirklin and Barrat-Boyes suggest that of any large cohort of patients with pulmonary atresia and ventricular septal defect, there is an almost equal division between those with a duct-mediated and primarily collateral mediated pulmonary circulation.[34] Between 1975 and 2000, we identified 206 patients with pulmonary atresia and ventricular septal defect.[30] Eighty-four (40.8%) of these patients had large aortopulmonary collaterals. As pointed out by McElhinney and his colleagues amongst others, these collaterals are highly variable in terms of number, size, origin course, arborization and they may constitute the sole source of pulmonary blood flow or they may supply only a single bronchopulmonary segment.[165] The size of the immediately pre-branching pulmonary arteries may approach a normal caliber in some patients with pulmonary atresia and ventricular septal defect, but this finding when it does occur is usually in those with a duct-dependent pulmonary circulation. In those with large and multiple aortopulmonary collaterals, the immediate pre-branching pulmonary arteries may be very small, with a McGoon ratio[207,208] in some patients of about 0.5. This corresponds to a Nakata index[209] of about 20, and a Z-value of –10. Kirklin and Barratt-Boyes state that the smallest pulmonary arteries are usually seen in those patients with non-confluence.[34] Furthermore there tends to be a reciprocal relationship in terms of caliber depending on the presence or absence of multiple important aortopulmonary collaterals. In the absence of these collaterals, the pulmonary arteries tend to be better developed when compared to those with luxurious and abundant collaterals, although exceptions do occur in each setting. Thus rest some of the challenges if one is to consider surgery in the young infant with pulmonary atresia, ventricular septal defect and multiple aortopulmonary collaterals hoping to reduce the early and important attrition. Again McElhinney and his colleagues working with Hanley at the University of California in San Francisco reviewed some of the literature that had reported the outcomes of staged unifocalization and repair in tetralogy of Fallot, pulmonary atresia, and multiple aortopulmonary collateral arteries.[165] The nine series reviewed by McElhinney and his colleagues encompassed the years from 1972 to 1993. The data summarized in this paper indicated that only 31.9% of those who underwent repair achieved a low right ventricular pressure.[165] Most of the patients in these series underwent their first operation after infancy. They went on to estimate that about 20–30% of a cohort of newborns with pulmonary atresia, ventricular septal defect and multiple aortopulmonary collaterals would achieve complete repair with acceptable right ventricular hemodynamics if a delayed staged approach was taken.[165] And that might be too optimistic! Thus beginning in 1992, Hanley and his colleagues began the odyssey of primary unifocalization and repair in infancy, hoping to improve the outcome of the entire cohort. Reddy and his colleagues with Hanley published their initial experience with primary complete unifocalization and repair of 10 patients at the severe end of the morphologic spectrum between August 1992 and March 1994.[210] The median age was 2.08 years and the median Nakata index of the true pulmonary arteries was 50. They emphasized tissue-to-tissue connections via anastomosis of collaterals to collaterals

or to true pulmonary arteries.[210] The ventricular septal defect was left open in only one patient. The postrepair peak systolic right ventricular/left ventricular pressure ratio ranged from 0.31 to 0.58 (median 0.47). There were no early deaths. They extended this experience in 1998 reporting on 72 patients with tetralogy of Fallot, pulmonary atresia and multiple aortopulmonary collaterals who were considered for complete unifocalization and repair.[165] Thirteen patients had undergone prior palliation elsewhere and 5 had been considered inoperable also elsewhere. The median age at surgery was 7.3 months, and 65% of the patients were under 1 year. The median number of collaterals was 4, and 20 patients had absent or rudimentary central pulmonary arteries at the time of surgery.[210] Complete unifocalization of the pulmonary blood supply was achieved in one stage via a midline approach in 67 patients (93%) and 5 patients with severe distal segmental stenoses or other comorbid conditions underwent staged unifocalization through bilateral thoracotomies usually during the same hospitalization. Among the 67 patients who underwent one-stage unifocalization, the ventricular septal defect was closed at the same operation in 46, thus accomplishing a single-stage unifocalization and repair in 64%. There were 8 early deaths (11%) and 6 late deaths, giving an actuarial survival 83% at 1 year and 79% at 2 years and beyond. Fourteen additional patients underwent completion of the repair. Nine patients, including 3 of the 5 who underwent staged unifocalization, are awaiting closure of the ventricular septal defect at a median of 7 months after the initial unifocalization procedure.[210] Among the early survivors, actuarial percentage with complete repair was 87% at 1 year and 95% at 2 years. In 2000, Reddy and his colleagues updated their entire experience with 84 patients with pulmonary atresia, ventricular septal defect, and multiple aortopulmonary collaterals operated from 1992 presenting their early and intermediate outcomes.[211] The patients were divided into 3 groups on the basis of operative strategy: group I (n = 56, 64%) underwent complete unifocalization of pulmonary blood supply and intracardiac repair in a single stage through a median sternotomy; group II (n = 23, 27%) underwent complete unifocalization through the midline, but the ventricular septal defect was left open; group III patients (n = 6, 7%) underwent staged unifocalization through sequential thoracotomies, often during the same hospitalization. The median age at repair of the group I patients was 6.5 months, group II 7 months, and group III 8.7 months. Five early deaths and 7 late deaths occurred in the group I patients, 4 early and no late deaths in the group II patients, and no early nor late deaths in the group III patients. There was a 10.6% early mortality and a 74% actuarial survival at 4 years in an unselected cohort of patients. Among the early survivors actuarial survival with complete repair was 88% at 2 years. Factors that correlated with poorer survival over time included longer duration of cardiopulmonary bypass, higher right ventricle to left ventricular pressure ratio in the early postoperative period (group I only), and chromosome 22q11 deletion. During the follow-up 7 late deaths occurred, all in group I patients, but apparently not related to right ventricular hypertension.[211] It is not surprising that reintervention on the newly constructed pulmonary arteries was common, with an actuarial reintervention-free survival of only 42% at 5 years. In this experience complete one-stage unifocalization was accomplished in 93% of the patients and most (66%) underwent complete repair at a single stage.[211] One of the issues faced by Hanley and his colleagues was the decision whether or not to close the ventricular septal defect at the time of the one-stage unifocalization and repair.[165,210] This group devised an intraoperative neopulmonary artery index and pulmonary flow study to guide this decision.[212] Others have reported the outcomes of unifocalization and repair of patients with tetralogy, pulmonary atresia, and multiple aortopulmonary collaterals, but most of these recent reports, like those summarized earlier by McElhinney[165] indicated that surgery was performed beyond infancy, and many operations were staged.[213–217] From these reports it is difficult to discern if these reflect just those referred for surgery, not the entire cohort. None the less, the papers of Yagihara and Ishizaki and their respective colleagues provide tremendous information about the various surgical techniques used in the unifocalization and the outcome of these procedures.[216,217] Of 125 anastomoses made in 51 patients (average age 5 years, 7 months) during 96 unifocalizations and subsequently imaged, Ishizaki and his colleagues found that 101 anastomoses were patent (80.2%) and 24 (19.2%) were occluded.[216] They found as well that the patency rate involving the intrahilar pulmonary arteries was 88%, while that for the extrahilar arteries was 71.9%. Yagihara and his colleagues also from the National Cardiovascular Center in Osaka provided information about the outcome of patients who underwent unifocalization.[217] Most of the patients were likely the same as reported by Ishizaki.[216] Fifty patients underwent unifocalization, and in 36 of these no central pulmonary arteries were detected. Five patients died after various types of unifocalization procedures. Twenty-six patients underwent complete repair, with 1 early death. The right ventricle to left ventricle systolic pressure ratio immediately after repair ranged from 0.24 to 0.91 with a mean of 0.54 ± 0.17. Postoperative cardiac catheterizations showed that pulmonary vascular resistance correlated significantly with the number of vascular segments functioning rather than with the morphology and caliber of the central pulmonary arteries, confirming the findings of Kirklin and Barratt-Boyes.[34] Others have also shown that microdeletion 22q11 has an adverse influence on the outcomes of patients with pulmonary atresia and ventricular septal defect, likely because of a more abnormal pulmonary artery anatomy.[217A]

Hadjo and colleagues reviewed the long-term course of 52 patients with pulmonary atresia and ventricular septal defect seen in a single institution and followed for a mean period of 8.6 years (range 2 days to 20 years).[218] Before the first operation, pulmonary blood supply was provided by an arterial duct supplying confluent pulmonary arteries in 26 patients (50%, group I), and was partially or entirely dependent on systemic collateral arteries in the other 26 patients (group II). The angiographic mean ratio of diameters of the right and left pulmonary artery/descending aorta (McGoon ratio) was significantly lower in group II than in group I, 0.76 ± 0.42 vs 1.04 ± 0.17 (P = 0.006). Severe arborization defects (with fewer than 10 pulmonary vascular segments connected to central pulmonary arteries) were present only in the group II patients (eight patients: 15%), six of whom had congenital absence of the central pulmonary arteries. Corrective surgery was performed in 23 patients (44%, 14 in group I, 9 in group II). All but 1, who died later, had a McGoon ratio > or = 1 (mean 1.19 ± 0.18) at time of repair. There was 1 hospital death (4%) and 2 late deaths (9%). All but 1 of the surviving corrected patients were in functional class I or II. Conduit replacement/reoperation was performed in 3 patients (14%), 6, 10 and 13 years, respectively, after repair. At the end of the study, among the 37 patients (71%) who were alive (17 in group I, 20 in group II), 20 (39%) were corrected

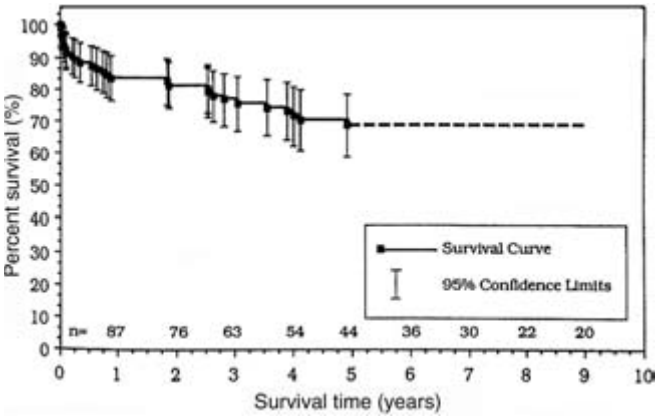


Fig. 18-10 Data from Toronto Hospital for Sick Children. Kaplan–Meier survival curve for 104 patients with tetralogy and pulmonary atresia. (Reprinted from Hofbeck *et al.*,[178] Copyright (1991), with permission from Excerpta Medica.)

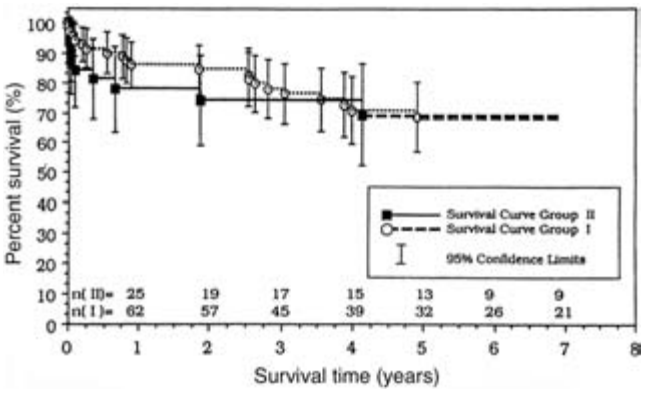


Fig. 18-11 Data from Toronto Hospital for Sick Children. Kaplan–Meier survival curves for patients with tetralogy and pulmonary atresia. Group I, pulmonary blood flow mediated by a unilateral arterial duct; group II, from one or more aortopulmonary collaterals. (Reprinted from Hofbeck *et al.*,[178] Copyright (1991), with permission from Exerpta Medica, Inc.)

(12 in group I, 8 in group II). Four await corrective surgery, and 6 (11.5%) were considered inoperable (all in group II) because of very hypoplastic or absent central pulmonary arteries.

We have recently re-reviewed our institutional experience with pulmonary atresia and ventricular septal defect.[30] This review included 206 patients seen at the Toronto Hospital for Sick Children from 1975 to 2000, thus overlapping with the review of Hofbeck *et al.* [178] also from Toronto (Figs 18-10, 18-11). The median age at presentation of the 206 patients was 2 days (range, birth to 10 months): 109 were male and 97 female. Major aortopulmonary collaterals (MAPCA) were the dominant source of pulmonary blood flow in 84 patients (41%). Among the 84 patients with collaterals 45 were male and 39 female. Among the remaining 122 patients without collaterals there were 64 boys and 58 girls. In 180 patients, 389 surgeries and 155 interventions were carried out. No surgery was performed in 32 patients (16%), 21 of whom have died. The initial procedure was a systemic-to-pulmonary arterial shunt in 99 patients (49%) and right ventricular outflow (RVOT) reconstruction in 24 (9%). Repair was performed in 62% of patients, with 38% of these having primary repair. Repair was less likely in the MAPCA group (46%) than in non-MAPCA group (71%; $P < 0.001$). Overall Kaplan–Meier estimates of survival from birth were 89% at 1 month, 76% at 1 year and 62% at 10 years up to 25 years. Patients who achieved repair had significantly better survival ($P < 0.001$), with survival estimates after repair of 91% at 1 month and 85% at 5 years up to 18 years. Survival was similar in the MAPCA and non-MAPCA groups, both overall ($P = 0.82$) and after repair ($P = 0.98$), with no significant change over the study period. Poorer overall survival from birth was significantly associated with younger age at presentation ($P < 0.001$), the presence of chromosomal abnormality ($P = 0.002$) and lower initial McGoon index ($P = 0.005$), absent infundibular septum ($P = 0.054$), and aortic valve stenosis ($P < 0.001$). We commented earlier on the observations of Bull and her colleagues who reported in 1995 the presentation and attrition of patients with complex pulmonary atresia.[180] From her estimate of overall survival of their cohort, their survival seems somewhat worse than seen in Toronto (Fig. 18-12).

For repaired patients, reoperations and catheter interventions were often required, with new RVOT surgery performed in 29/113 (26%) and catheter dilations of the RVOT and/or pulmonary arteries in 49/112 (44%). Kaplan–Meier estimates of freedom from any procedure after repair were 80% at 1 year, 41% at 5 years and 23% at 10 years. Thus in our experience mortality associated with pulmonary atresia and ventricular septal defect remains high, with associated anomalies and adequacy of the native pulmonary arteries being significant risk factors. This experience in terms of re-intervention is very similar to that reported by Fyler in 1992 who summarized the Boston Children's experience.[219] Survival and re-intervention are but two of the considerations for the survivors of these operations, whether staged or conducted in one stage. As shown by Hanley, Reddy and their colleagues, many patients after a one-stage or multi-staged approach to unifocalization and repair will early on have favorable right ventricular and pulmonary artery hemodynamics, but not all.[165,210,211] Shimazakie, Blackstone and Kirklin and their colleagues have presented considerable data about the medium and long-term outcome of these patients.[220–222] These reports indicated that the poorest postoperative hemodynamics were found in those patients with the

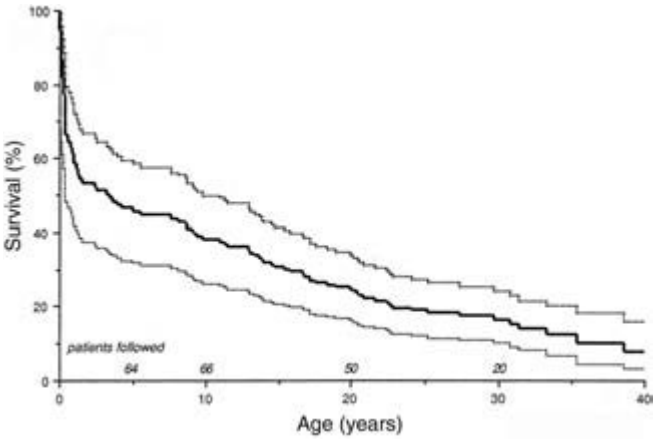


Fig. 18-12 Estimate of overall survival from birth for complex pulmonary atresia (218 patients) with 95% CL (dotted lines). (Reprinted from Bull *et al.*,[180] Copyright (1995), with permission from The American College of Cardiology Foundation.)

most underdeveloped central pulmonary arteries and in those with important arborization anomalies and distal stenoses. There was also the inference that some of these changes were age-related, and that these findings support the notion of earlier repair.[220–222] Thus there are a number of issues that could be argued in favor of early repair. This approach should reduce the attrition that is so prevalent in infancy. It may tend to obviate some of those progressive vascular changes that lead to downstream obstruction. Earlier intervention might protect against pulmonary vascular obstruction in those patients and in those pulmonary segments perfused by unprotected collaterals. In addition Rosenberg working with Rabinovitch showed that elastin was more prevalent in the pulmonary arterial walls of younger when compared to older patients.[223] This could suggest that there was more potential for vascular remodeling and growth in younger as compared to older patients.

Cho and his colleagues of the Mayo Clinic sought to determine the results of surgical treatment of patients with tetralogy of Fallot and pulmonary atresia with or without major aortopulmonary collateral arteries, to clarify variables affecting early and late mortality, and to expose late, nonfatal events affecting surgical patients.[223A] To accomplish this goal, the records of 495 patients operated on from 1977 to 1999 were reviewed. Patients were divided into those who did not undergo complete repair (group A) and those who did (group B). Group A consisted of 160 patients. Eighty-one (51%) had palliative procedures, 45 (28%) had preliminary surgical stages (unifocalization and right ventricular outflow tract reconstruction) as initial operations, and 34 (21%) had all surgical stages but were rejected for complete repair. Early and late mortality were 16.3% ($n = 26$) and 23.1% ($n = 31$), respectively. Mean follow-up was 72.3 months. The presence of major aortopulmonary collateral arteries was a risk factor for late mortality ($P = 0.0182$). Group B consisted of 335 patients. For this group, the mean age at complete repair was 11.3 years (SD, 9.2). One hundred and three (30%) patients had single-stage complete repair, whereas 232 (69%) had staged reconstruction. Twenty-two (6.6%) patients underwent reopening of the ventricular septal defect for high right ventricular pressure. Early and late mortality were 4.5% ($n = 15$). Risk factors were a peak right ventricular/left ventricular pressure ratio of > 0.7 and reopening of the ventricular septal defect ($P <$ or = 0.05). Late mortality was 16% ($n = 51$). The mean follow-up was 11.4 years (SD, 7.5). Risk factors included male sex, nonconfluent central pulmonary arteries, reopening of the ventricular septal defect, and postrepair conduit exchange ($n = 137$). Ten- and 20-year results were an actuarial survival of 86% and 75% and freedom from reoperation of 55% and 29%, respectively. On the basis of this extensive experience they concluded that surgical repair of patients with simple or complex forms of tetralogy of Fallot with pulmonary atresia can be achieved with low early mortality. Late mortality and need for reoperation, especially conduit replacement, continue to affect the long-term well-being of these patients.[223A]

Thus far we have addressed surgical intervention in these patients. There is some experience albeit limited with radiofrequency perforation of the distal pulmonary infundibulum and valve in the patient with pulmonary atresia and ventricular septal defect followed by further balloon dilatation to widen the once imperforate pulmonary outflow tract.[224,225] These procedures are bold and imaginative, but too few have been done to comment on their merit other than in the individual case. Others have positioned an endovascular stent in a stenotic collateral, thereby increasing the pulmonary blood flow.[226–230] Certainly an anatomy that is considered inoperable in one unit may not be so considered elsewhere.

For patients with unoperated complex pulmonary atresia, one complication seen in the older child or adult is hemoptysis.[231–234] This could reflect hemorrhage from areas of pulmonary vascular obstructive disease or infection in areas of lung supplied by other types of collaterals. Embolotherapy may be helpful in some of these patients. In those patients with severe polycythemia and hyperviscosity, spontaneous pulmonary thrombosis can lead to infarction and bleeding in areas of cavitation.[235–237] Rupture of thin-walled aortopulmonary collaterals or transpleural vessels may also result in pulmonary hemorrhage and hemoptysis.[235,236] In this regard, Haroutunian and her colleagues described the pathological and clinical findings of pulmonary pseudofibrosis in cyanotic heart disease.[238] These pulmonary changes are ascribed to apical capping caused primarily by a plexus of transpleural collateral arteries and pleuritis following multiple small bleeds from these vessels and from parenchymal lesions caused both by varicosities of transpleural, bronchial, and other collateral vessels and by thromboses in small pulmonary arteries. These findings were found primarily in older adolescents and adults with longstanding cyanosis and polycythemia.[238] Not only can these changes result in hemoptysis, they can mimic tuberculosis.[238]

One of the interesting findings in patients with pulmonary atresia and ventricular septal defect is persistent airway hyperresponsiveness and airflow limitation after repair.[239–243] This association had been commented upon in earlier publications, but in only a few patients.[239,240] However, Ackerman and his colleagues of the Mayo Clinic found an extremely strong association between pulmonary atresia with ventricular septal defect and persistent airway hyperresponsiveness.[241] Haploinsufficiency at chromosome 22q11.2 did not contribute to this predilection for airway hyperresponsiveness.[241] In this particular study, 33 patients who had undergone repair for pulmonary atresia and ventricular septal defect were assessed for persistent airway hyperresponsiveness. Thirteen had the velocardiofacial syndrome all with 22q11.2 microdeletion and 20 were nonsyndromic. Overall, 66.7% met the criteria for airway hyperresponsiveness. This included 14 of 20 (70%) of the nonsyndromic group and 8 of 13 (62%) with the velocardiofacial syndrome. In the patients in this study diagnosed with airway hyperresponsiveness, pulmonary function testing revealed a nearly uniform reduction in both forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1). Ohuchi and coworkers measured the ventilatory response to exercise in patients with major aortopulmonary collateral arteries after definitive surgery.[243] They compared findings in this group with three other groups: (1) patients who had undergone repair of pulmonary atresia with ventricular septal defect, but without major aortopulmonary collateral arteries; (2) patients with tetralogy of Fallot who had undergone one-stage repair; (3) normal subjects. Those who had undergone repair of pulmonary atresia with ventricular septal defect with major aortopulmonary collateral arteries demonstrated a marked ventilatory impairment with a low diffusion capacity along with a pulmonary obstructive change contributed to the abnormal pulmonary gas exchange during exercise.[243] They showed that these patients had severe restrictive changes in the lung with a marked decrease in diffusion capacity and an elevated mean

pulmonary artery pressure; these changes were closely related to an increase in the perfusion–ventilation mismatch and dead space ventilation. This resulted in a decreased capacity for CO_2 excretion. Furthermore, they documented that the older the age at definitive repair, the lower the ventilatory efficiency during exercise. These patients also demonstrated poor exercise capacity with a markedly impaired response of stroke volume and a blunted chronotropic response.[243]

Aortic regurgitation is a well-known finding in these patients and likely reflects both dilatation of the aortic root in face of increased flow through the aortic valve, and as well lack of muscular support for the aortic valve.[166,180,244–248] In addition, aortic regurgitation may follow an episode of infective endocarditis. Dodds and his colleagues from the Mayo Clinic reported aortic valve replacement in 16 patients with pulmonary atresia and ventricular septal defect ($n = 12$) or tetralogy of Fallot ($n = 4$).[248] The median age of these 16 patients at the time of the initial repair was 13.5 years, and only 2 patients were younger than 10 years of age at the time of the repair. The median age of these patients at the time of aortic valve surgery was 30.5 years, and the median time from repair to the aortic operation was 13.5 years.[248] In 11 patients the authors were able to determine the degree of aortic regurgitation before operation. In 8 patients the severity was assessed at the time of the initial repair as none or trivial, and in 3 mild. At the time of aortic surgery, the 8 patients with none/trivial aortic regurgitation has progressed to moderate in 4 patients and severe in 4. Of those three patients with mild insufficiency, 1 had progressed to moderate and 2 to severe.[248] These data certainly demonstrate progression of aortic valve dysfunction after surgery.

Clearly, survival is but one indicator of outcome, but so many of these patients who survived heroic surgery will require repeated investigations and it is likely that in some, progressive right ventricular hypertension reflecting the intrinsically abnormal pulmonary circulation, will result in chronic right heart failure and death. We are reminded as we contemplate the fate of these children that these results of this early intervention as advocated by Hanley and his colleagues must be appreciated within the context of the natural history of this lesion. Only about 65% of patients survive to 1 year of age and slightly > 50% survive to 2 years even with surgical intervention. The initiative of early repair of tetralogy of Fallot ± pulmonary atresia as advocated by Castaneda, Hanley, Jonas and their colleagues should certainly reduce the morbidity and attrition of patients with these malformations.[165,182–185,210,211] Pigula and his colleagues reported the outcomes of 99 neonates and young infants < 90 days of age with tetralogy of Fallot or tetralogy with pulmonary atresia who underwent repair at the Boston Children's Hospital from 1988 to 1996.[249] There were 3 early deaths and actuarial survival was 94% at 1 year and 91.6% at 5 years. Freedom from re-intervention was 86% at 1 year and 73% at 5 years, acknowledging that those patients with tetralogy with pulmonary atresia had a significantly lower freedom from re-intervention.[249] But as stated earlier the long-term outcome of these patients is irrevocably linked to the necessity of conduit replacement during growth, and the resistance imposed by the often intrinsically abnormal pulmonary vascular bed (Fig. 18-9). From the global experience with these children, many will require repeated conduit changes and balloon angioplasty of their pulmonary arteries ± stenting. The fate of the endovascular stents and their effect on the remodeling of the proximal branches has not been completely defined. Not only are the outcomes of these patients related to the complexity of the pulmonary circulation, the 22q11 microdeletion may also influence speech and learning ability.[17–29,250–252] It is strange that those with the most disordered pulmonary circulation also have the predilection for the 22q11 microdeletion and the other disadvantages associated with this genetic disorder.[20,21,26,250] Finally, many of the follow-up issues will be the same as in the postoperative tetralogy patient (see Chapter 16). The need for pulmonary valve replacement is a reality for most of these patients, but the ability to implant percutaneously a pulmonary valve as achieved by Bonhoeffer and colleagues may be of great benefit to some of these patients.[253]

All references can be found at the end of the book. See pp. 697–704 for Chapter 18.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

19A

Robert M. Freedom and Shi-Joon Yoo

The Divided Right Ventricle

First described or recognized by Peacock in 1867,[1] the so-called double-chambered or divided right ventricle describes those conditions in which the morphologically right ventricle is divided or septated by muscular or fibrous structures.[2–22] This division can be identified in patients where the morphologically right ventricle has a right-hand pattern of internal organization, or where there is a left-hand pattern. The majority of reported cases of the divided right ventricle are characterized by muscular obstruction, which usually but not invariably produces some degree of obstruction within and between the component parts of the right ventricle. It is not surprising to find such patients defined as having "anomalous muscle bundles" of the right ventricle. Division of the right ventricle can occur at the junction between the inlet and trabecular components of the right ventricle, or more distal at the level of the infundibulum.[6–10,22] It has been suggested that the morphologically right ventricle is a tripartite structure with confluent inlet, apical trabecular, and infundibular or outlet components.[23] Anderson and his colleagues have argued that a number of congenitally malformed hearts including those with isolated right ventricular hypoplasia, Ebstein's malformation of the tricuspid valve with or without atresia, and divided right ventricle support the concept of the morphologically right ventricle as tripartite, not bipartite.[24] While this view is not universally held,[25] the concept has been widely assimilated.[26,27] One of the earliest full clinical descriptions of the patient with divided right ventricle was published in 1961 by Tsifutis and colleagues.[7A]

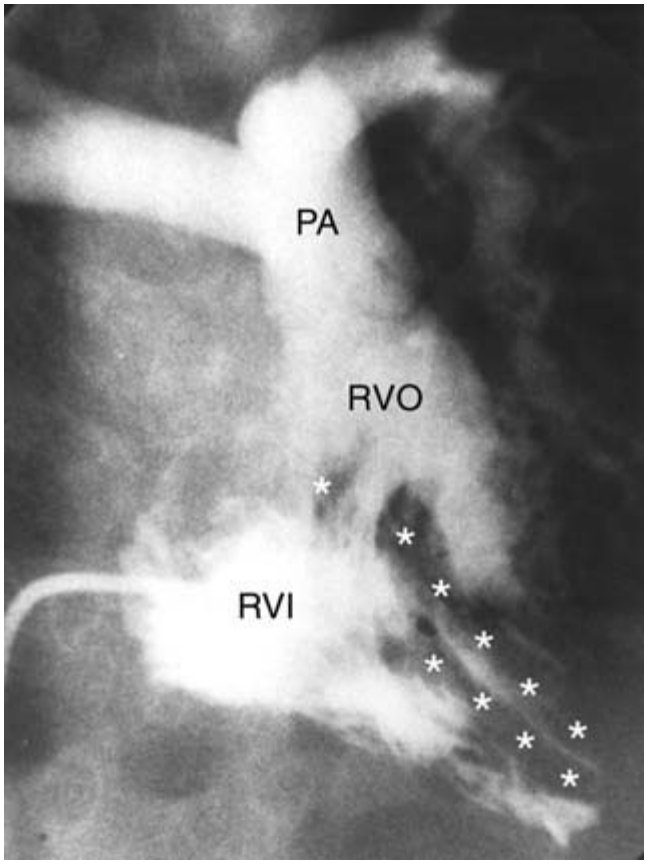
Restivo and his colleagues reviewed some years ago those forms of divided right ventricle, reminding us that anomalous muscle bundles of the right ventricle are but one of several conditions producing division of the right ventricle, and that an anomalous muscle band does not invariably produce a double-chambered ventricle.[28] Amongst those conditions producing a divided right ventricle in Restivo's *et al.*'s review is the anomalous septoparietal band; anomalous apical shelf, a condition resulting from an abnormal septoparietal band and hypertrophy of apical trabeculations; anomalous apical shelf with Ebstein's anomaly; an apical shelf confluent with the outlet septum in a heart with a two-chambered right ventricle giving the impression of a two-chambered left ventricle;[29] and sequestration of the outlet portion of the ventricle from a circumferential muscular diaphragm in a patient with tetralogy of Fallot (Fig. 19A-1). Indeed, the morphologic and angiocardiographic findings of muscular division of the right ventricle are quite diverse. Alva and colleagues suggested in 1999 that double-chambered right ventricle is likely the consequence of a high or low muscular division of the apical component of the right ventricle. They believe that the abnormal muscular bundle probably represents accentuated septoparietal trabeculations, rather than always being an abnormal moderator band.[30] The divided right ventricle may occur in isolation; with ventricular septal defect with or without left ventricular outflow tract obstruction; in complete or corrected transposition of the great arteries; in double-outlet right ventricle and in patients with pulmonary atresia and intact ventricular septum, amongst others.[27] Yoo and his colleagues have described four patients in whom the apical trabecular component of the right ventricle is sequestered from the rest of the right ventricle,[31] findings also published by Karczenski[22] (Fig. 19A-1C).

The divided right ventricle and ventricular septal defect

The divided morphologically right ventricle on the basis of abnormal muscle bundles can occur in isolation, but it is more commonly associated with a perimembranous, juxtatricuspid ventricular septal defect, usually occurring in > 50–75% of patients.[2–22,28,30,32] While the perimembranous defect can be large, it tends to be moderate in size, or smaller, and thus it is not surprising that the ventricular septal defect in patients with anomalous right ventricular muscle bundles tends to become smaller, or even close. When this occurs, and if the anomalous muscle bundles are severe, right ventricular pressure will become suprasystemic. In some patients when first seen the ventricular septum will be intact. The perimembranous ventricular septal defect is usually below the level of muscular division of the right ventricle, and thus the magnitude of the left-to-right shunt at ventricular level is usually hemodynamically independent of the muscular obstruction, and related to the size of the ventricular septal defect. We have commented elsewhere that the classic morphological features of tetralogy of Fallot may be complicated by more proximal muscular division of the right ventricle.[27] It is less common for the ventricular septal defect to be muscular or apical. Wang and colleagues have commented on the association between malalignment-type of ventricular septal defect and double-chambered right ventricle,[32] noting how common this is in this Oriental population.

Mechanism of acquired right ventricular outflow tract obstruction in ventricular septal defect

The development of right ventricular outflow tract obstruction is an important event in the patient with ventricular septal defect and may irrevocably alter the natural history.[18,19] It has



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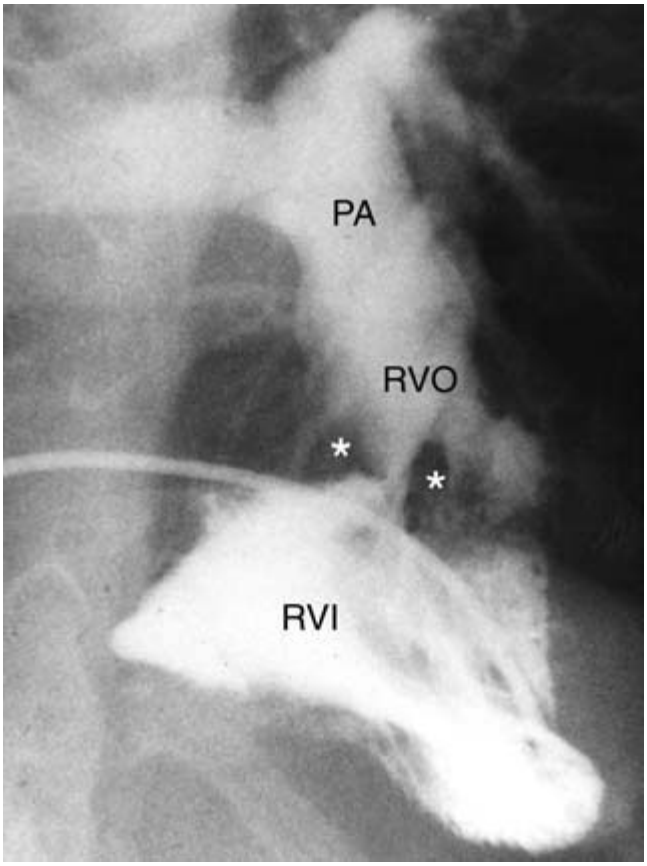

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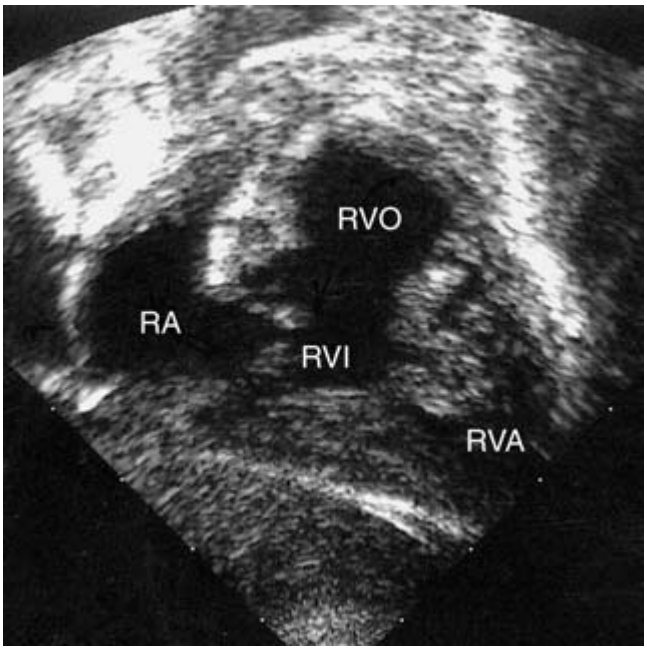

C

Fig. 19A-1 Various forms of divided right ventricle. **A**. Classic form of divided right ventricle. Muscular ring or shelf (asterisks) divides the right ventricle into two equal parts; the inlet (RVI) and outlet (RVO) components. The muscular ring consists of hypertrophied septomarginal trabecula, moderator band and ventriculoinfudibular fold. **B**. So-called os infundibular stenosis. The mouth of the infundibular or outlet part of the right ventricle shows circumferential constriction due to muscular or fibromuscular shelf or ring (asterisks). **C**. Apical sequestration. The apex of the right ventricle (RVA) is isolated from the inlet and outlet components by a dividing muscular shelf (asterisks). The blood flow from the inlet to the outlet of the right ventricle is not obstructed. The pulmonary valve (arrows) is stenotic. PA, pulmonary artery. (Reprinted from Yoo, *et al.*,[31] Copyright (1997), with permission from Excerpta Medica.)

been suggested that from 3% to 7% of patients with ventricular septal defect will acquire pulmonary outflow tract obstruction, usually within the first few years of life.[33–35] Those mechanisms responsible for the development of right ventricular outflow tract obstruction are diverse and have been summarized elsewhere.[27,35–39] However, since the report of Gasul and colleagues more than four decades ago of the development of infundibular obstruction in the patient with ventricular septal defect and transformation of an acyanotic patient into a cyanotic one, there was the inference that the anatomy responsible for this change was related to tetralogy of Fallot.[36] We addressed the mechanisms responsible for acquired right ventricular outflow tract obstruction in 20 patients with ventricular septal defect undergoing serial catheter studies, acquiring a pressure

gradient of > 25 mmHg over a period of nearly 4 years.[39] Of the 20 patients in this study, the mechanism of acquired right ventricular outflow tract obstruction was related to progressive hypertrophy and obstruction from anomalous right ventricular muscle bundles in 19, and hypertrophy of a malaligned infundibular septum in only 1 patient. The presence of a right-sided aortic arch in the patient with ventricular septal defect may be the harbinger of right ventricular outflow tract obstruction, but this does not invariably conclude in classic tetralogy.[27,33,40] Tyrrell and his colleagues have suggested that a right ventricular outflow tract more horizontal than normal is suggestive of the patient who will acquire the hemodynamics and morphology of tetralogy of Fallot.[41] These observations do not exclude the reality that some patients with the morphology of tetralogy of Fallot have initially only mild right ventricular outflow tract obstruction which may worsen with time.

The divided right ventricle and subaortic stenosis

A well-known relationship has been established in patients with a perimembranous ventricular septal defect, right ventricular anomalous muscle bundles and a subaortic abnormality, but the frequency of this association as stated varies widely.[27,32,42–49] We have addressed in an echocardiographic study this association in 36 patients with perimembranous ventricular septal defect and right ventricular anomalous muscle bundles.[44] Eighty-eight per cent of these patients had echocardiographic evidence of an associated subaortic abnormality, and in a number of these patients, Doppler evidence of progression of the left ventricular outflow tract gradient was provided. We have observed progression of a subaortic deformity initially producing no obstruction, to some years later severe left ventricular outflow tract obstruction after surgical closure of a ventricular septal defect ± resection of anomalous muscle bundles of the right ventricle. Others in their cataloging of patients with ventricular septal defect and left ventricular outflow tract obstruction have commented on the association with anomalous right ventricular muscle bundles.[45] Vogel when in Toronto reported on 41 patients with ventricular septal defect and subaortic stenosis, six of them having anomalous right ventricular muscle bundles.[43] The ventricular septal defect may be perimembranous or malaligned, with those having the malalignment defect more likely to have a subaortic abnormality.[32,43] From clinical experience, it has become clear that the subaortic abnormality may progress to severe left ventricular outflow tract obstruction, before closure of the ventricular septal defect and resection of the right ventricular muscle bundles, or after.[46] For this reason, we recommend that at the time of surgical repair of ventricular septal defect and right ventricular muscle bundles the subaortic abnormality be addressed and resected.[27]

Outcome analysis

A divided right ventricle is an uncommon congenital heart malformation, and the diagnosis is made only infrequently in the fetus. Thus there is not a substantial body of data indicating outcome of this disorder once recognized prenatally.[50–52] Lougheed and her colleagues have reported the development of acquired right ventricular outflow tract obstruction in the recipient of fetal twin-to-twin transfusion, a complication that occurred in about 9.6% of such pregnancies.[52] There is a suggestion of a possible relationship between a divided right ventricle and Down syndrome, and a divided right ventricle has been diagnosed in the patient with Noonan's syndrome.[53,54] Muscular division of the right ventricle is usually recognized in infancy or childhood, but some patients with this condition will only be recognized as adults, at times a difficult diagnosis to establish in the adult.[55–57] The initial methodology to establish this diagnosis was cardiac catheterization with angiography,[27,58–63] but today the diagnosis can be reliably established with cross-sectional echocardiography or MR imaging.[64,64A]

Despite the morphological differences between patients with tetralogy of Fallot and those with muscular division of the right ventricle, these patients are often grouped together. While some patients with tetralogy of Fallot will also have muscular division of the right ventricle[27,65] and some patients with tetralogy of Fallot may develop muscular obstruction after repair (about 3%), these are two fundamentally different conditions.[66] The ventricular septal defect in patients with anomalous muscle bundles dividing the right ventricle tends to be only moderate in size, and some may close, or nearly close.[27] This is much less common in patients with tetralogy of Fallot. Pulmonary annular hypoplasia is much less common in patients with a divided right ventricle when compared to patients with classic Fallot anatomy. Perhaps one of the most striking differences between these two groups of patients is the predilection for a subaortic abnormality in patients with anomalous muscle bundles dividing the right ventricle, a situation very uncommon in patients with tetralogy of Fallot.[27,44,45]

Although the pressure difference across the site of muscular obstruction tends to increase, this does not invariably occur, and we have observed in some patients a stable and non-threatening pressure gradient for many years. We have found it difficult to predict those in whom progression is likely to occur, or in those where it tends to worsen.[39] Clearly, in other patients the obstruction may worsen with time, and in a number of these patients, coincidentally, the ventricular septal defect will become smaller, or close, with the right ventricle becoming supra-systemic.[27,39] Right ventricular dysfunction is more likely to occur in those patients in whom the ventricular septal defect has become restrictive, or closed. Vogel when in Toronto and his colleagues called attention to the association of ventricular septal defect, right ventricular anomalous muscle bundles and a fixed subaortic abnormality.[44] In most of these patients the fixed subaortic abnormality did not pose a significant obstruction, but the finding was confirmed at surgery.[44]

There is considerable surgical experience with the resection of dividing muscle bundles of the right ventricle, with repair of associated anomalies, usually ventricular septal defect, pulmonary valvular stenosis, aortic valve prolapse, a fixed subaortic abnormality, or double-outlet right ventricle.[7,8,27,44,55,67–73] Indeed Kirklin and Barratt-Boyes state that in-hospital mortality after repair of this anomaly should approach zero.[67] Surgery is rarely required in infancy, and mortality is very low, usually less than 1%, with little requirement for reintervention. Surgical exposure and resection/division of the anomalous muscle bundles of the right ventricle can usually be accomplished through the right atrium, but a small right ventricular incision may be necessary.[67–73] In those patients where the right ventricle is severely impaired in function preoperatively, function improves, usually dramatically so, once the obstruction is relieved. Kveselis and colleagues reported in 1984 the long-term follow-up of 20 patients who underwent repair of a double-chambered right ventricle.[73] At a mean follow-up of 19 years, 17

patients were in New York Heart Association functional class I, 1 patient was in class II and 2 patients were in class III. Reoperation was performed in 2 patients (10%), and at present only 1 patient (5%) is considered to have hemodynamically significant cardiac compromise. Aortic regurgitation, not present in any patient preoperatively, developed in 5 patients (25%). Mild residual right ventricular outflow obstruction was present in 2 (10%) and the murmur of a hemodynamically insignificant residual ventricular septal defect or tricuspid regurgitation was present in 5 patients (25%). One patient (5%) had cardiomegaly (cardiothoracic ratio > 0.55). The frequency of infective endocarditis in the postoperative follow-up period was 1 per 388 patient-years. Thus, 20 years after repair of double-chamber right ventricle carried out albeit in a considerably earlier era, mild residua and sequelae were common, but serious cardiac compromise was infrequent.[73] In a more recent study published in 2000, Galal and his colleagues reported on the outcome of surgical repair of 73 patients with divided right ventricle.[70] Of these 73 patients, 31 had a large ventricular septal defect, 25 a small ventricular septal defect, and in 17 the ventricular septum was intact. No surgical mortality was encountered in the entire series. Five of the 17 with an intact ventricular septum had preoperative findings of right heart failure. Seven patients had a small residual VSD, and in all but 5 patients, Doppler echocardiography showed normal right ventricular flow velocities. Twenty-five patients had mild tricuspid regurgitation, 7 had trivial tricuspid regurgitation, and the remainder had no tricuspid regurgitation.[70]

Finally, Massin reported the development of a divided right ventricle after repair of a large, hypertensive ventricular septal defect.[74] This child underwent surgical repair of perimembranous ventricular septal defect at the age of 7 months because of severe pulmonary artery hypertension and growth retardation. At this time, no pressure gradient was measured within the right ventricle and no muscle proliferation was observed on echocardiography or right ventriculography. Postoperative follow-up revealed hypertrophy of the moderator band accompanied by progressive development of a right midventricular pressure gradient, which reached 60 mmHg at the age of $3\frac{1}{2}$ years. The child was operated after invasive confirmation of the diagnosis of double-chambered right ventricle and the hemodynamic data. Postoperative prophylaxis against bacterial endocarditis is warranted in most if not all patients who have undergone repair of a divided right ventricle.

All references can be found at the end of the book. See pp. 704–6 for Chapter 19A.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

19B

Robert M. Freedom and Shi-Joon Yoo

Isolated Right Ventricular Hypoplasia

Isolated right ventricular hypoplasia is a very rare congenital cardiac malformation characterized by absence or severe attenuation of the apical trabecular component of the right ventricle (Fig. 19B-1).[1–7] This condition frequently occurs with an atrial septal defect and this combination is a rare cause of "silent" cyanotic congenital heart disease. The tricuspid valve may be abnormally small, or frankly obstructive.[1–9]

Prevalence and genetics

Isolated right ventricular hypoplasia is very uncommon and is not cataloged in any of the studies of the prevalence of congenital heart disease. Interestingly, however, there does appear to be a familial tendency and several publications have emphasized this aspect of this disorder.[10–12] In the report of Chessa and colleagues, a 1-day-old male child and his 34-year-old father were both found to have isolated right ventricular hypoplasia with atrial septal defect.[12] An autosomal dominant mode of inheritance was thought likely for this rare congenital anomaly in this particular family.[12]

Morphology

As one assesses the form of the morphologically right ventricle, there are those that consider this ventricle to be a tripartite structure, with an inlet, apical trabecular zone, and outlet or infundibular zone.[9,13–15] Intrinsic to those hearts with so-called isolated right ventricular hypoplasia is marked attenuation or absence of the trabecular component (Fig. 19B-1). Virtually all of the reported cases have been in situs solitus and the internal organization of the right ventricle conforms to a right-hand pattern. In frontal right ventriculography, it appears that the apex of the right ventricle is amputated.[8,9] The tricuspid valve annulus may be small and tricuspid stenosis has been described in some of these patients. What leads to cardiac symptomatology in these patients is the atrial septal defect that permits an obligatory right-to-left shunt.[1–9] Right ventricular hypoplasia can occur with a wide range of associated cardiac malformations. This association will be considered in the individual chapters.

Outcome analysis

There are no data on fetal recognition, and patients with disorder can present in infancy, childhood, or even as adults.[1–7,10–12,16–23] The most common presenting finding is that of progressive cyanosis and/or a heart murmur. In some patients with a restrictive interatrial communication, hepatomegaly may become conspicuous.

The treatment options for patients with isolated right ventricular hypoplasia depend on the severity of the apical attenuation and form and function of the tricuspid valve.[1–9,19–21,24–31] Complete or partial closure of the atrial septal defect, closure of the atrial septal defect with a bidirectional cavopulmonary shunt (the so-called one-and-a-half ventricle repair) and a Fontan-type operation have all been used to treat patients with isolated right ventricular hypoplasia. Quantification of the right ventricular cavity size and calculation of the tricuspid valve *Z*-value may be helpful preoperatively in trying to identify the most appropriate form of surgical therapy.[32,33] Temporary balloon occlusion of the atrial septal defect performed either pre- or intraoperatively may also be helpful in determining whether the patient can tolerate closure of the atrial septal defect alone.[34–36] Patients treated with a so-called one-and-a-half ventricle repair would not be anticipated to develop pulmonary arteriovenous fistulae as hepatic venous blood is conveyed into the pulmonary circulation (see Chapters 38 and 39). With pulsatile pulmonary blood flow conveyed into the cavopulmonary anastomosis, one potential complication is an anastomotic aneurysm involving the superior caval vein.[37]

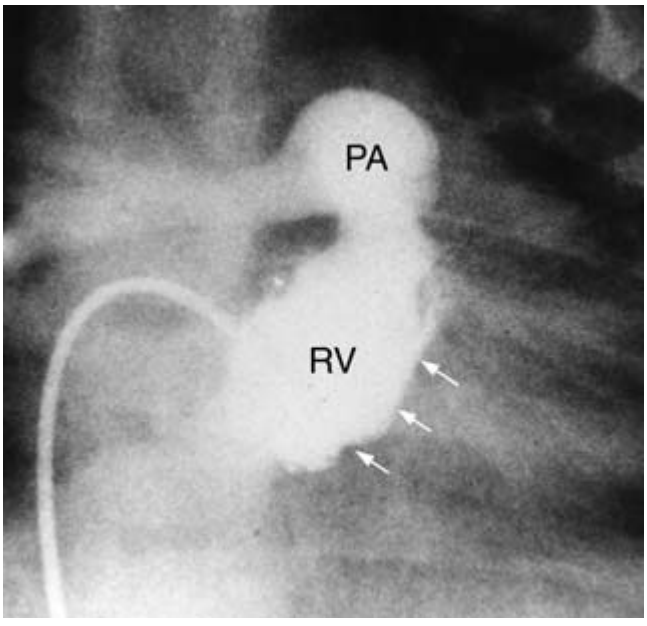

Fig. 19B-1 Isolated hypoplasia of the right ventricle (RV). Right ventriculogram shows small right ventricular cavity with marked attenuation of the apical trabecular zone (arrows). PA, pulmonary artery.

All references can be found at the end of the book. See pp. 706–7 for Chapter 19B.

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20

Rajesh Bagtharia, Robert M. Freedom, and Shi-Joon Yoo

Aortopulmonary Window

The aortopulmonary window, first described by Elliotson in 1830,[1] and first diagnosed during life by Dadds and Hoyle[2] is an uncommon cardiac anomaly characterized by a communication, often large, between the ascending aorta and pulmonary trunk or right pulmonary artery (Fig. 20-1).[2–11] This malformation is clearly different from a fifth aortic arch which also originates from the ascending aorta proximal to the brachiocephalic arteries, but clearly has length.[12–16] The aortopulmonary window is considered by some clinically related to common arterial trunk and located in the same area of the heart. Yet evidence marshalled by Kutsche and Van Mierop suggests that these two anomalies are likely pathogenetically unrelated.[7] The shape and size of the aortopulmonary window are variable, but it is always related to the aortic wall above the aortic sinuses. It is certainly not an arterial duct, although it has certainly been confused with this structure.[10,11] The aortopulmonary window may occur in isolation, but it has been found with a wide variety of other cardiac anomalies. Yen Ho and her colleagues remind us that the designation of this defect as an "aortopulmonary septal defect" is inappropriate because usually there is no or little septum between the arterial trunks.[5]

Incidence

The New England Regional Infant Cardiac Program identified only 7 of 2251 infants with an aortopulmonary window.[17] Two of these occurred in isolation; 3 were in patients with associated interruption of the aortic arch; and one each with coarctation of the aorta and tetralogy of Fallot. Kutsche and Van Mierop defined an incidence of this anomaly of 0.2% (13 of 6522 children with congenital heart disease).[7] The incidence for this lesion from the Hospital for Sick Children in Toronto is 0.171.[18] Of 4390 patients surveyed by the Baltimore–Washington Infant Study, an aortopulmonary window was identified in only 8.[19] In the recently published Prospective Bohemia Survival Study only 8 patients with an aortopulmonary window were identified among 815 569 children born between 1980 and 1990.[20]

Non-association with 22q11 deletion

There is a well-known association between abnormalities of aortic arch, interruption of the aortic arch; truncus arteriosus, and other conotruncal abnormalities and 22q11 deletion. This association has *not* been documented with aortopulmonary septal defect.[7,21–24]

Morphology and morphogenesis

Kutsche and Van Mierop define three types of aortopulmonary window: (1) a defect with a more or less circular border, located between the arterial valves and the bifurcation of the main pulmonary artery; (2) a similarly located fenestration in which the border represents a helix; (3) a large defect with no posterior or distal border.[7] These authors suggest a different pathogenesis for each of the three types. The first type may reflect nonfusion of the embryonic aorticopulmonary and truncal septa. The second type suggests malalignment of the embryonic aorticopulmonary and truncal septa, while the third type results from total absence of the embryonic aorticopulmonary septum.

Yen Ho and her colleagues have examined 25 specimens with aortopulmonary window.[5] The window was in a proximal position in 3 specimens; intermediate in 3 specimens; distal in 16; and confluent in 3. Of the 16 specimens with the distal type of aortopulmonary window, the right pulmonary artery arose from the aorta in 7. This is a well-known association.[7,25–27]

Associated malformations

Data compiled by Kutsche and Van Mierop reviewing 249 patients with aorticopulmonary window (including 13 of their own) showed that in *c*. 48% of the patients where information was available no other cardiac lesions were identified, while in 52% associated cardiac malformations were present.[7] Perhaps the most common associated lesion was either type A interruption of the aortic arch or severe preductile coarctation of the aorta (Figs 20-1C, 20-2).[5,7,9,10,11,25–27] Other lesions include anomalous origin of one or both coronary arteries from the pulmonary trunk; right pulmonary artery from the ascending aorta, especially in those with a distal type of aortopulmonary window; tetralogy of Fallot; bicuspid aortic valve; ventricular septal defect; pulmonary atresia and ventricular septal defect; or cor triatriatum.[10,11] Aortic atresia has been found in patients with an aortopulmonary septal defect and interruption of the aortic arch.[10,11,28–30] Delayed recognition of anomalous origin of the circumflex coronary artery originating from the pulmonary artery many years after repair of aortopulmonary window has been reported.[31] Complete transposition of the great arteries has been complicated by a large aortopulmonary communication.[32,33] A double aortic arch has also been reported in a patient with an aortopulmonary window.[34] An anomalous left coronary artery from the main pulmonary trunk was noted in a patient with tetralogy of Fallot and aortopulmonary window.[34A]

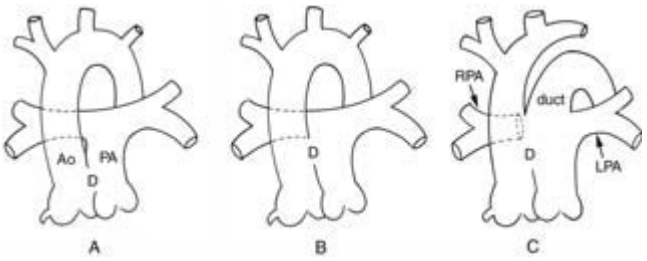


Fig. 20-1 Types of aortopulmonary window. **A**. Proximal type involving the midway between the arterial valves and the pulmonary arterial bifurcation. **B**. Distal type involving the pulmonary arterial bifurcation with both pulmonary arteries arising from the pulmonary trunk. **C**. Distal type involving the pulmonary arterial bifurcation with the right pulmonary artery (RPA) arising from the ascending aorta. Association with interruption of the aortic arch is common. Ao, aorta; D, defect; LPA, left pulmonary artery; PA, main pulmonary artery.

Gerlis and his colleagues have reviewed the literature addressing the presence or absence of the arterial duct in the patient with an aortopulmonary window.[35] Obviously an arterial duct is present in those patients with an aortopulmonary septal defect and interruption of the aortic arch. Gerlis reminds us that Coleman and his colleagues[36] consider the association between aortopulmonary window and patent arterial duct to be rare. However, data compiled by Neufeld and his colleagues indicated that among 66 cases of aortopulmonary window, a patent arterial duct was found in 8,[36] similar to that reported by Deverall and his colleagues (2 of 8 having an arterial duct).[37] A fifth aortic arch with a systemic-to-systemic connection was identified in a patient with an aortopulmonary septal defect, discordant ventriculoarterial connections, pulmonary atresia, a right aortic arch, and an aortic coarctation.[14,15,35]

Extracardiac malformations

We have identified at the Toronto Hospital for Sick Children, 42 patients with an aortopulmonary window from 1969 to 1999. Noncardiac abnormalities were identified in 15 patients and included musculoskeletal [arthrogryposis (n = 2), scoliosis (n = 2), cervical spine fusion (n = 1), torticollis (n = 1), congenital dislocation of hip (n = 1)], CNS [microcephaly (n = 2), trigonocephaly (n = 1), Dandy–Walker variant (n = 1), syrinx in cervical cord (n = 1)], renal [renal crossed ectopia (n = 1), bilateral hydronephrosis (n = 1), double ureter (n = 1)], pulmonary [double right main bronchi (n = 1), main stem bronchus stenosis (n = 1), tracheal stenosis (n = 1)], hand and feet abnormality [bilateral simian crease (n = 2), polydactyly and syndactyly (n = 1)], gastrointestinal [anal stenosis (n = 1)] and VACTERL association (n = 1).

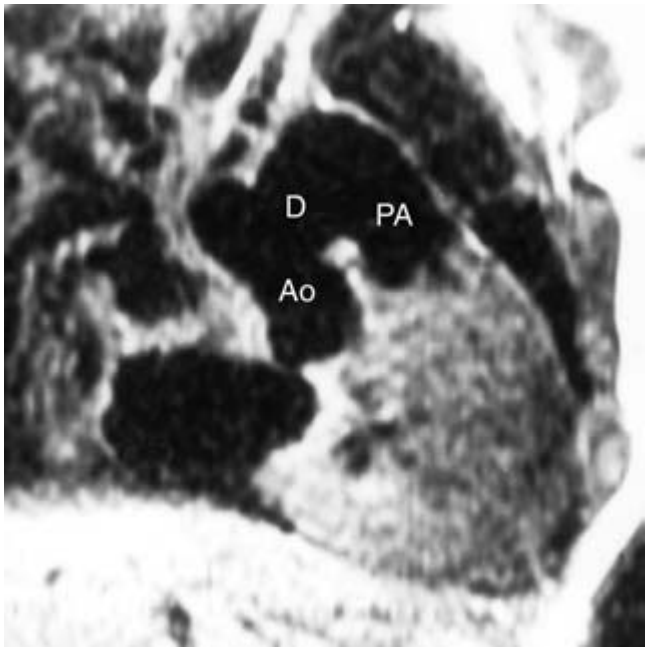
Outcome analysis

There are few if any data on fetal recognition of the aortopulmonary window.[37A] The timing of clinical presentation of patients with aortopulmonary window may be in part determined by the associated lesions. Those with associated interruption of the aortic arch or severe preductile coarctation of the aorta will present in the neonatal period coincident with ductal closure. The defect is small in about 10% of all patients with aortopulmonary septal defect, and thus these fortunate few would present considerably later, much like the child with a small-to-moderate sized patent arterial duct in isolation. Because in most patients with this anomaly, the defect is moderate to large, it is not surprising that symptoms related to a large pulmonary blood flow and pulmonary hypertension, tachypnea, dyspnea, poor feeding, and diphoresis are observed late in the first month of life coincident with maturation of the fetal pulmonary vascular bed. Rarely a patient will present late in life, usually with pulmonary vascular obstruction, as in the 58-year-old patient described by Muller *et al.*[38A]

It is just over half a century ago in 1952 when Gross of the Children's Hospital in Boston first surgically closed an aortopulmonary window by ligating the connection between the arterial trunks.[39] This technique fell out of favor because one could distort the semilunar valves or impinge on the left coronary artery. Since that initial report there have been many reports of the repair of this malformation using a variety of techniques.[11] Repair has been accomplished via the main pulmonary artery or the aorta. For a number of years most now favor the aortic approach as this allows close inspection of the coronary ostia. A Dacron patch is used to close the defect. When the operation is carried out before the development of significant pulmonary vascular disease in those patients with the aortopulmonary window in isolation, the outlook is excellent. For those with more important associated anomalies including anomalous origin of the right pulmonary artery from the ascending aorta, interruption of the aortic arch, and/or abnormal origin of the right coronary artery, surgery has a higher risk. During the past decade there have been a number of substantial series reporting the surgical outcomes of this uncommon malformation. The Pediatric Cardiac Care Consortium has reported its experience with 26 patients with an aortopulmonary window identified between 1985 and 1993.[39] Twenty-five were infants and the other patient was 3.2 years of age. In this series, only 3 did not have any associated anomalies. All the patients underwent surgery to close the defect, with 1 death.

McElhinney and his colleagues published in 1998 the early and late results after repair of aortopulmonary septal defect and associated anomalies in infants < 6 months of age.[40] This group identified 24 patients with aortopulmonary septal defect between 1972 and 1995 who underwent repair at a mean age of 34 days, ranging from 2 to 172 days. Twelve patients had complex associated anomalies including 9 with interrupted or hypoplastic arch, tetralogy of Fallot with (1) and without (1) pulmonary atresia, and one patient with transposition. There were no early or late deaths among the 12 patients with uncomplicated aortopulmonary window. Four early deaths occurred in the complex group, with 1 late death. Most of the survivors in the complex group have or will require re-intervention for recurrent arch obstruction.

Hew and colleagues have analyzed the experience of the Boston Children's Hospital with repair of 38 patients with aortopulmonary septal defect seen between July 1975 and March 1999.[41] These patients underwent repair at a median age of 5 weeks, with a median weight of 3.9 kg. The median follow-up was 6.6 years, ranging from 0.8 to 26 years. Additional defects were encountered in 25 (65%) patients, including 7 with interrupted aortic arch, tetralogy of Fallot in 7, ventricular septal defect in 5, "single" ventricle anatomy in 3, coarctation of the aorta in 3, and anomalous origin of the coronary artery in 1 patient. There were 3 in-hospital deaths (7.9%). Actuarial sur-



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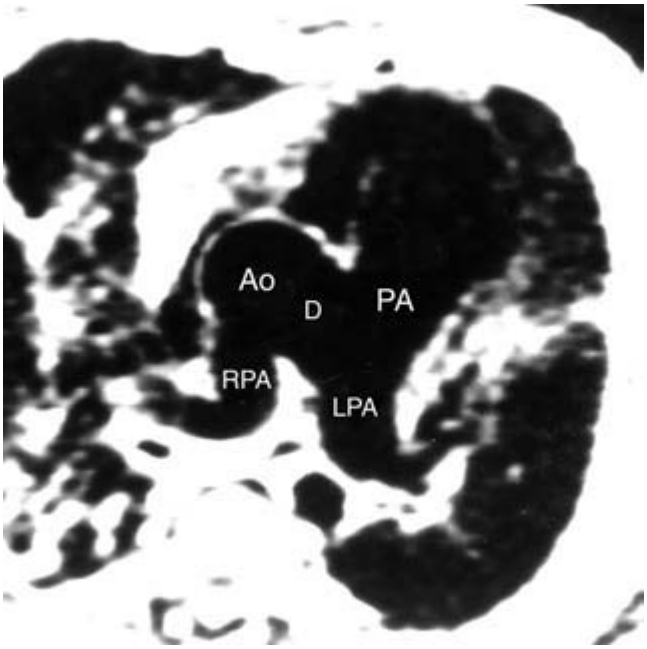

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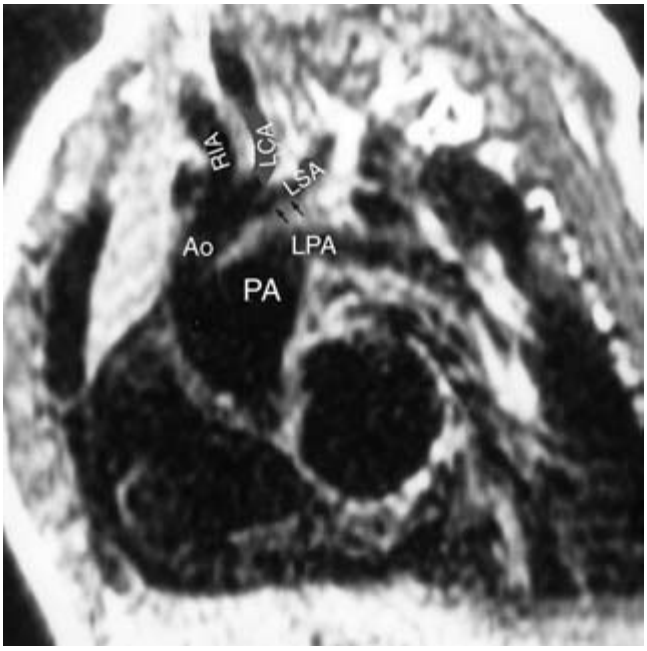

C

Fig. 20-2 Distal type of aortopulmonary window (D) with the right pulmonary artery (RPA) arising from the ascending aorta and interruption of the aortic arch. **A**. MR in right anterior oblique view shows the aortopulmonary septal defect. **B**. MR in transverse view shows the aortopulmonary septal defect and the anomalous right pulmonary artery. **C**. MR in oblique coronal view shows interrupted aortic arch distal to the origin of the left subclavian artery (LSA). Ao, aorta; PA, pulmonary artery; LCA, left common carotid artery; RIA, right innominate artery. (Reprinted from Yoo *et al*.[25A] with permission from the American Journal of Roentgenology.)

vival was 88% at 10 years (Fig. 20-3). Three patients required re-intervention for stenosis of the great artery(s). Freedom from re-intervention was 70% at 10 years. Three surgical approaches were used in this series: (1) via an aortotomy in 45%; (2) an incision through the defect in 31%; (3) via an incision in the pulmonary artery in 24%. A single patch was used in 30 patients (79%). In 4 patients direct suture closure was accomplished and in 3 patients a double-patch was required. The 1 patient with "single" ventricle anatomy underwent narrowing of the aortopulmonary window and an atrial septectomy. These authors found that closure of the defect through the pulmonary artery had a higher need for re-intervention. Also, the group with associated tetralogy of Fallot had a higher rate of re-intervention.[41] Similar results have been published by Backer and Mavroudis.[38]

Data from the Toronto Hospital for Sick Children was recently analyzed by Bagtharia and our colleagues.[41B] We reviewed all consecutive cases of aortopulmonary window (n = 42) presenting at the Toronto Hospital for Sick Children from 1969 to 1999. We analyzed the data in terms of the following birth cohorts as follows: 1970–79, n = 12; 1980–89, n = 11; and 1990–99, n = 19. There were 23 females and 19 males, with a median birth weight (n = 37) of 3.10 kg (range 1.88–4.7 kg) and a median gestational age (n = 38) of 39 weeks (range 35–42 weeks). The median age of presentation was 62 days, ranging from birth to 6 years. Type I aortopulmonary defect was seen in 37 patients (92%). Type II defect with aortic origin of right pulmonary artery was present in 2 patients (5%) while type III defect was recognized in 1 patient (3%). The size (n = 32) of the defect ranged from 2 to 30 mm with a mean of 10 mm. Two

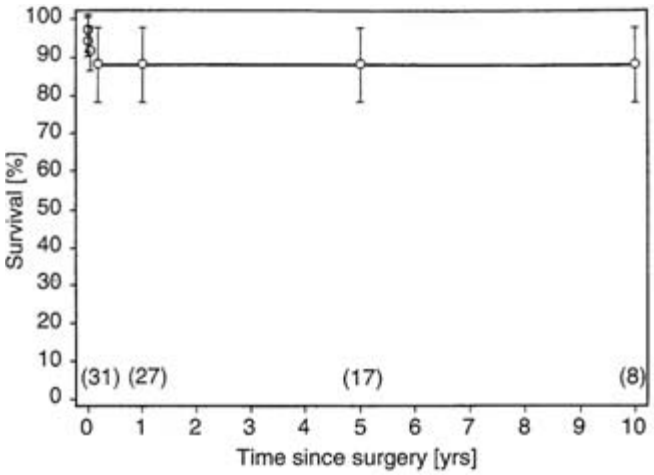

Fig. 20-3 Kaplan–Meier actuarial survival of 35 patients treated at the Children's Hospital in Boston with aortopulmonary window after hospital discharge. (Reproduced from Hew *et al*.,[41] *Cardiology in the Young* 2001; **11**: 385–390, with kind permission.)

patients (5%) had a small fistulous defect. Eight patients had an aortopulmonary window in isolation while 34 patients had an associated cardiac abnormality. Subsequent birth cohorts did not show any trend with associated cardiac abnormalities (P = 0.29). These were as follows: 1970–79, 67%, (n = 8); 1980–89, 91%, (n = 10); and 1990–99, 84%, (n = 16). Left ventricular outflow obstruction in association with other cardiac anomaly was the most common concomitant abnormality. This included (n = 17) subaortic stenosis, tunnel narrowing of the left ventricular outflow tract, type A and B interruption, aortic atresia, coarctation, and isthmal hypoplasia together accounting for 50% of association with aortopulmonary window. Type A interruption of aortic arch was seen in 5 patients and severe coarctation in 3 patients, aortic isthmal hypoplasia in 3 patients, aortic atresia in 2 patients, and type B interruption in 1 patient. All the aortic obstructive cases were associated with an arterial duct. Two patients with aortopulmonary window had associated fibromuscular subaortic stenosis and 1 patient had tunnel narrowing of the left ventricular outflow tract. This patient also had concomitant pulmonary vein stenosis and mitral stenosis. Two patients were found to have superior inferior ventricles (topsy-turvy heart) with aortic isthmal hypoplasia.[10,11] There were 5 cases with a right aortic arch in association with other cardiac abnormality of atrial and ventricular septum and 1 patient with vascular ring. None of the patients with right aortic arch had tetralogy of Fallot. Tetralogy of Fallot was seen in 2 patients one of whom had nonconfluent pulmonary arteries with the left pulmonary artery arising from a left-sided arterial duct.[42] Significant trends were related to groups defined by year of birth: 1969–79, n = 12; 1980–89, n = 11; 1990–99, n = 19. The median age at first assessment was 3.7 months, 6 months, and 2.4 months, respectively. Death before repair occurred in 17%, 18%, and 5%, respectively. The median age at repair was 5 months, 2.2 months and 3.3 months. Repair of other cardiac defects (25%, 44%, and 72%), death on first day after repair (0%, 11%, and 6%), total deaths (33%, 27%, and 11% respectively) showed these trends over the three eras. In our analysis, shock (P = 0.02), cyanosis (P = 0.01) on presentation, "topsy-turvy" heart or superoinferior ventricles (P = 0.004), type A (P = 0.05) and type B (P = 0.02) interruption of aortic arch, aortic isthmal hypoplasia (P = 0.03), aortic origin of the right pulmonary artery (P = 0.04) and prostaglandin therapy (P = 0.04) before aortopulmonary window repair were significant risk factors for mortality. Other series with somewhat smaller cohorts showed similar results.[43,44] One of the more difficult management issues is those patients with an aortopulmonary window and "single" ventricle malformation.[45,46]

A small aortopulmonary window or a residual communication has been closed with a transcatheter technique.[47–49] Whether this could compromise a coronary ostium is unclear.

In summary, repair of aortopulmonary window can be carried out with low mortality. Re-intervention may be necessary, often in those with associated cardiac anomalies, including interruption of the aortic arch or tetralogy of Fallot. Stenosis of the ascending aorta or pulmonary artery is uncommon after repair, remembering that repair through a pulmonary arteriotomy may be associated with a greater requirement for re-intervention. In those patients old enough to exercise, this testing is probably important to exclude myocardial ischemia reflecting damage to the coronary ostia adjacent to the defect.

All references can be found at the end of the book. See pp. 707–8 for Chapter 20.

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Lee N. Benson

Hypertrophic Cardiomyopathy

Introduction

Hypertrophic cardiomyopathy (HCM) is a common, complex, inherited myocardial disorder. Described over a century ago, it has, only since the late 1950s, been the subject of systematic investigation.[1–10] An important cause of disability and death in patients of all ages, sudden death in the young patient is the most devastating consequence of its natural history.

The characteristic morphological presentation is that of inappropriate myocardial hypertrophy in the absence of other obvious causes, such as valvular heart disease, systemic hypertension, catecholamime secreting tumors, coarctation of the aorta, hyperthyroidism or any other condition that results in myocardial hypertrophy. HCM is a heterogeneous group of disorders, the diversity of which is most apparent in the pediatric age group. The disorders can be divided into primary and secondary forms, where the primary form is familial (so-called "familial HCM"), and typically devoid of clinical findings outside of the heart (and the main subject of this chapter). The secondary form encompasses syndromes such as Friedreich ataxia or Noonan syndrome or metabolic disorders such as mitochondrial myopathies or carnitine deficiency states (Table 21-1).[11–13] Indeed, secondary HCM accounts for 30–40% of all HCM patients < 2 years of age.[13A]

Non-familial hypertrophic cardiomyopathy

There are many isolated reports which describe various syndromes and disease states where HCM is a component of the clinical presentation. However, there are also a number of disorders where HCM is seen with sufficient frequency that it has become a component, within the overall constellation of the specific disorder (Table 21-1).

Friedreich ataxia (FA) is a progressive spinocerebellar degenerative disease characterized by ataxia of the limbs and trunk, dysarthria, loss of deep tendon reflexes, sensory abnormalities, skeletal deformities, and cardiac involvement. It is an autosomal recessive genetic disorder, linked to a gene on chromosome 9, encoding the protein frataxin. Frataxin is a mitochondrial protein involved in iron homeostasis, and abnormalities in its structure lead to mitochondrial dysfunction, and poor cell stability to oxidative stress. FA is frequently associated with concentric HCM[14] although asymmetric hypertrophy can also be observed. Not infrequently, this HCM may evolve into a dilated form[15] as observed by Casazza and Morpurgo, who found 17% of 66 FA patients developing a hypokentic dilated cardiomyopathy. The prevalence of HCM varies amongst studies, but is more likely the younger the age at presentation,[16,17] and with increasing repetitions of the gene mutation.[15,18] Ninety-five per cent of neurologically symptomatic patients may have cardiac involvement.[19] No specific proven therapy is available, although the use of idebenone, a coenzyme Q_{10} analog appears promising, as a free radical scavenger.[20] Progressive neurological dysfunction is common, with death from respiratory failure in later life. Cardiac death can also occur, primarily in those developing a dilated cardiomyopathy.

HCM can be seen in 20–30% of patients with the autosomal dominant Noonan syndrome, which is characterized by hypertelorism, a downward slant to the eyes and low set posteriorly rotated ears.[21] The cardiac manifestations include an unusual type of pulmonary valvular dysplasia, which shows a familial tendency with first-degree relatives. Additionally, a number of studies have defined the association of a hypertrophic cardiomyopathy, clinically indistinguishable from familial HCM in 20–30% of affected patients.[22–24] Histological examination reveals similar findings to familial HCM, with myocellular disarray in the interventricular septum and free wall[25] in up to 20–24% of histologically examined fields, compared to normal controls with 2.5–3.8% cellular disarray. The risk of congestive heart failure is more common, however, than in familial HCM[24] and there is an increased risk of sudden death. Morphologically, in addition to left heart involvement, infundibular subvalvular right ventricular hypertrophy can occur in the absence of pulmonary valvular stenosis, as a component of the generalized myocardial disorder.[26,27]

Infants or neonates exposed to corticosteroids or adrenocorticotrophic hormone[28,29] often develop a transient biventricular hypertrophy, occasionally with outflow tract obstruction. Similarly, elevated levels of insulin during organogenesis in the fetus, owing to maternal hyperglycemia or fetal β-cell hypertrophy,[30–32] can result in a HCM-like picture with septal hypertrophy and outflow tract obstruction in up to 30% of affected mothers, 10% of such patients presenting with cardiac dysfunction. Follow-up studies of this population[32] suggest, despite symptomatic presentations (e.g. cardiorespiratory distress) the course is benign with resolution of the septal hypertrophy within 2–12 months. Most infants need only supportive care, and if pharmacological support is required, propanolol is the drug of choice. Indeed, improved glucose homeostasis during pregnancy has resulted in resolution of fetal hypertrophy observed during gestation.[33] Remodeling of the ventricle toward normal is the rule and the prognosis is excellent.[34,35]

Table 21-1 Conditions associated with non-familial hypertrophic cardiomyopathy*

Syndromes	Beckwith–Wiedemann syndrome
	Cardiac–facial–cutaneous syndrome
	Costello syndrome
	Down syndrome
	Friedreich's ataxia
	Lentiginosis (LEOPARD syndrome)
	Naxos syndrome
	Noonan's syndrome
	Williams syndrome
Secondary forms	Anabolic steroid therapy and abuse
	Infant of a diabetic mother
	Prenatal and postnatal corticosteroid therapy
Metabolic disorders	Carnitine deficiency (carnitine palmitoyltransferase II deficiency, carnitine-acylcarnitine translocase deficiency)
	Fucosidoses type 1 glycogenoses type II, III and IX (Pompe's disease, Forbes' disease, phosphorylase kinase B deficiency, adenosine monophosphate-activated protein kinase deficiency)
	Glycolipid lipidosis (Fabry's disease)
	I cell disease
	Lipodystrophy, total
	Mannosidosis
	Mitochondrial disorders (multiple forms)
	Mucopolysacchardidoses types I, II, and V (Hurler's syndrome, Hunter's syndrome, Schere's syndrome)
	Selenuim deficiency
	Lysosomal associated membrane protein deficiency (LAMP-2)

*Adopted from Braunwald *et al.*[13B] with permission.

A number of other genetic disorders can also be accompanied by cardiac hypertrophy, but often, systemic involvement can be detected, differentiating them from familial HCM. In autosomal recessive Pompe's disease (glycogen storage disease type II), a generalized glycogenosis takes place due to a deficiency in alpha-1, 4-glucosidase (acid maltase), a lysosomal enzyme that hydrolyzes glycogen into glucose and involves heart, skeletal muscle and liver. Glycogen deposition into the myocardium is uniform, although occasionally the interventricular septum is prominently involved, producing subpulmonic obstruction or features indistinguishable from obstructive HCM.[36,37] The disorder is uniformly fatal.

Other metabolic disorders[38–40] or mitochondrial cytopathies[41,42] may be tissue specific and result in a diagnostic dilemma where myocardial biopsy is required for diagnosis.[43] There are few effective therapies for these disorders and the prognosis without organ transplantation is poor.

Familial hypertrophic cardiomyopathy

Incidence

Various epidemiological investigations have identified the prevalence of the phenotypically expressed disorder in young adults at about 0.2% (1 in 500).[44] As such, the disorder is not rare, and one of the most common genetic cardiovascular diseases. Indeed a substantial number of individuals have a mutant gene for HCM, but are not detected clinically. However, the clinical presentation is uncommon in routine cardiologic practice, seen in no > 1% of adult outpatients.[45] In this study, the prevalence of HCM was 0.5% spanning a patient age range of 50–69 years. A population-based study from Finland[44A] conducted over a 12 year period between 1980 and 1991, found an average occurrence of HCM to be 0.24/100 000/year (95% CI, 0.17–0.33), and at the end of 1991 a prevalence of 2.9/100 000 (95% CI, 2.0–4.0).

Nomenclature

Although studies have shown that only a minority of patients (25%)[3,4,7] demonstrate left ventricular outflow tract obstruction, it is this unique morphological finding that has drawn so much attention to the disorder and a myriad of names (> 75). Hypertrophic cardiomyopathy[46] is the preferred name as it describes the disease spectrum without inference to the left ventricular outflow tract pathology, as is invariable when the terms hypertrophic obstructive cardiomyopathy, or idiopathic hypertrophic subaortic stenosis are used.

Genetics

HCM is inherited as an autosomal dominant trait due to mutations in any of a number of known genes.[47] These genes code for proteins involved in the functioning of the cardiac sarcomere (contractile,structural or regulatory in function),[9,48–56] and therefore, unify the disparate diverse phenotypical manifestations into a single disease entity representing a primary sarcomere disorder. The mechanism(s) by which such mutations lead to myocardial hypertrophy, however, are unresolved.[56]

Three HCM causing mutations predominate within the affected population, β-myosin, heavy chain (30%), cardiac troponin T (15%) and myosin-binding protein C (15%) (Fig. 21-1). Other gene mutations account for a minority of HCM cases (Table 21-2). This diversity is further compounded by intragenic heterogeneity, with > 150 mutations identified, most being missense mutations where a single amino acid residue is substituted with another.[9,48–55] It is thought that some, if not most, sporadic cases are due to spontaneous mutations,[57,58] and at present, not all mutations have been identified.[59] Molecular genetic studies have provided important insights into the diverse heterogeneity of HCM, including the preclinical diagnosis without phenotypical manifestations.[58,60] Unfortunately, DNA analysis for mutant genes has not become a routine clinical strategy.[9] Phenotypical evidence of the disease can be found in one-quarter of first degree relatives, where the disease may appear milder than the probands, with more localized and less severe hypertrophy, and less outflow tract obstruction. Symptoms are generally absent or minimal in such patients, the disorder identified only by echocardiography.

There is a wide variation in the phenotypical expression with a given gene mutation, in any given pedigree, affecting symptom expression, and the degree, localization and severity of hypertrophy.[61–63] Of particular interest, are mutations of the troponin T gene, which phenotypically results in little or no cardiac hypertrophy, but is associated with a poor prognosis and an increased risk of sudden death[47,51,64] (Fig. 21-2). In contrast,

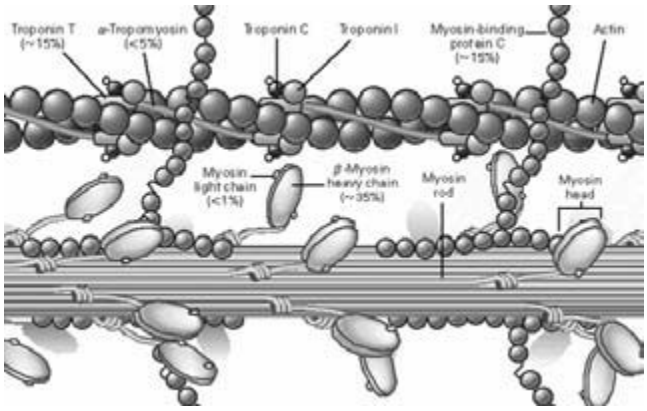


Fig. 21-1 Components of the sarcomere. Cardiac contraction occurs when calcium binds the troponin complex (subunits C, I, and T) and tropomyosin, making possible the myosin–actin interaction. Actin stimulates ATPase activity in the globular myosin head and results in the production of force along actin filaments. Cardiac myosin-binding protein C, arrayed transversely along the sarcomere, binds myosin and, when phosphorylated, modulates contraction. In hypertrophic cardiomyopathy, mutations may impair these and other protein interactions, result in ineffectual contraction of the sarcomere, and produce hypertrophy and disarray of myocytes. Percentages represent the estimated frequency with which a mutation on the corresponding gene causes hypertrophic cardiomyopathy. (Reprinted from Spirito *et al.*,[7] *N Engl J Med* 1997; **336**: 775–85, Copyright © 1997 Massachusetts Medical Society. All rights reserved.)

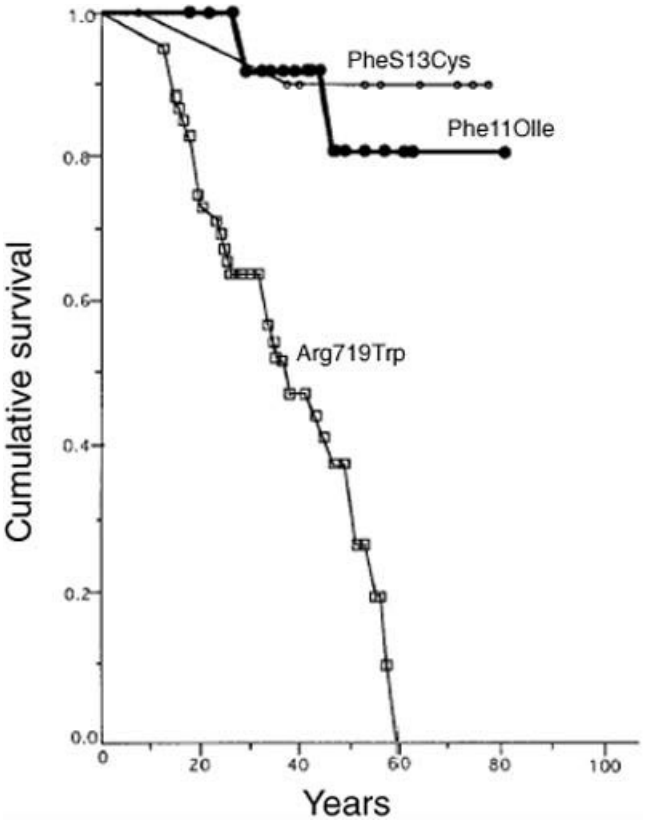


Fig. 21-2 Kaplan–Meier product-limit curves for survival of individuals with Phe110Ile mutation and two other mutations in b-cardiac myosin heavy chain gene. Survival was good in patients with Phe110Ile mutation in cTnT gene and similar to that for benign Phe513Cys b-cardiac myosin heavy chain gene mutation. A significant difference ($P < 0.0002$) in life expectancy was observed in individuals with Phe110Ile vs. malignant Arg719Trp mutation in b-cardiac myosin heavy chain gene. (Reprinted from Anan *et al.*,[64] Copyright (1995), with permission from The American College of Cardiology Foundation.)

certain mutations are associated with the more favorable prognosis, such as myosin-binding protein C.[55,65] Interestingly, in patients with no echocardiographic findings, but carriers of a mutant gene, the ECG can be abnormal. Thus, in an otherwise normal first-degree relative of the proband, an abnormal ECG may indicate a preclinical state. Recently, Charron *et al.*[65A] examined both echocardiographic and ECG criteria in genotype positive children (< 18 years of age) from 13 families. Using restricted criteria, of an increased left ventricular wall thickness on echocardiography, abnormal Q-waves, ST–T wave changes and left ventricular hypertrophy on ECG, specificity for the diagnosis of HCM was 100% for both, but sensitivity poor. When additional criteria were added (QRS axis, left atrial dimensions, ratio of septum to posterior left ventricular wall thickness) sensitivity increased to 88% and specificity remained high (95%). Thus, nearly all children considered healthy carriers could be identified.

Table 21-2 Hypertrophic cardiomyopathy causing mutant proteins and chromosome locations

β-myosin heavy chain	Chromosome 14q11–12
Cardiac troponin T	Chromosome 1g3
Myosin-binding protein C	Chromosome 11p11
Cardiac troponin I	Chromosome 19p13
Regulatory and essential myosin light chains	Chromosome 3p21 and 12q23
α-tropomyosin	Chromosome 15q2
α-actin	Chromosome 15q11–14
α-myosin heavy chain	
Titin	

Morphology

Macroscopic findings

There is considerable structural heterogeneity in the presence and distribution of the cardiac hypertrophy in HCM (Fig. 21-3).[3,6,60,66–69] The left ventricle is typically more involved in the hypertrophic process than the right. The latter, however, is frequently seen in the infantile expression of the disease[70,71] where commonly there is marked obstruction to right ventricular outflow, the magnitude of which is often at least as severe as that of the left heart. Its appearance in the adult suggests a more severe disease process, but in childhood, its prognostic value is unknown.[71A]

While most patients show diffuse myocardial hypertrophy, almost 30% have only mild wall thickening localized to one wall segment[42,53] including an apical hypertrophic form.[72–74] In diagnosed patients, increased wall thickness ranges widely, from

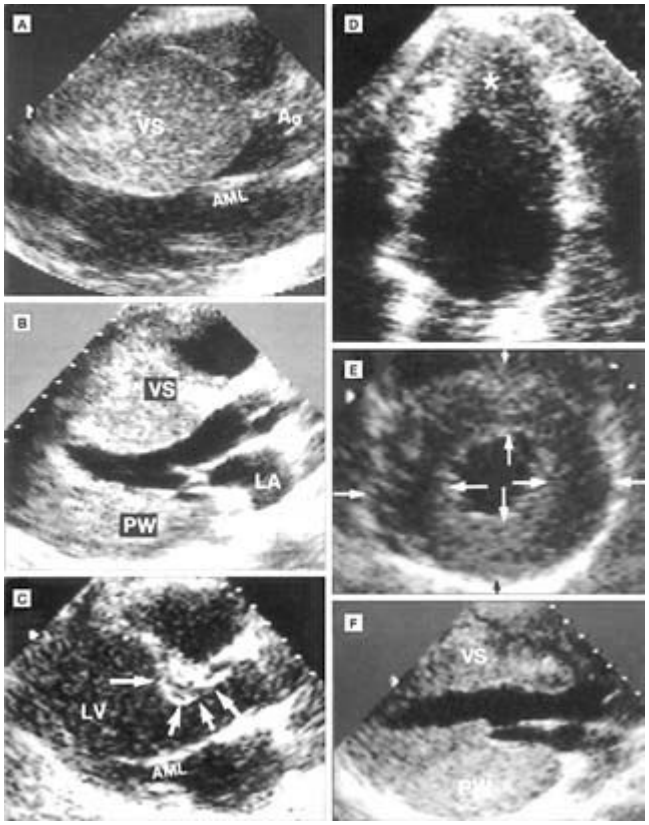


Fig. 21-3 Heterogeneity in the pattern and extent of left ventricular (LV) wall thickening in hypertrophic cardiomyopathy (HCM). Echocardiographic parasternal long-axis images obtained in diastole showing **A**, massive asymmetric hypertrophy of ventricular septum VS with wall thickness > 50 mm; **B**, pattern of septal hypertrophy in which the distal portion is considerably thicker than the proximal region at mitral valve level; **C**, hypertrophy sharply confined to basal (proximal septum) just below aortic valve (arrows); **D**, hypertrophy confined to LV apex (asterisk), consistent with the designation of apical HCM; **E**, relatively mild hypertrophy in a concentric (symmetric) pattern with each segment of ventricular septum and LV free wall showing similar or identical thicknesses (paired arrows); **F**, inverted pattern of hypertrophy in which anterior VS is less substantially thickened than the posterior free wall (PW), which is markedly hypertrophied (i.e. 40 mm). Calibration marks are 1 cm apart. Ao, aorta; AML, anterior mitral leaflet; LA, left atrium. (Reprinted from Klues *et al.*,[67] Copyright (1995), with permission from The American College of Cardiology Foundation.)

mild (13–15 mm)[3,7,75] to massive (> 30 mm)[68,69,76,77] (Fig. 21-3). The pattern and extent of hypertrophy vary greatly from patient to patient, although disproportionate interventricular septal hypertrophy and anterolateral wall hypertrophy are a feature found in most patients compared to the posterior segment of the free wall of the left ventricle[3,9] (Fig. 21-4). A few patients show a concentric pattern of wall hypertrophy.[66,67] The distribution of left ventricular wall thickening appears not to show any linkage to outcome, although distal (apical) hypertrophy is associated with fewer symptoms.[47,48] As noted above, young children may present with left ventricular hypertrophy as a component of other systemic disorders (Noonan syndrome, mitochondrial myopathies, metabolic disorders) unrelated to the HCM sarcomere protein mutations.

The degree of hypertrophy is dynamic in most patients, although prominent chamber hypertrophy can develop in infants;[70,71] it typically develops during adolescence.[3] The development of hypertrophy after puberty or 18 years of age is unusual,[3,78–80] although it may occur during adult life with a mutation of the cardiac myosin-binding protein C, or be absent in troponin T mutations.[50-53,81,82] Such observations dictate that it is no longer possible to use a normal echocardiogram at maturity in symptom free family members to rule out the presence of the disease, and requires a strategy of post-adolescent echocardiographic examinations when genotyping is not possible. There appears to be an inverse relationship between the extent of hypertrophy in HCM and age. Whether this is a reflection of premature death in the younger patient with greater hypertrophy (likely), or a progressive reduction in wall thickness with age, is unknown.[3] Additional morphological cardiac features include enlargement and elongation of the mitral valve leaflets and anomalous insertion of papillary muscles directly into the anterior mitral valve leaflets.[83,84]

Microscopic findings

There are several histological features, which characterize HCM. Left ventricular myocellular architecture is disorganized, hypertrophied and arranged in bizarre shapes with multiple intercellular connections (Fig. 21-5). This cellular disorganization can be widely distributed, occupying large proportions of the left ventricular wall (averaging 33%), and appears to be more extensive in young patients who have the disease.[85–87] In a study by Varnava,[86] looking at the relationship between outcome and cellular disarray, 18 patients were < 21 years of age (mean 5 ± 4 years) at the time of death or transplantation. Ten had premorbid symptoms, including syncope in 3, and 4 had

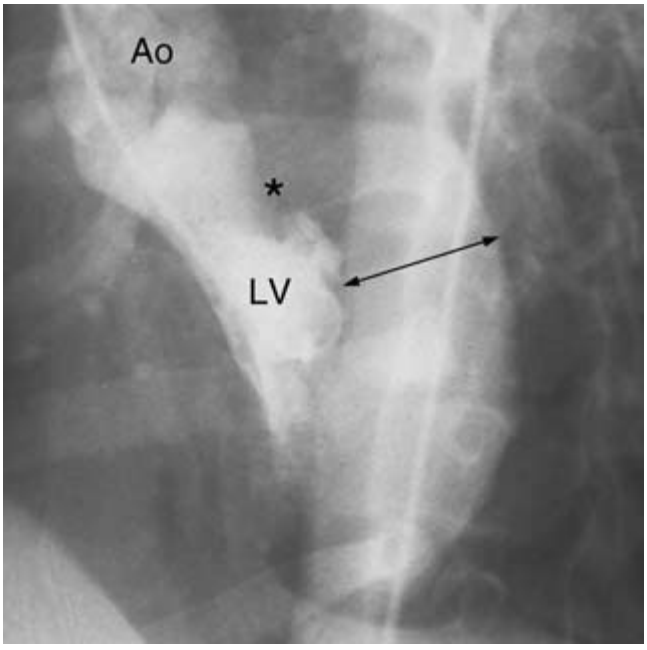
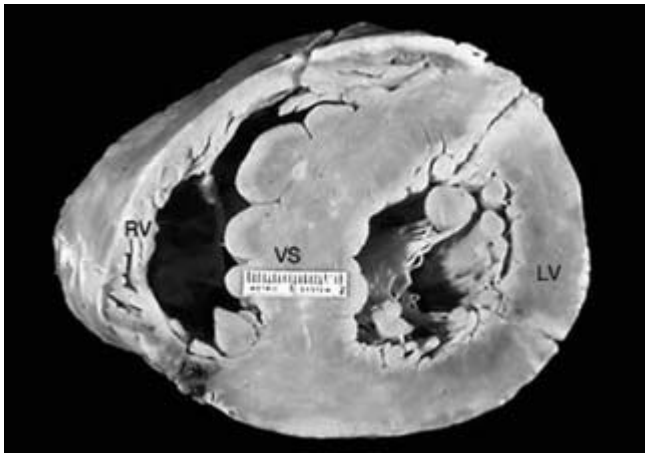
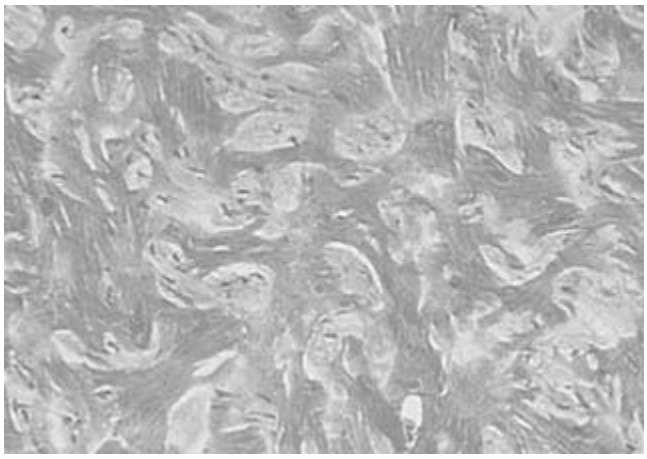


Fig. 21-4 Massive septal hypertrophy is apparent during this systolic frame from a youngster with familial hypertrophic cardiomyopathy. An outflow tract gradient was due to anterior motion of the mitral valve (asterisk) toward the interventricular septal surface during ejection.



A



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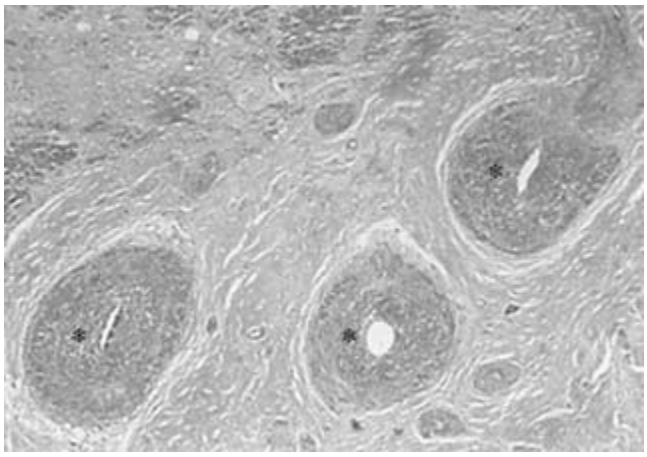

C

Fig. 21-5 Morphologic features of the myocardial substrate for sudden death in hypertrophic cardiomyopathy (HCM). **A**. Gross heart specimen from a 13-year-old male competitive athlete showing disproportionate thickening of the ventricular septum (VS) with respect to the left ventricular (LV) free wall (RV indicates right ventricular wall). **B**. Marked disarray of cardiac muscle cells in the disproportionately thickened ventricular septum with adjacent hypertrophied cells arranged in a chaotic pattern at oblique and perpendicular angles, forming the typical disorganized architecture of HCM. **C**. Left ventricular myocardium showing several abnormal intramural coronary arteries (asterisks) with markedly thickened walls and narrowed lumens, dispersed within replacement fibrosis (hematoxylin and eosin stain in B and C; original magnifications 50). (Reprinted from Maron,[129] Copyright (1993) Mosby Inc., with permission from Elsevier.)

Table 21-3 Triggers associated with sudden cardiac death in hypertrophic cardiomyopathy

Myocardial ischemia
Systemic hypotension
Supraventricular tachyarrhythmias
Environmental variables (e.g. intense physical exertion)

abnormal (hypotensive) blood pressure responses to exercise. While mean heart weight, per cent of microscopic fibrosis and small vessel disease did not significantly differ from the rest of the cohort (patients > 21 years of age), macroscopic scarring was significantly less (15% had marked scarring vs. 47% of adults), and disarray was significantly greater (35 ± 22% vs. 21 ± 14%). Among those who died suddenly, heart weight, wall thickness, and microscopic fibrosis were all less in the younger patients, while disarray was more severe.

Abnormal intramural coronary arteries, characterized by thickened walls with increased intimal and medial collagen and narrowed lumens, may be regarded as a form of small vessel disease (Fig. 21-5).[88] These architectural abnormalities, as well as a mismatch between myocardial mass and the coronary circulation are likely responsible for the observed impaired coronary vasodilator reserve[89] and episodes of ischemia[90–92] leading to cell death and replacement fibrosis (Fig. 21-5). This observed myocardial scarring supports clinical observations that ischemia is a significant component within the natural history of HCM,[2–8,91,93–95] and may serve as a substrate for heart failure related death.[86] The disorganized cellular architecture, myocardial scarring and expanded interstitial collagen content,[96] contributes to an arrhythmogenic substrate for life threatening electrical instability. This substrate is the likely source of primary ventricular tachycardia and ventricular fibrillation, which may be the predominant mechanism of sudden death,[97–101] either primary or in association with triggers (Table 21-3).

Natural history

Fetal

There is some experience with the fetal recognition of hypertrophic cardiomyopathy.[101A] More recently in a report from this institution Hornberger and her colleagues reported a substantial fetal cohort of cardiomyopathies.[101B] Of the 55 affected fetuses with cardiomyopathies, 22 were diagnosed with a dilated from of cardiomyopathy (see Chapter 45), and 33 had a hypertrophic cardiomyopathy. Of these 33, 7 were associated with maternal diabetes, 2 with Noonan's syndrome, 2 with alpha-thalassemia, 18 with twin–twin transfusion syndrome, 1 with familial cardiomyopathy, and 3 with idiopathic hypertrophy. Biventricular hypertrophy was seen in all the fetuses with hypertrophic cardiomyopathy. Systolic dysfunction was found in 15 of the fetuses with hypertrophic cardiomyopathy. Of the 19 fetuses assessed for diastolic dysfunction, 12 were found to have diastolic dysfunction. The outcome for the fetuses with hypertrophic cardiomyopathy was unfavorable. Excluding 2 with termination of pregnancy and 2 lost to follow-up, intrauterine demise occurred in 11 and early neonatal demise in 4. While the outcome was poor in the hypertrophic group, it was worse

in the dilated group with an overall mortality in this group of 82%.

Postnatal

In almost half the index cases, a family history of HCM or sudden death can be obtained. The clinical course of HCM is varied with many patients having absent or only mild symptoms; they remain stable and in some instances improve over a number of years. The annual mortality is about 3–6% in adults managed through large referral centers'[102–104] specialized care, but closer to 1% when all HCM patients are included.[105–110] The risk of sudden death is higher in children and reported as high as 6% per year.[13A,111,112] Recently, Bruno *et al.*[13A] reviewing a 25 year experience with both primary and secondary HCM, reported a 4.3% per year overall mortality and 3.1% risk of sudden death. In 1976, Maron *et al.*[112] reported on 46 children with familial HCM, 24 having outflow tract obstruction, and 11 asymptomatic with only echocardiographic evidence of disease. The average follow-up in 35 patients was 7.4 years, noting a variable clinical course, 14 (40%) improving or remaining stable, 10 (29%) deteriorating clinically, and 11 (31%) dying suddenly (4% mortality per year). No parameter could be identified placing those at risk of sudden death, including symptomology, electrocardiographic abnormalities, heart size, the magnitude of the outflow gradient, ejection time, or end-diastolic pressure. In a recent study from the Hospital for Sick Children, Toronto, Yetman *et al.*[113] reviewed 99 patients followed since 1958. Median age at diagnosis was 5 years, and medical follow-up 4.8 years. Death or resuscitated sudden death occurred in 18 patients, a rate of 2.7% per year after the age of 8 years (Fig. 21-6). Cox's proportionate survival modeling revealed an increased QT_c interval on the electrocardiogram, ventricular tachycardia on ambulatory electrocardiography and myocardial bridging of the left anterior descending coronary artery associated with a decreased time to death or resuscitated sudden death. Azzano *et al.*,[114] from Lyon, France, reported on the outcomes of 40 children (mean age 11 years). A positive family history and/or sudden death was present in 21 (53%), and 21 (53%) were symptomatic with dyspnea, chest pain, syncope or palpitations. A variety of medications were used, including verapamil, amiodarone, and propanolol, and 7 patients had surgery. Follow-up was a mean of 10 years (13 patients died, including 8 sudden deaths) for an annual mortality of 3.2%, the actuarial 5- and 10-year survival was 90% and 85%, respectively. Comparing survivors to patients who died, only a history of syncope correlated with global mortality. In another study evaluating 37 consecutive children followed for a mean of 9 years, with HCM (< 14 years of age),[113A] Romeo *et al.* reported 9 deaths, 7 of which occurred during exercise. Multivariate analysis revealed left ventricular dysfunction and syncopal episodes as independent predictors of survival at time of diagnosis.

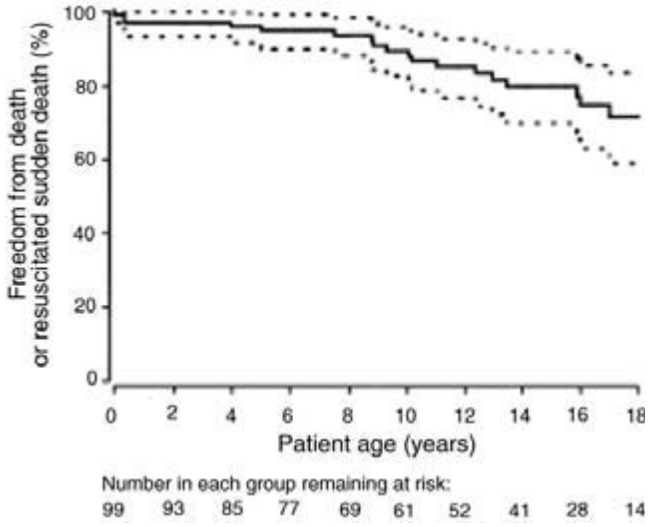

Fig. 21-6 Kaplan–Meier life-table analysis of freedom from death or resuscitated sudden death vs. patient age. Dashed lines, standard deviations. (Reprinted from Yetman, *et al.*,[113] Copyright (1998), with permission from The American College of Cardiology Foundation.)

Generally, however, clinical deterioration, aside from sudden death is gradual, with symptoms unrelated to the severity or presence of an outflow tract gradient.[103,113–115] In a recent study from the Bristol Royal Hospital for Sick Children[115] assessing 21 patients with familial HCM and 8 with Noonan syndrome with HCM between 1969 and 1994, presentation was cardiac failure in 59%, a murmur only in 30%, cyanosis or a family history of HCM in 7% each. There were 5 deaths (7%) all under 1 year of age from progressive congestive heart failure (4 of 5 not receiving medical therapy). In the 24 survivors (followed for a median 5.5 years), hypertrophy resolved in 9 (38%, including 8 with familial HCM, 1 with Noonan syndrome), was mild and asymptomatic in 7 (29%) and symptomatic and severe in 8 (33%). All infant presentations with a septal thickness of > 1.3 cm had persistent hypertrophy in follow-up. The mortality in infant HCM appeared much lower than previously reported[116] with resolution in morphology and improved symptoms. In other series,[13A,24,116A] congestive heart failure was a common mode of disease presentation and death, in infants and small children. This may be particularly true, as the expression of the disorder when identified in the infant is more severe.[116B] This may reflect an increased detection of less severe forms, in addition to the success of aggressive medical and surgical management. This is in contrast to that observed in the older child and adult where electrocardiographic progression of hypertrophy is the rule and regression rare.[117] In this regard Panza and Maron[118] examined the relationship between electrocardiographic abnormalities and evolving left ventricular hypertrophy in HCM patients diagnosed in childhood. Thirty-eight patients were followed for a mean of 5.5 years, noting that between the initial and most recent evaluation, the electrocardiographic voltages did not change significantly, despite an increase in left ventricular hypertrophy in some patients. Indeed, only 9 of the 38 patients showed a significant change in the overall electrocardiographic pattern of hypertrophy. However, the magnitude of the electrocardiographic voltages at initial evaluation (age 11 ± 4 years) revealed a significant correlation with the extent of left ventricular hypertrophy at the most recent examination (age 16 ± 4 years). Interestingly, of the 7 patients who developed left ventricular hypertrophy during the period of observation, the electrocardiographic abnormalities at the initial examination preceded echocardiographic appearance of left ventricular hypertrophy.

In a study by McKenna and Deanfield[119] a retrospective analysis was performed on 37 patients with HCM, which was diagnosed in childhood (mean age 9 years). Eighteen presented

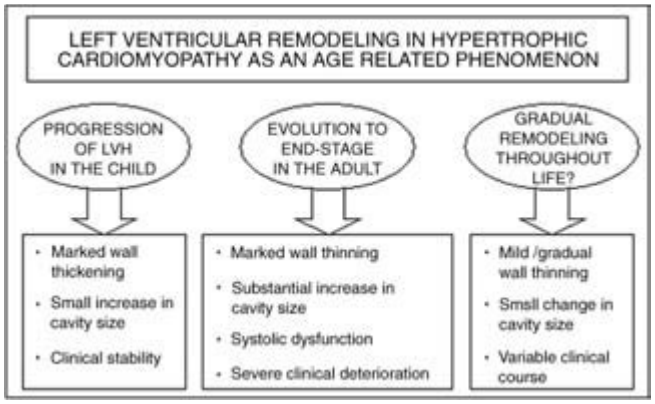

Fig. 21-7 Patterns of left ventricular remodeling in the natural history of hypertrophic cardiomyopathy. LVH, left ventricular hypertrophy. (Reprinted from Maron and Spirito,[78] Copyright (1998), with permission from Excerpta Medica.)

with chest pain, and either dyspnea, syncope or both. Nineteen were asymptomatic and referred for abnormalities noted on physical examination. During follow-up, 18 patients died, an accumulative annual mortality of 4.8%. The 19 survivors, when compared to the 11 sudden deaths, noted 11 survivors and 5 sudden deaths were asymptomatic. Of a variety clinical, electrocardiographic and hemodynamic features only syncope and right ventricular hypertrophy on the electrocardiogram were associated with sudden death. Overall, in infancy, the clinical course of HCM appears to carry a poor prognosis, especially when the clinical presentation is that of congestive heart failure and cyanosis. In an early paper by Maron *et al.*,[71] 9 of 11 infants presenting with congestive heart failure died within the first year of life, and 10 of 19 patients diagnosed at a median age of 1 day of life died within the first year, in a study by Suda *et al.*[116A] In this series, nonsurvivors had metabolic or Noonan syndrome with associated HCM. This contrasts to the observations noted earlier from the group in Bristol[115] and that of Schaffer *et al.*, from Toronto[70] who noted 100% survival in infants, through 6 years of age, and that of Moran *et al.*, from Boston[24] noting 85% survival at 12 years follow-up. These differences reflect the heterogeneous patient population of earlier studies and perhaps small patient numbers in the various series.

Beyond infancy, relative symptom stability exists, although the incidence of symptomatic patients beyond childhood increases.[120,121] Limitations in exercise tolerance due to dyspnea or chest pain are often the primary and most disturbing symptoms in familial HCM. Exercise capacity in childhood appears normal[121A] in the presence of normal left ventricular diastolic performance. In a case-controlled study, Yetman *et al.*[121A] evaluated 17 children with familial HCM, finding no significant differences compared to normal controls in regards to peak oxygen consumption, anaerobic threshold, systolic blood pressure increase or exercise duration. However, when patients with diastolic dysfunction were compared to those without, patients with diastolic dysfunction were younger, more likely to have symptoms of exercise intolerance, have lower peak oxygen consumptions, lower anaerobic thresholds, and fewer increases in systolic blood pressure. In an older patient group (mean age 35 ± 14 years), Jones *et al.*[121B] found that peak oxygen uptake and anaerobic threshold were uniformly decreased in all patients studied, supporting the increased symptomatic expression of the disease with age.

The development of atrial fibrillation may lead to an increase in symptoms but not a risk for sudden death.[122–126] In the pediatric age group atrial fibrillation is rare.[127,128]

Progression of HCM to a dilated form without an outflow tract gradient occurs in 10–15% of patients.[129,130] It is rare in childhood, although it has been reported in two adolescents[131,131A] and carries a poor prognosis. This phenomenon appears to result from ongoing myocardial ischemia, from small vessel disease, with concomitant wall thinning and scar formation.[129] In adults, the extent of hypertrophy generally remains stable over time, although in the majority of children, there are increasing degrees of hypertrophy (often substantial), and many adults demonstrated some very gradual degrees of regression[78] (Fig. 21-7). As noted above, some children may develop HCM despite a previously normal electrocardiogram, or develop electrocardiographic abnormalities before echocardiographic evidence of disease.

Sudden death

Death is often sudden in the HCM patient, even in those previously asymptomatic or having an otherwise stable course. It is most difficult to identify those at risk for sudden death. Characteristics, which most reliably identify the high risk patient, are listed in Table 21-4.

The presence of, or severity of an outflow tract gradient may affect the degree of functional limitations, and symptoms, in general however, do not correlate with sudden death risk.[103] A history of syncope in childhood is an ominous sign, but less so in the adult. Non-sustained ventricular tachycardia has some predictive value for subsequent sudden death, although > 75% of non-sustained ventricular tachycardia patients do not die suddenly.[132] The absence of such arrhythmias is a strong predictor of a good prognosis rather than its presence a bad one.[133] In this regard, it is presumed, although not established, that sudden death is due to ventricular arrhythmias, particularly in adults. While difficulty exists in identifying patients at risk for sudden death, the absence of high risk characteristics identifies a low risk group who require little in directed therapy. Sudden

Table 21-4 Features identifying high risk patients for sudden death

Young age (< 30 years)
Family history of hypertrophic cardiomyopathy with sudden death (so-called malignant family history)
An abnormal blood pressure response to exercise (related to subendocardial ischemia)
Genetic abnormalities associated with an increased prevalence of sudden death
Syncope
Prior cardiac arrest or spontaneous sustained ventricular tachycardia
Near-syncope with exertion
Multiple or repetitive or prolonged bursts of nonsustained ventricular tachycardia on ambulatory ECG monitoring
Extreme left ventricular hypertrophy, with wall thickness > 30 mm, particularly in the adolescent and young adult

death occurs commonly during mild exertion or sedentary activities, but is not infrequently related to strenuous exertion. HCM is the most common cause of cardiovascular death in young people, including trained competitive athletes,[134] although the true incidence of familial HCM in athletes is unknown. Indeed, some patients with familial HCM tolerate vigorous competitive athletics without symptoms or sudden death.[135] Avoidance of competitive sports is appropriate; participation in recreational sports is not believed to be contraindicated.[7]

In children, the mechanism of sudden death may be different because spontaneous ventricular arrhythmias and inducibility on electrophysiological testing are less common. It is thought that ischemia may play an important role.[136,137] Recently, from our institution, Yetman *et al.*[138] reviewed the clinical significance of myocardial bridging in the children with HCM as a cause of ischemia leading to sudden death or resuscitated sudden death (Fig. 21-8). Angiograms from 36 children with HCM were reviewed to assess the characteristics of systolic narrowing of the left anterior coronary artery. Myocardial bridging was present in 10 (28%) of the patients. Compression of the left anterior descending coronary artery persisted for > 50% of diastole. Compared to those patients without bridging, patients with bridging had a higher incidence of chest pain (60% vs. 19%), cardiac arrest with resuscitation (50% vs. 4%) (Fig. 21-9), and ventricular tachycardia (80% vs. 8%). Additionally, those patients had an average reduction in systolic blood pressure of 17 ± 27 mmHg during exercise compared to a 43 ± 31 mmHg elevation in those without bridging. Additionally, patients with bridging had greater ST-segment depression (median, 5 vs. 0 mm) and shorter durations of exercise (mean 6.6 ± 24 vs. 9.1 ± 1.4 min). The degree of QT interval depression corrected for heart rate was also greater in patients with bridging (104 ± 46 vs. 48 ± 31 ms). A Kaplan–Meier estimate of the proportion of patients who had died or who had cardiac arrest with subsequent resuscitation 5 years after the diagnosis of HCM was 67% of patients with bridging, and 94% without (Fig. 21-9). These observations are controversial; Mohiddin *et al.*[139,140] examining 57 children with HCM were not able to confirm these findings. However, these authors noted that LV septal thickness and septal branch compression and not bridging were independent predictors of thallium perfusion abnormalities. They comment that bridging and compression of septal branches of the left anterior descending coronary artery are common in HCM children and related to the severity of the hypertrophy.

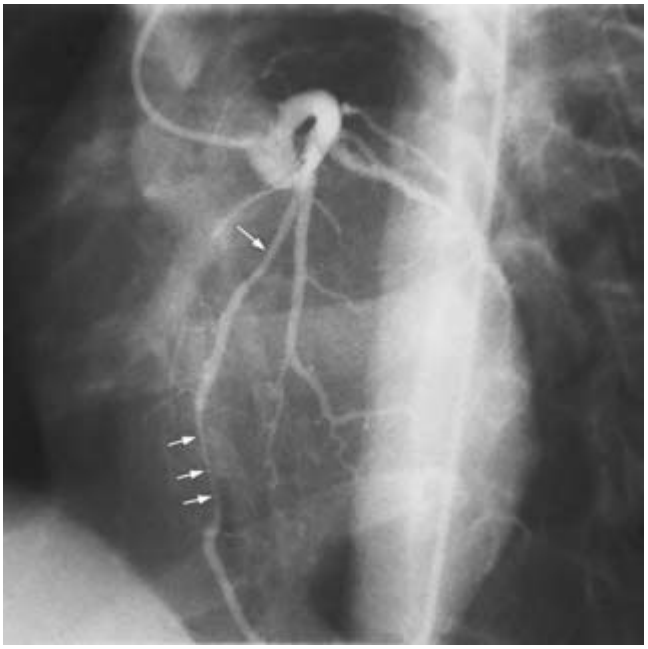

Fig. 21-8 A selective left coronary artery angiogram in the long axis oblique projection, showing significant and persistent compression of the left anterior coronary artery in a patient with hypertrophic cardiomyopathy.

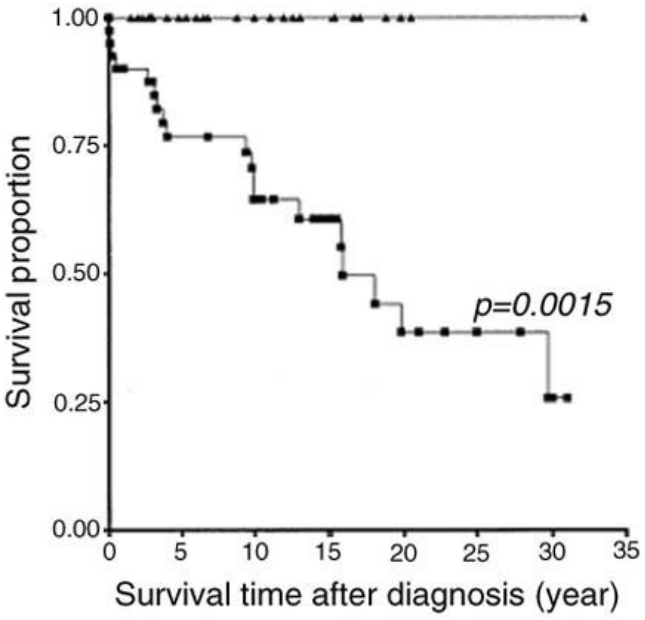

Fig. 21-9 Kaplan–Meier survival time analysis of total survival after diagnosis. Patients in the high-dose β-blockade group ($n = 26$); filled triangles are compared with all the other patients, "conventional management" ($n = 40$); filled squares showing a significantly improved survival in the patients on high-dose β-blockade (log-rank $P < 0.0015$). (Reprinted from Ostman-Smith, *et al.*,[141] Copyright (1999), with permission from The American College of Cardiology Foundation.)

Hemodynamic mechanisms may also be involved in childhood sudden death, as children may demonstrate abnormal changes in peripheral vascular resistance with exercise. Note however, that while sudden death may occur during exercise it demonstrates a circadian distribution, with clustering in the morning and early evenings. Those patients free of all risk factors (Table 21-4) are considered low risk for sudden death and no medical interventions are indicated. With two or more risk factors or syncope alone in children, risk is considered high and aggressive management (implantable cardioverter-defibrillator, ICD) is recommended. The absence of additional prognostic factors such as QT dispersion, myocardial bridging, and ischemia on myocardial perfusion studies is additional supportive information for reduced risk. No single disease feature or test is capable of stratifying risk in all patients.

Interventions to reduce risk sudden death

Treatment strategies to reduce the risk of sudden death are not fundamentally different from those applied in adults. No studies

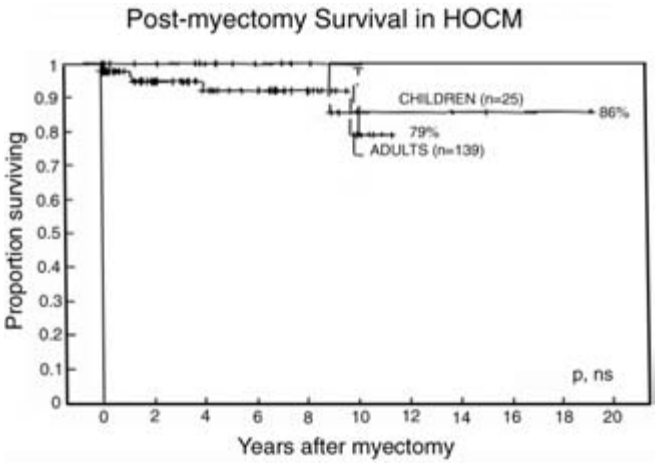

Fig. 21-10 Actuarial survival of 25 children and 139 adults after subaortic myectomy for hypertrophic cardiomyopathy. The survival rate at 10 years was 86% for children, 79% for adults, not statistically different. Crosshatches on the survival lines indicate the current end of the follow-up for each patient. (Reprinted from Williams and Rebeyka,[142] Copyright (1992), with permission from Elsevier.)

however, are available which have addressed these alternatives in infants and children. Nevertheless, there is little evidence that prophylactic pharmacological strategies or rhythm modulating drugs reduce the risk for sudden death.[141] In a retrospective study, examining childhood HCM,[141] 66 patients (25 with Noonan syndrome) were followed for 12 years. Risk factors for death were congestive heart failure, ECG voltage criteria for left ventricular hypertrophy, and septal and posterior wall hypertrophy. Only treatment with high-dose β-blockade (5–23 mg/kg/day) was shown to significantly reduce risk of sudden death (Fig. 21-9). Nineteen of 40 patients treated conventionally (no therapy or β-blockade < 5 mg/kg/day) died at a median 15 years' follow-up, with no deaths among the 26 high dose β-blockade patients. A hazard ratio analysis suggested that high dose β-blockade reduces sudden death risk 5- to 10-fold. However, there is little comparative prospective evidence to justify the application of pharmacological therapy to the asymptomatic HCM patient.

At present, the ICD appears to be the most effective mortality for the high risk patient with HCM.[97–99] ICDs aborted potentially lethal ventricular tachyarrhythmias, restoring sinus rhythm in just under 25% of patients followed for 3 years with familial HCM. Patients receiving appropriate shocks were young (mean 40 years of age), although the ICDs remained dormant for prolonged periods before discharge (for up to 9 years).

Surgical therapy

In symptomatic patients with obstructive HCM, myotomy/myectomy[142] has resulted in symptomatic improvement in nearly all patients, although symptom severity correlates poorly with the degree of obstruction. Results in children are similar to those in adults. From the Hospital for Sick Children, Toronto, through 1993, 25 children ages 2 months through 17 years have undergone subaortic myectomy for obstructive HCM. Most children were symptomatic, despite medical therapy, and had outflow gradients of > 60 mmHg. Compared to adults, the children had lower left ventricular end-diastolic pressures, and less mitral insufficiency, despite similar degrees of outflow tract obstruction. Actuarial survival following myectomy was 100% at 5 years and 86 ± 13% at 10 years (1 late death). Survival after the procedure was not different from a contemporary series in adults (Fig. 21-10). Although survival was not different, the children appeared to have an increased risk of reoperation for recurrent left ventricular outflow tract obstruction. Three of the 25 children required reoperation between 10 months and 9 years. Reoperation rates are compared to the 139 adults in Fig. 21-11.

Stone *et al.*[143] retrospectively reviewed the 26 year experience at the National Institute of Health with pediatric HCM. Left ventricular outflow tract obstruction, with symptoms, was the indication for surgical intervention. Seventeen patients underwent 19 procedures, with 10 years' follow-up. Ages at operation were a mean 15 years (range 9–17 years). The mean left ventricular outflow tract gradient was 74 ± 9 mmHg (range 20–175 mmHg) at rest. Eighty-eight per cent of the patients underwent a left ventricular myotomy/myectomy, 2 having a mitral valve replacement, and 2 requiring a later mitral valve replacement. There was 1 perioperative death, and 5 late sudden deaths, for an 86 ± 8% 5-year and 77 ± 12% 10-year survival. Similarly, the Mayo Clinic reported their 20 year experience with 25 patients, ages ranging from 2 months to 20 years (mean 11 years).[144] Seventeen patients had moderate to severe mitral insufficiency, and medical therapy had failed to control symptoms in all. Left ventricular outflow tract gradients ranged from 50 to 150 mmHg (mean 99 mmHg). Intraoperative mean gradients were 60 mmHg and after myectomy, 6 mmHg. After myectomy, mitral insufficiency was significantly reduced in all, and no patient required a mitral valve replacement. There was no early mortality, aortic insufficiency, mitral valve damage, or traumatic ventricular septal defects. Follow up was 6 years with no late deaths, left ventricular outflow tract gradients, by echocardiography, were a mean of 14 mmHg. Recurrent operation for left ventricular outflow tract obstruction was performed in 2 patients, 3 and 12 years after the initial procedure. All patients were symptomatically improved.

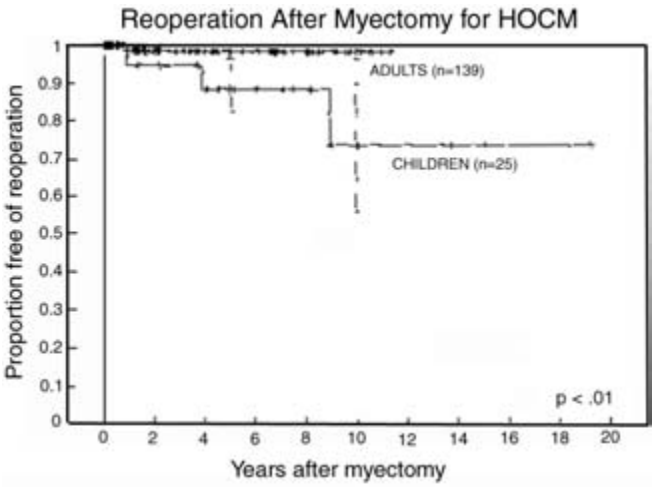

Fig. 21-11 Reoperation rates for recurrent persistent left ventricular outflow tract obstruction in children (3 of 25) significantly higher than that of a contemporary adult group (1 of 139). (Reprinted from Williams and Rebeyka,[142] Copyright (1992), with permission from Elsevier.)

While such studies document significant improvements in the symptom complex, there are few data to suggest a survival benefit as such; surgery should be limited to patients with severe symptoms despite maximum medical therapy. Interventions based on gradients alone have not improved survival. Atherosclerosis causing coronary stenosis is not uncommon in adults with HCM, but rare in children. Yet, coronary stenosis may be caused by myocardial bridging over the coronary artery. Its presence is a risk factor for sudden death[138] and can be successfully removed at surgery.

All references can be found at the end of the book. See pp. 708–12 for Chapter 21.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Lee N. Benson and Peter R. McLaughlin

Coarctation of the Aorta

Introduction

Coarctation of the aorta is a discrete lesion of the proximal aorta located near the aortic end of the arterial duct or ligament. While anatomically the lesion may appear straightforward, it indeed has a complex anatomy, pathophysiology, clinical presentation, and, as detailed in this chapter, treatment options and outcomes. On gross external examination of the outer contour of the aortic wall, an obtuse indentation of the posterolateral wall can be seen, which corresponds with the location of an internal ridge or shelf, eccentrically narrowing the aortic lumen. In older children and adults, the narrowing is usually localized in the postductal or ligament region. In neonates and infants, on the other hand, the narrowing frequently involves a long segment of preductal aorta, with hypoplasia of the transverse arch, and a patent arterial duct. While coarctation of the thoracic aorta is the most frequent expression of arch obstruction, a more distal narrowing in the abdominal aorta may also occur. While the lesion may exist as an isolated defect, the obstruction may also be an expression of disordered intracardiac anatomy, favoring pulmonary blood flow, at the expense of aortic blood flow, particularly in those neonates and infants with complex intracardiac lesions. Clinical manifestations vary from a murmur in the asymptomatic hypertensive child or adolescent, to heart failure and shock in the newborn. Treatment options include surgical repair (e.g. resection or subclavian flap angioplasty) or interventional catheter based (balloon dilation or vessel stenting).[1–4]

Incidence

Coarctation of the aorta occurs in 1 of 2323 live births and ranks sixth in frequency of all congenital heart lesions.[5,6] In the newborn period, coarctation of the aorta accounts for 7% of patients presenting with cardiac lesions, and is present in 17% of autopsies from newborn infants dying of congenital heart lesions.[7] The lesion presenting in infancy is slightly more common in males (male:female ratio, 1.27:1 to 1.74:1)[8,9] and was the fourth most common lesion requiring intervention during the first year of life from the New England Infant Registry.[8] Data from the Baltimore–Washington Infant Study defined the prevalence for coarctation as 0.239 per 1000 live births[10] and on the island of Malta, it was found to be 0.32 per 1000 live births.[11] The lesion is particularly frequent (15–35%) in children with Turner's syndrome (45 XO) and especially prevalent in those with webbing of the neck,[12–14] as well as its occurrence in other syndromic conditions, such as Adams–Oliver syndrome[15] or in association with a right artic arch and cutaneous hemangiomas.[16,17] While most cases are sporadic, recent data note that there are important genetic influences on the occurrence of left heart lesions, with reports of aortic coarctation occurring in twins, siblings and first-degree relatives.[18–20] The expression of aortic coarctation may also be influenced by the environment, with a study detecting a seasonal variation, the incidence increased in the late fall and winter.[21] Aortic coarctation may be present at sites other than the aortic isthmus (see abdominal coarctation above), at > 1 site in an individual,[22,22A] occurs proximal to the innominate artery[22–24] or in the descending thoracic aorta.[25]

Embryology

A normal left sided aortic arch is derived from the left fourth branchial arch; and the arterial duct is derived from the dorsal aspect of the left sixth branchial arch. The left subclavian artery originates from the seventh segmental artery, the ostium of which migrates cephalid along the dorsal aorta. The artery crosses the junction of the fourth and sixth arches and the dorsal aorta, its final position on the aortic arch, proximal to the isthmus. The fourth and sixth arches join with the dorsal aorta at the level of the isthmus.[26]

Etiology

A number of mechanisms have been proposed to account for the localized narrowing of the aortic arch since Reynaud in 1828,[27] suggested that an obstructing membrane developed at the site of union between the cephalic aspect of the dorsal aorta and end of the sixth arch.[26] Contemporary theories take into account the observed quantitative morphology and differential growth, which have been noted in the normal fetus by prenatal fetal ultrasonography and perinatal observations.[28–31] Machii and Becker [31] reported the aorta in newborns rapidly adapts by growth to postnatal circulatory conditions, and that structural features are associated with growth, and differences occur between the various arch segments. In their study, 19 specimens were studied: 7 from babies < 1 month, 7 from 1 month to 1 year, and 5 from 1 to 4 years. In each baby, the diameter of the aortic segments and its branches were measured and the number of elastin lamellae were counted, as well as the collagen density quantified at several measurement sites. The diameter of each segment increased rapidly after birth and more so than that of the descending aorta, except for the brachiocephalic artery and

its branches and the left common carotid artery, albeit not at the same rate. The ascending aorta was the only segment that showed a decrease in the ratio of elastin lamellae to diameter. Collagen density was always highest in the descending aorta. These observations suggest that postnatal growth of the thoracic aorta is associated with distinct structural remodeling after birth; and are of clinical relevance in cases of aortic arch abnormalities. Such studies have found a progressive tapering of the aortic arch at all gestational ages, with the smallest area localized to the aortic isthmus.[28] This reduction in diameter throughout the arch is believed to reflect the amount of the fetal cardiac output, which traverses the arch segment. *In utero* blood flow from the left ventricle is directed into the ascending aorta and brachiocephalic arteries, while right ventricular blood flow traverses the arterial duct from the main pulmonary artery into the descending aorta. Thus, the diameter of the aortic isthmus relative to the arch is narrowed at birth, though it subsequently enlarges over the next 2 or 3 months, with closure of the arterial duct and establishment of a normal postnatal circulation. In infants with coarctation of the aorta, reduced blood flow through the isthmus may be exaggerated and promotes narrowing in this region. Similarly, transverse arch hypoplasia of varying severity is commonly seen and likely results from such deranged flow patterns, as produced by obstructive left heart lesions.[29,32] Another proposed mechanism, the so-called skodiac theory, suggests that a sling of ductal tissue extends into the aortic wall and contracts after birth, resulting in luminal obstruction.[33–36] This view is supported by the observation that the localization of the stenosis is often at or near the arterial ligament, and arterial duct closure in a previously normal aorta can result in arch obstruction.[37] Additionally, the clinical improvement noted in infants with coarctation after beginning a prostaglandin infusion, underscores the pivotal role of the arterial duct in this lesion.[38] In the normal aorta, ductal tissue inserts partially around the aorta, but does not exceed 30% of the circumference.[39] In children with coarctation, ductal tissue has been noted to extend more completely around the circumference. Extension of the fibrotic process noted with ductal obliteration into the aortic wall, has been confirmed histologically.[39,40] From a surgical series, Van Son *et al*.[41] reported histological findings after examination of excised coarctation specimens from end-to-end anastomotic repairs, in a consecutive series of 25 neonates and young infants (median age 22 days, range 5–39 days). Fifteen patients had a preductal and 10 patients a paraductal coarctation. Histologic examination of the resected specimens demonstrated the presence of ductal tissue in the descending aorta with maximal extension into its lateral wall. In all specimens of the paraductal subtype, there was also extension of ductal tissue into the lateral wall of the isthmus. As the ductal tissue contracts and undergoes fibrosis, this results in a fixed obstruction, which with intimal proliferation further reduces the lumen.[39–42] Histologic examination of the shelf or ridge forming the coarctation has also detailed smooth muscle, fibrosis, and tissue similar to that seen in the muscular arterial duct.[39,40] Recent immunohistologic and ultrastructural studies have characterized the components of this intimal thickening. These observations indicated that human coarctation is characterized by intimal recruitment of non-proliferating smooth muscle cells with a dedifferentiated phenotype. The additional presence of smooth muscle cells with an intermediate phenotype in the narrowest part of the coarctation suggests that a redifferentiation process could participate in the pathogenesis as well.[43] It has also been postulated that the presence of a left sided obstructive lesion, such as a bicuspid aortic valve, results in an increase in right-to-left flow through the arterial duct during *in utero* development, and promotes migration of ductal tissue into the adjacent arterial wall. Conversely, in right sided lesions, such as Fallot's tetralogy, right-to-left ductal flow results in the commonly seen stenosis of the left pulmonary artery origin.[44] Additionally, it is also believed that the ridge represents the original wall of the distal left sixth aortic arch (arterial duct).

As the site of coarctation in a few patients (3%) is distant from the area of the arterial ligament, other mechanisms, than that of the arterial duct in evolution of the narrowing, are also possible[45] (Fig. 22-1). Some investigators have proposed that the narrowing could result from vessel injury occurring before birth, with consequential smooth muscle proliferation and fibrosis.[46–48] Finally, maldevelopment of neural crest cells,[20] marked differential cell growth, and disturbed growth patterns affecting cellular migration from the left sixth arch (see above) have been evoked in playing a role in the development of arch obstruction.[49–51]

The etiology of the "abdominal coarctation" is at best, uncertain.[52–59] Consensus would suggest that the obstructive lesion is an expression of a generalized aortitis, infantile hypercalcemia, rubella[60] or a component of neurofibromatosis. Anatomically, the narrowing typically involves the areas proximal or distal to the renal vessels, which are often involved[61–64] in the stenotic process. Other systemic (renal, coronary, brachiocephalic) and pulmonary arterial vessels may too be involved.

With aortic coarctation, the constriction can be at the level of the arterial duct (juxtaductal or paraductal), above, or below (postductal) the arterial duct.[32,27,65–67] The designations "preductal" and "postductal" do not refer to the old distinctions between "infantile" and "adult" coarctation.[68] As such, "infan-

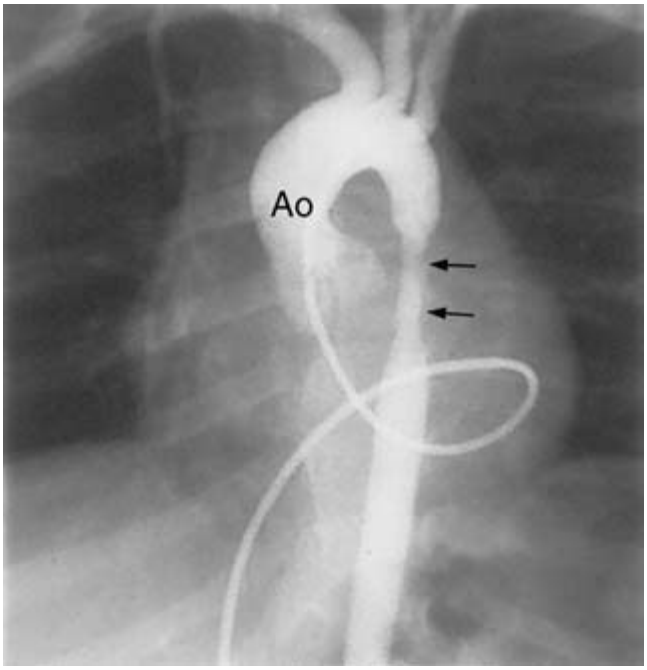

Fig. 22-1 Long segment coarctation of the aorta, with a hypoplastic irregular isthmus and discrete web-like obstruction. Note that there is little if any poststenotic dilation of the descending aorta.

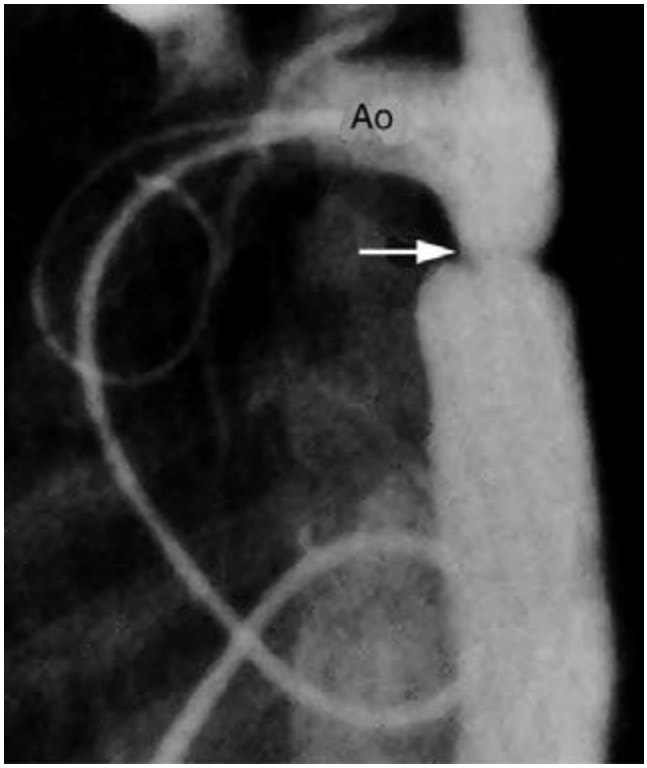

Fig. 22-2 Typical coarctation (arrow) of the aorta (Ao) with dilated origin of the left subclavian artery.

tile" coarctation refers to the expression of the disorder with a coexistent patent arterial duct, tubular hypoplasia of the aortic (transverse) arch with or without intracardiac defects. In the so called "adult" form, a discrete localized constriction is present without the associated patent arterial duct or intracardiac defects, but with the secondary development of degenerative aortic wall changes above the lesion and arterial collateral vessels to the lower thoracic aorta.

Anatomy

In "classical" coarctation, the narrowing is located just distal to the left subclavian artery, and at or just distal to the arterial duct. The proximal portion of the left subclavian artery is dilated and may be distally displaced from normal (Fig. 22-2).[69–71] Rarely, the coarctation lies at or immediately proximal to the left subclavian artery, compromising the orifice of that vessel[72] and/or the right subclavian artery arises anomalously at or below the coarctation.[73] This will result in a lower pressure in one or both arms.[74,75] If the subclavian artery arises anomalously, this may result in reduction or reversal of flow in the ipsilateral vertebral artery and a subclavian steal syndrome may develop.[76] The aorta exhibits a localized indentation from external view, involving all but the ventral portion where the arterial duct originates.[40,76–78] The narrowing is localized and the aorta just distal to the coarctation is typically dilated. The external indentation corresponds internally to the ridge or shelf-like infolding which narrows eccentrically the aorta lumen.

Clinical evidence of the presence of the obstruction may only occur after closure of the arterial duct. In the neonate (although also seen in a significant number of older patients),[78] a more uniform narrowing of the aortic arch can also be observed termed "tubular hypoplasia".[40,77] A localized coarctation and tubular hypoplasia may coexist or occur independently[36,78–80] (Fig. 22-3). As the coarctation is localized just proximal or at the level of the arterial duct, its presence in early life may obscure angiographic definition. The aortic isthmus in the normal newborn is typically smaller than the ascending and descending aorta (see above) and, in the presence of a patent arterial duct, can be appreciated as a posterior indentation opposite the opening of the arterial end of the duct. In the presence of an exaggeration of this posterior indentation (i.e. the coarctation), the aortic end of the arterial duct acts as a conduit that bypasses the potential obstruction produced by the posterior aortic indentation. With ductal closure, this conduit no longer exists and the juxtaductal coarctation declares itself.[37] The presence of such a lesion may be uncovered after surgical ligation or occlusion of the patent arterial duct[81,82] or after palliative pulmonary artery banding.

Finally, a rare anomaly termed "pseudocoarctation" is characterized by a buckling or kinking of the aorta, in the region of the arterial ligament (which may contribute to the kinking), and can result in elongation, tortuosity and dilatation of the distal aortic arch or proximal descending aorta.[83–96] The arch can be serpiginous, but there is no narrowing of the aortic lumen, with the ligament of the arterial duct perhaps contributing to the kinking. Collateral arterial circulation, such as occurs with true coarctation, is not a feature. While a hemodynamically benign lesion, anatomically thin walled saccular aneurysms have been observed in the distal segment of the arch,[83] as have dissecting aneurysms of the ascending aorta with associated bicuspid aortic valve.[91,93] Differentiation from coarc-

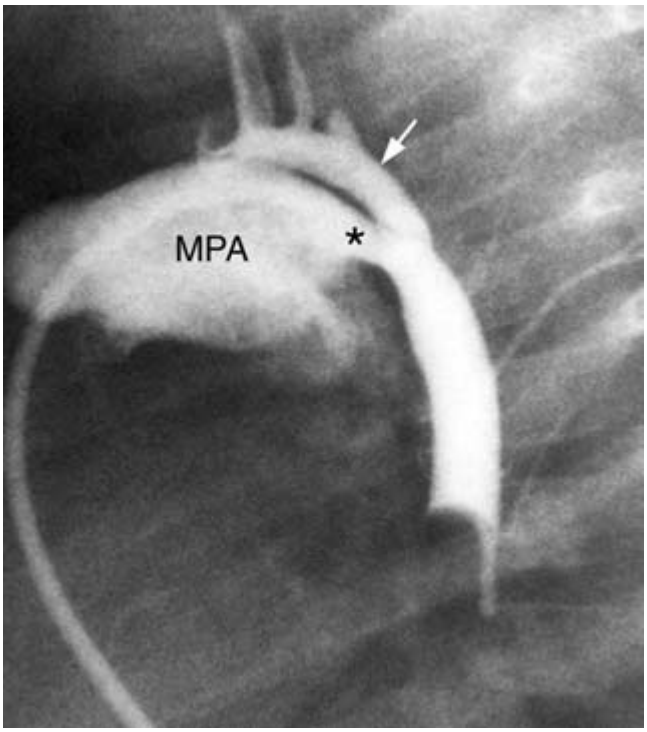

Fig. 22-3 Neonatal coarctation (arrow) with transverse arch hypoplasia, and a patent arterial duct (star). MPA, main pulmonary artery.

tation of the aorta may be difficult in the adult, though this is not usually the case in infancy, although a case in a 2-month-old has been reported.[95]

Associated lesions

A number of congenital cardiac and vascular malformations may coexist with coarctation of the aorta and are present in about half (usually infants) (Table 22-1) of the children with the disease.[97] The most common association is with a bicuspid aortic valve (80%), whether functionally normal, stenotic or incompetent.[20,98–103] Such bicuspid valves tend to have a centrally located orifice between two equal sinuses of Valsalva.[100] The valve is prone to stenosis, although less commonly in infancy. The significance of the associated bicuspid aortic valve highlights a unique marker for the increased aortic wall fragility, which predisposes to dissecting aortic aneurysms.[104,105]

An extensive collateral circulation to the post-coarcted segment is generally well developed even in infancy,[106] particularly if the obstruction is the sole lesion. However, when there is an associated cardiac malformation, the collateral circulation may not be as well formed. The development of the collateral circulation is also related to the site of the obstruction. If the coarctation is distal to the arterial duct then blood flow to the descending aorta is impaired, and an adequate collateral circulation *in utero* must be present. With the proximal obstruction, fetal blood flow through the arterial duct is not impaired and stimulation for development of collateral vessels is absent. In this latter situation, ductal closure may be life threatening. Such collateral vessels are often dilated and tortuous, most frequently arising from branches of the subclavian arteries above the obstruction. The internal thoracic aorta is a major pathway to the descending aorta, via connections of the anterior intercostal vessels with posterior branches, and the superior epigastric and inferior epigastric arteries. The vertebral artery branch of the subclavian artery contributes to collateral supply through the anterior spinal artery. The thyrocervical trunk also communicates with the descending aorta through cervical, scapular and mediastinal branches. Additionally, the costocervical trunk supplies the first two intercostal arteries via the internal thoracic artery (anteriorally) and the thoracoabdominal and descending scapular arteries contribute also to descending aortic blood flow.

Table 22-1 Associated conditions in neonates with coarctation of the aorta*

Cardiac	
Patent ductus arteriosus	647
VSD	586
Atrial septal defect	304
Aortic valve abnormality	286
Hypoplastic left heart syndrome	164
Transposition of the great arteries	116
DORV	102
Mitral valve abnormality	74
ECD	66
Common ventricle	55
Tricuspid atresia	36
Pulmonary stenosis	15
Tetralogy of Fallot	6
Noncardiac	
Chromosomal abnormality	94
Turner syndrome	35
Trisomy 21	28
Trisomy 13	13
Trisomy 18	4
Other	14
Prematurity	88
Diaphragmatic hernia	18
Tracheo-esophageal fistula	14
Hydrops fetalis	15
DiGeorge syndrome	13

*Numbers indicate the frequency with which the condition was coded among any of the first six discharge diagnoses. Many patients had more than one of these conditions.
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Coarctation may be associated with a right aortic arch[16,17,107–111] but is rare, and highlighted by atypical arch branching as a prominent feature, with an anomalous left subclavian,[108–110] mirror image brachiocephalic artery branching,[110] or an anomalous left innominate artery[111] being reported. Rarely, coarctation of the aorta may complicate a cervical aorta,[112] or be associated with a single trunk from which the head and neck vessels originate.[113]

Anomalies of the mitral valve apparatus are not uncommon and occur in up to half of the children.[98,114–121] Involvement may vary in severity from clinically occult to grossly overt, producing stenosis or incompetence. The anatomical spectrum encompasses minor decreases in interpapillary muscle distance (common) to a single papillary muscle with a parachute mitral valve or displacement.[82,114,116,120–125] Endocardial fibroelastosis is present occasionally, is usually patchy rather than confluent[126,127] and more common with an isolated coarctation of the aorta then when a ventricular septal defect coexists.

Rarely, right heart lesions have been identified with coarctation of the aorta, such as Fallot's tetralogy[128,129] or absent pulmonary valve syndrome with ventricular septal defect,[129A] atrial septal defects (both primum and secundum),[130,131] as well as non cardiac diseases such as Moyamoya,[132] neuroblastoma,[133] congenital diaphragmatic hernia[134] and coronary artery anomalies.[135]

A ventricular septal defect is the most common intracardiac anomaly,[136–144] and often of the variety associated with posterior malalignment of the infundibular septum.[140,143–145] As such reduced flow across the isthmus is exaggerated due to the obstruction to flow from the left ventricle outflow tract. Subaortic stenosis may be encountered relatively frequently, particularly in the infant group with coarctation of the aorta.[146] The mechanisms for subaortic stenosis in the first year of life in association with coarctation of the aorta and ventricular septal defect include conoventricular malalignment, adherent mitral valve or accessory endocardial cushion tissue.[147]

Dilation of the aortic root may occur, particularly if there is an associated aortic valve anomaly, while dilatation of the descending aorta is the rule. Dissecting aneurysms can occur in the long-term natural history of the lesion, particularly if there is a bicuspid aortic valve,[105,106] but are unusual in the pediatric age group. The morphological basis for the event is not known for certain, although cystic medial necrosis is a feature of the histopathology in coarctation of the aorta.[148,149] Intracranial

aneurysms or abnormalities of the Circle of Willis are not infrequently associated with coarctation of the aorta and the substrate for fatal intracranial hemorrhage.[150–152] In addition, aneurysms may develop involving the distal aortic arch and intercostal vessels[153–157] as well as changes in coronary perfusion, thought secondary to the proximal hypertension.[158,159] The retroesophageal anomalous right subclavian artery that occasionally accompanies coarctation of the aorta does not cause tracheoesophageal compression, while a vascular ring caused by a double aortic arch has been reported from one of the limbs of the double arched vessel.[160] A persistent fifth arterial arch can also be associated with coarctation of the aorta, most often in the setting of complex intracardiac anomalies including: a double outlet right ventricle where atresia of the fourth aortic arch occurred between the left common carotid and left subclavian arteries,[161] tricuspid and pulmonary atresia and a "ductal dependent" pulmonary circulation, the fifth arch functioning as a systemic-to-pulmonary artery connection on the same side as the definitive aorta,[162] aortic atresia with interruption of the aortic arch,[163–165] or rarely as an isolated lesion with or without coarctation.[166–173] Finally, aortic thrombosis in the neonate may simulate an obstructive anomaly of the aorta,[174–177] as might various systemic arteriovenous malformations.[178]

Modified natural history

Untreated coarctation of the aorta has a poor prognosis. Campbell,[179] in 1970, reviewed autopsy and clinical outcome data from 465 patients with aortic coarctation (although only patients surviving beyond the first year of life were included) documenting a mean age of death at 34 years of age (median 31 years), of whom 75% died before 46 years of age. Congestive heart failure was the most common cause of death (26%), followed by aortic rupture (21%), bacterial endocarditis (18%), and intracranial hemorrhage (12%). In a more contemporary study, Kuehl *et al.* examined all fatal cases compiled from the Baltimore–Washington Infant Study, which included 4390 cases of infants with congenital cardiovascular malformations identified in this population based study between 1981 and 1989.[180] Death occurred in 800 such infants in the first year of life, and in 76 of these infants, death occurred before diagnosis of heart disease was made. The authors found that the diagnoses of coarctation of the aorta, Ebstein's anomaly, atrial septal defect, and truncus arteriosus were overrepresented in infants found by the community search, particularly in those infants without associated malformations, suggesting that the natural history of the undiagnosed lesions was indeed poor.

Surgical repair

Coarctation in the fetus, newborn and infant

Coarctation of the aorta presenting in the newborn and infant with heart failure requires aggressive, timely therapy. Such patients present with poor peripheral perfusion, resulting in ischemia to the renal, hepatic and mesenteric beds, metabolic disturbances, including acidosis, hypothermia and hypoglycemia. Recognition of the lesion in the newborn with emergent surgical repair has resulted in improved outcomes.[181] In the early 1980s the management of such newborns was revolutionized by the ability to maintain or restore patency of the arterial duct. As most newborns present with "preductal" coarctation, the ability to perfuse the lower body, albeit with systemic venous blood, allowed the temporary reversal of the physiological derangements caused by reduced systemic blood flow. Coceani and Olley in 1973 first demonstrated that ductal patency could be maintained through an infusion of prostaglandin E_1 under both aerobic and anaerobic conditions.[182] In 1984, Leoni and colleagues[183] examined the effects of preoperative prostaglandin infusion on surgical mortality on patients aged < 28 days for obstructive lesions of the systemic circulation. Forty patients had coarctation of the aorta, 5 interrupted aortic arch, and 7 critical aortic stenosis. Fourteen patients received intravenous prostaglandin before operation. Among preoperative variables a low cardiac output was identified as a risk factor for hospital death, whereas an elevated urea was significantly associated with hospital mortality only in patients not treated with prostaglandin. The preoperative administration of prostaglandin had a favorable influence on outcomes with 11 out of 38 (29%) patients not receiving prostaglandin dying compared with none of 14 treated with the drug. Freed *et al.*[184] noted that while the maximal response to the drug can occur within 15 min, response times as long as 4 hours are occasionally required. Infants as old as 5 weeks have had ductal patency restored, usually requiring high dose infusions.[184,185] Side-effects occur with drug administration,[185] but from a study of 492 infants receiving the drug, only half of these were found related to prostaglandin and the majority required only minor changes in management. Cardiovascular events were the most common (18% incidence) with cutaneous vasodilation (and occasional hypotension) and edema occurring more frequently during intra-aortic infusion than during intravenous administration. Central nervous system events were reported in 16% of the patients. Respiratory depression in 12%, and was particularly common in infants weighing < 2 kg at birth (42%). No deaths were attributed to prostaglandin administration. There can also be jitteriness (which can rarely lead to seizures), fever, diarrhea, susceptibility to infections, and rarely a coagulopathy. The development of fever or jitteriness may require reduction of the infusion rate and, in view of the possible increased incidence of infections, the prophylactic use of antibiotics was recommended.[185]

If the diagnosis is made antenatally,[186–194] prostaglandin E_1 should be commenced at birth. Indeed, a number of centers advocate antenatal transfer and delivery in a tertiary center. Recently, Franklin and colleagues from the Fetal Cardiology Unit, John Radcliffe Hospital, at Oxford, in the United Kingdom,[194] investigated whether the antenatal diagnosis of coarctation of the aorta resulted in reduced mortality and improved preoperative hemodynamic stability compared with those diagnosed postnatally. A retrospective review of all cases of coarctation of the aorta presenting between January 1994 and December 1998 was undertaken and a univarate and multivariate analysis was conducted on a number of clinical variables. A cumulative score was created and subjected to logistic regression analysis. Both collapse and death were more common in the postnatally diagnosed group ($P < 0.05$). Femoral pulses were more likely to be palpable and there was echocardiographic evidence of duct patency in the antenatally diagnosed infants ($P < 0.001$ and $P < 0.05$, respectively) while infants with hemodynamic instability preoperatively were more likely to have been diagnosed postnatally ($P < 0.01$).

The accuracy of prenatal ultrasound diagnosis of coarctation of the aorta has been established in a number of studies,[188–193]

although the diagnosis can be difficult and requires inferred as well as direct ultrasound observations. Hornung *et al.*[195] noted that right ventricular dilatation was an infrequent finding at fetal echocardiography and its presence has been associated with aortic coarctation. However, there are associations with other congenital abnormalities. To determine the sensitivity of this finding on fetal ultrasound, all fetuses with right ventricular dilatation over a 5-year period were reviewed. Forty-three fetuses with right heart dilatation were seen, 15 had associated cardiac abnormalities: most commonly coarctation ($n = 4$) and ventricular septal defect ($n = 4$). Seven had associated non-cardiac abnormalities and 7 fetuses also had chromosomal abnormalities, concluding that fetal right heart dilatation is frequently associated with both cardiac and non-cardiac congenital abnormalities. Hornberger and colleagues from Toronto, Canada [191] further tested observations that might aid in the prenatal prediction of the presence of a coarctation of the aorta in newborn infants with and without other forms of heart disease. Reviewed were the prenatal echocardiograms and postnatal outcomes of 20 infants (gestational age at initial study 18–36 weeks) with coarctation of the aorta established postnatally. Associated cardiac lesions included double inlet left ventricle anatomy ($n = 5$), double outlet right ventricle ($n = 4$), abnormal aortic valve ($n = 5$), unbalanced atrioventricular canal ($n = 3$), and a membranous ventricular septal defect ($n = 1$). Chromosomal abnormalities included XO karyotype ($n = 1$), trisomy 18 ($n = 1$), and trisomy 21 ($n = 1$). Hypoplasia determined by measurement of the distal aortic arch was the most frequently observed finding among the fetuses with coarctation. In 12 of 15 fetuses with a well-visualized transverse arch at initial prenatal study, the diameter of the transverse arch was ≤ third per centile for gestational age as compared with that in a normal group of fetuses. Ten of 10 fetuses with adequate images of the isthmus had isthmus hypoplasia at prenatal study with a diameter ≤ third per centile for gestational age. On serial study in 6 of 7, including 3 fetuses with normal distal arch measurements at initial study, the distal arch became progressively more hypoplastic for gestational age. In 3 there was no growth of the transverse arch or isthmus on serial study, and in 3 there was reversal of flow from antegrade to retrograde through the distal arch. Quantitative hypoplasia of the isthmus and transverse arch appeared the most consistent observation and therefore the most definitive antenatal sign of postnatal coarctation.

The potential for progression of distal arch hypoplasia necessitates serial study in fetuses with associated cardiac and non-cardiac lesions. Sharland[190] and colleagues made similar observations from London, England. They also attempted to formulate echocardiographic criteria for the prenatal diagnosis of coarctation of the aorta. This retrospective study examined the echocardiograms from fetuses with a verified aortic arch abnormality and those in whom the diagnosis was suspected prenatally but was not subsequently confirmed. There were 87 fetuses examined, in whom the diagnosis of coarctation of the aorta was correctly made in 54, suspected but unproved in 24, and overlooked prenatally in 9. Not unlike that of the Hornberger study,[191] measurements of the ventricular widths, diameters of the great arteries, or the diameters of the atrioventricular valvar orifices, did not allow clear distinction between cases that definitely had a coarctation and those in whom the diagnosis was unproved. The appearance of the aortic arch, particularly in the horizontal ultrasound projection, was most helpful in distinguishing cases of coarctation, although this also was not always diagnostic. A predominantly left-to-right shunt across the foramen ovale was detected more often in cases with a substantiated coarctation (58%) than in those with an unproved diagnosis (12%). The most severe forms of coarctation were associated with relative hypoplasia of the left heart structures compared with the right. The milder forms of coarctation, however, were consistent with a normal early fetal echocardiogram. In late pregnancy it may be impossible to exclude coarctation categorically as the right heart structures appear larger than the left in the normal fetus. Thus, although a combination of echocardiographic features can correctly identify aortic arch anomalies in the fetus, none, either alone or in combination, can clearly distinguish between real and false positive cases, particularly in late gestation.

Newborns presenting with congestive heart failure in the anatomical setting of an isolated coarctation may, with medical management alone, stabilize and improve. However, due to the associated morbidity and mortality, early repair is warranted. In a recent study from England,[196] reviewing mortalities for various congenital heart lesions, the overall hospital mortality was 4.4% (95% confidence limits (CL), 3.7–5.3%), for open operations 12.6% in neonates, 5.1% in infants, and 3.5% in children, and for repair of coarctation of the aorta, 1.1%[196–201] (Fig. 22-4). Van Son *et al.*[197] reported their experience with 70 consecutive infants who underwent repair of coarctation of the aorta, at 80 ± 77 days of age and a mean weight of 3.0 ± 0.5 kg. An isolated coarctation was present in 25 patients (group 1); in 19 patients the lesion was in association with a ventricular septal defect (group 2); and in 26 patients the coarctation was associated with major intracardiac defects (group 3). Subclavian flap angioplasty was performed in 19 patients and resection and end-to-end anastomosis in 51 patients. Hospital mortality was not significantly different between subclavian flap angioplasty (11%) and resection and end-to-end anastomosis (24%). Freedom from reintervention for recoarctation after 5 years was 87% in the subclavian flap angioplasty group and 95% in the group having resection and end-to-end anastomosis. Actuarial survival at 5 years was 100% for group 1, 73% for group 2, and 28% for group 3. In the subclavian flap angioplasty group, detrimental effects of the sacrifice of the left subclavian artery were noted: 1 patient had a 2.5 cm shortening of the left upper arm, and 5 others complained of claudication in the left upper limb during strenuous exercise. As no major advantage in terms of

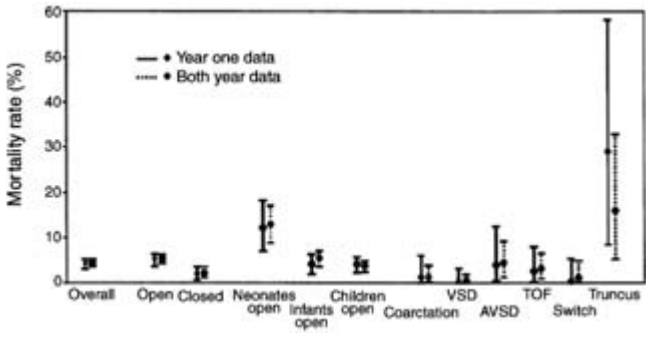


Fig. 22-4 Comparison of mortality rates for various groups of operations. AVSD, atrioventricular septal defect; TOF, tetralogy of Fallot; VSD, ventricular septal defect. (Reprinted from Stark *et al.*,[196] Copyright (2001), with permission from The Society of Thoracic Surgeons.)

mortality or recoarctation to either technique of coarctation repair was found, and as subclavian flap angioplasty carried the possible disadvantage of late contracture of isthmic ductal tissue and possible detrimental effects on the left upper limb, resection and end-to-end anastomosis was recommended as the surgical procedure of choice. A similar experience was noted by Rubay and colleagues[198] who reported upon 146 consecutive infants who had surgical repair of coarctation of the aorta. Age at operation varied from 2 days to 11 months (median 1 month). Ninety-two (63%) were < 2 months of age. An isolated lesion was present in 65 patients (group 1), an associated ventricular septal defect in 49 patients (group 2) and complex anomalies in 32 patients (group 3). The majority of infants (65%) were in congestive heart failure and 45 patients (31%) required artificial ventilation. A subclavian flap angioplasty was performed in 39 patients and resection and end-to-end anastomosis in 107 patients. Neither hospital mortality was significantly different between subclavian flap angioplasty (15%) and end-to-end anastomosis (18%) nor was the postoperative hypertension. Actuarial survival at 10 years was 100% for group 1, 94% for group 2, and 62% for group 3. Seventeen patients had recurrent coarctation. No significant difference was found in terms of types of repair or age at operation. No major advantage in terms of mortality and morbidity to either technique was found, and resection and end-to-end anastomosis appeared the preferred technique as it not only relieved the obstruction whatever the level, but also eliminated ductal tissue, preserving the subclavian artery and avoided the use of prosthetic material.

Despite novel innovations in surgical techniques during these procedures, alterations in cerebral blood flow do occur and are age dependent, as noted by a study by Rodriguez *et al*.[198A] These authors assessed hemodynamic changes as a consequence of application and release of aortic clamps for surgical repair of aortic coarctation using transcranial Doppler in 13 children (aged from 5 days to 14 years). Patients were stratified by age into two groups: age < 6 months (group 1) and age > 6 months (group 2). In both groups, with aortic clamping, systemic blood pressures and cerebral blood flow velocities changed only slightly ($P > 0.05$) from initiation to end of the aortic clamping. In group 1, release of the aortic clamps resulted in moderate fluctuations in systemic blood pressures ($P > 0.05$) and a marked reduction in cerebral blood flow velocities ($P < 0.01$). At the time of surgical closure, flow velocities had improved in all but 1 infant. Group 2 did not show major reductions in either cerebral blood flow velocity or systemic blood pressures throughout all measurements ($P > 0.05$). During aortic clamp release, young infants responded with lower brain blood flow velocities as compared to older children ($r = 0.68$, $P < 0.05$). In young infants transient central nervous system hypotension resulted as a consequence of flow redistribution during aortic declamping. Older children showed a faster autoregulatory compensation to these hemodynamic changes. The observed age to related physiologic differences suggests that young infants may be at risk for cerebral blood flow compromise and may require higher systemic blood pressures during declamping to prevent the cerebral blood flow reduction.

In those newborns with associated intracardiac lesions, presenting with congestive heart failure, the surgical risks are higher.[197–207] Levine *et al*.[201] reported in 2001, there is a risk of having additional obstructive left heart lesions (some not apparent on the initial diagnostic examination), or appearing late, which may further affect outcomes. This authors reviewed the frequency of additional, late appearing, stenotic lesions within the left heart, excluding those with complex cardiac disease or definite additional stenotic lesions at presentation, from 101 patients. At follow-up, 31 stenotic lesions were diagnosed in 23 patients. Mitral stenosis was diagnosed in 11 patients, aortic stenosis in 10, subaortic stenosis in 8, and supravalvar aortic stenosis in 2. The probability for freedom from obstructive lesions was 81% at 1 year, 74% at 3 years, and 70% at 5 years. Such observations underscore that associated stenoses in the left heart are common in the setting of aortic coarctation and underscore the need for vigilant anatomical reassessments.

The need for intracardiac repair (or pulmonary artery banding) at the time of coarctation repair in this setting is not always clear. Indeed, at times, repair of the arch obstruction alone may improve the pathophysiology such that medical management can maintain stability (e.g. reduction in the right-to-left shunt at ventricular level, allowing reduction in signs and symptoms of congestive heart failure). Intracardiac repair for those infants with a large ventricular defect, or more complex intracardiac lesions (such as d-transposition of the great arteries or double outlet right ventricle, and a ventricular defect) is appropriate. In the Rubay study,[198] the 10-year actuarial survival for those infants with complex intracardiac lesions (other than a ventricular septal defect) was 62%, and Van Son *et al*.[197] 5-year survival, 28%. Merrill *et al*.[199] further reported the risk factors for the operative mortality and long-term durability of repair in 139 patients < 1 month of age after surgical correction of coarctation of the aorta. Complex intracardiac defects were present in 59 patients, and another 44 patients had an associated ventricular septal defect. Subclavian artery flap repair was performed in 92 patients, end-to-end anastomosis in 38 patients and patch angioplasty in 9 patients. The hospital mortality was significantly higher in patients with complex intracardiac defects (9 of 59 patients; 15.2%) than in those with a ventricular septal defect (1 of 44 patients; 2.3%) or with isolated coarctation (none of 36 patients; $P = 0.007$). An elevated pulmonary artery diastolic pressure ($P = 0.041$) and complex intracardiac anomalies ($P = 0.048$) were found to be independent predictors of hospital mortality, and the presence of a complex cardiac defect ($P < 0.001$) was an independent predictor of poor long-term survival. Recurrent stenosis requiring reoperation occurred or balloon dilation had been necessary in 28% of the children at 5 years after surgery. In patients followed up for at least 5 years, the recurrence free survival was better in those who had undergone subclavian artery flap repair than in those who had undergone end-to-end repair ($P = 0.017$).

Tchervenkov *et al*.[199A] from Montreal, Canada, reviewed their experience with a single staged biventricular repair of complex intracardiac defects associated with aortic arch hypoplasia by means of a pulmonary homograft patch aortoplasty, between 1988 and 1997. Here, 39 of 40 consecutive patients underwent a single stage biventricular repair, the median age at operation being 17 days and the mean weight 3.7 ± 1.1 kg. Nineteen patients had either d-transposition of the great arteries or the Taussig–Bing anomaly. Sixteen patients had multiple left sided obstructive lesions (2 cases of critical aortic stenosis, 3 of subaortic stenosis and a ventricular septal defect, and 11 cases of hypoplastic left heart complex), 1 had an associated complete atrioventricular septal defect. Four patients had only an associated ventricular septal defect. Through a median sternotomy, the hypoplastic aortic arch was enlarged with a pulmonary homograft patch in 36 patients. In 4 patients an extended end-

to-end anastomosis was performed. There were 2 early deaths (5%) and 2 late deaths (5%), 1 late death was not cardiac related. The mean follow-up time was 36 months (range 1 month to 9 years). The recoarctation rate was 8.3%, but after exclusion of those patients with associated left sided obstructive lesions this decreased to 0%. No aneurysm formation in the aorta occurred. The actuarial survival at 8 years was 89% ± 10%.

From a multi-institutional study, Quaegebeur *et al.*[200] reviewed 326 severely symptomatic neonates with coarctation of the aorta with or without a ventricular septal defect, 4 died before the initial procedure. Among the 322 undergoing surgical repair, survival for at least 24 months was 84%; the hazard function for death was lower initially, but more prolonged in patients without than in those with a ventricular septal defect. Important mitral valve anomalies coexisted in 5% of patients, left ventricular hypoplasia in 5% (more commonly in patients without ventricular septal defect), narrowing of the left ventricular outflow tract in 9% (more common in patients without ventricular septal defect), and narrowing of the proximal arch in 1%; one or more of these anomalies was present in most patients without ventricular septal defect who died. Five per cent of the 322 patients had more than one of these coexisting anomalies, and 8% had just one. The most commonly used technique of repair of the coarctation was resection and end-to-end anastomosis, but no technique was a risk factor for death by multivariable analysis. Patch graft repair was associated with the highest prevalence (21%) of reintervention to the coarctation repair contrary to the observations of Tchervenkov *et al.*[199A] Among patients with coexisting moderate sized or large ventricular septal defects, repair of the coarctation, pulmonary trunk banding, and subsequent repair of the defect were associated with the highest 2-year survival, 97% in those with single ventricular septal defect (Fig. 22-5).

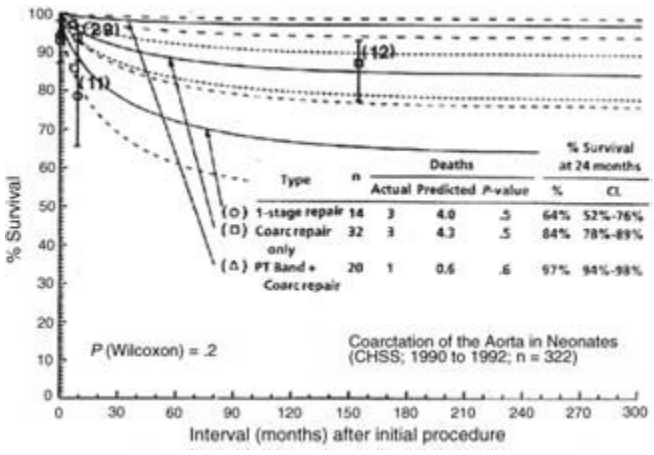


Fig. 22-5 Non risk-adjusted effect of the type of initial procedure on time-related survival (Kaplan–Meier estimates) in neonates with coarctation and single, moderate sized, or large ventricular septal defects and no coexisting obstructive lesion in the left heart aortic complex, stratified according to type of initial procedure. Circles, squares, and triangles, actuarial estimates; vertical bars, 70% CL (± 1 SE). A comparison of the actual numbers of deaths and the time related probability of death (Kaplan–Meier estimates) are shown in each group; solid lines, those obtained parametrically. CHSS, Congenital Heart Surgeons Society; CL, 70% confidence limits; PT, pulmonary trunk. (Reprinted from Quaegebeur *et al.*,[200] Copyright (1994) Mosby Inc., with permission from Elsevier.)

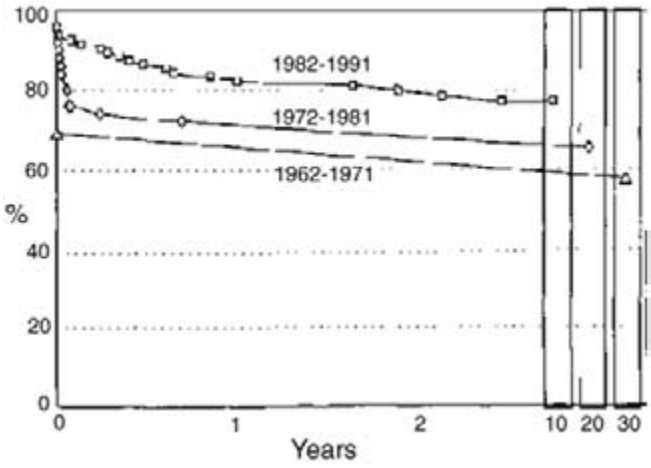


Fig. 22-6 Actuarial survival after coarctation repair by surgical era. (Reprinted from Zehr *et al.*,[202] Copyright (1995), with permission from The Society of Thoracic Surgeons.)

Zehr *et al.*[202] reported outcomes from 179 children < 1 year of age who underwent repair of coarctation of the aorta between 1962 and 1991. The patients were separated into three surgical eras: group 1 (1962–71) consisted of 19 patients, group 2 (1972–81) of 57 patients, and group 3 (1982–91) of 103 patients. Neonates (< 30 days old) made up 60% of group 1, 57% of group 2, and 70% of group 3. The proportion of infants with associated complex cardiac abnormalities was 7% in group 1, 25% in group 2, and 39% in group 3. Techniques of repair included resection with end-to-end anastomosis ($n = 65$), subclavian flap repair ($n = 85$), patch aortoplasty ($n = 18$), and other procedures ($n = 11$). The early mortality (< 30 days) was lowest in group 3 (group 1, 21%; group 2, 21%; group 3, 7%; $P < 0.05$), but the late mortality was similar in all groups (group 1, 11%; group 2, 13%; group 3, 15%), (Fig. 22-6). The overall actuarial survival was 58% at 27 years in group 1, 66% at 20 years in group 2, and 78% at 9 years in group 3 (P = not significant). Twenty-five restenoses requiring intervention occurred in 23 patients, for an overall restenosis rate of 16%. The incidence of restenosis was 23% for the patients who underwent end-to-end anastomosis, 11% for those who underwent subclavian flap repair ($P < 0.1$), and 27% for those who underwent patch aortoplasty ($P < 0.01$). Balloon angioplasty was successful in relieving 11 of the 12 restenoses in groups 2 and 3. The mean interval between repair of coarctation of the aorta and definitive intracardiac repair decreased from 62 ± 43 months in group 1 to 42 ± 45 months in group 2 and 10 ± 14 months in group 3 ($P < 0.001$). Twenty-eight variables (various patient characteristics, presenting signs and symptoms, management and operative variables, and severity of disease) were subjected to a Cox proportional hazards multivariate regression analysis to determine predictors of restenosis and mortality. Only patch aortoplasty was significantly associated with restenosis ($P < 0.01$). Increasing age at operation and the use of monofilament nonabsorbable suture were significantly associated with freedom from restenosis ($P < 0.02$). Younger age at operation, the need for concomitant pulmonary artery banding, and the existence of associated cardiac abnormalities were significantly associated with early mortality ($P < 0.01$). In this retrospective review it was noted that: (1) subclavian flap aortoplasty was associated with the lowest rate of restenosis after repair of coarctation

Table 22-2 Early and late mortality from neonates undergoing a single-staged repair of coarctation of the aorta and intracardiac defects

Group*	Number	Early mortality	Late mortality	Weight at operation (kg) (mean ± SEM)	Age at operation (days) (median)
Coarc. With VSD	19	1 (5%)	0	1.4–4.7 (3.1 ± 0.2)	1–29 (11)
IAA with VSD	18	2 (11.1%)	1	1.3–4 (3.0 ± 0.2)	2–15 (6)
Coarc./IAA/complex intracardiac defects	23	4 (17.4%)	1	2.1–4 (3.1 ± 0.1)	2–24 (8)

*Coarc., coarctation; IAA, interrupted aortic arch; VSD, ventricular septal defect.
(Reprinted from Sandhu *et al*.,[203] Copyright (1995), with permission from Excerpta Medica.)

during infancy, and, conversely, patch aortoplasty was significantly associated with restenosis; (2) the restenosis rate was significantly lower in association with the use of monofilament nonabsorbable suture than other suture materials; (3) the early mortality after coarctation repair had decreased significantly during this time period, despite a higher proportion of infants with complex cardiac malformations; (4) late mortality was associated with younger age at operation and the presence of severe associated cardiac anomalies, and remained constant during the three decades covered by the study.

Sandhu *et al*.[203] and colleagues recently reported successful single stage repairs of both coarctation of the aorta and the intracardiac defects in neonates. These authors reviewed their experience with 60 neonates (median age 8 days, range 1–28 days) who underwent a single stage repair, between 1986 and 1994. Nineteen (32%) had a coarctation with ventricular septal defect, 18 (30%) had interrupted aortic arch with a ventricular septal defect, and 23 (38%) had a coarctation or interrupted aortic arch with complex intracardiac anatomy (Table 22-2). The arch obstruction was repaired using resection and primary anastomosis in 54 patients, synthetic patch aortoplasty in 3, subclavian flap aortoplasty in 2, and an interposition Gortex™ graft placement in 1. There were 7 early postoperative deaths (12%; 70% CL 8–17%). The 53 survivors were followed for a mean of 23 months (range, 1–78 months) for a total of 1219 patient months. Recurrent arch obstruction ≥ 20 mmHg occurred in 2 of 53 patients (4%; 70% CL 2–8%), both undergoing successful balloon angioplasty. There were 2 late deaths, 1 of which was noncardiac. Gaynor *et al*.[207] from Philadelphia, also reported their institutional experience following a single stage repair of coarctation and a ventricular septal defect between 1994 and 1999. A single stage repair was performed in 25 infants (12 males, 13 females) at a median age of 12 days (range 1–87 days) and median weight of 3.3 kg (range, 1.3–4.4 kg). The ventricular defect was conoventricular in 10 patients, malalignment type with posterior deviation of the infundibular septum in 10, muscular in 4 and conal septal hypoplasia in 1. Arch hypoplasia was present in all patients and bicuspid aortic valve in 13. At least moderate subaortic narrowing was present in 6 patients (secondary to prolapse of tricuspid valve tissue across the ventricular defect in 4). Overall patient survival was 96% with 1 operative death and no late deaths at a median follow-up of 16 months (range, 1–50 months). Reinterventions included balloon dilatation of recurrent coarctation ($n = 5$), closure of residual ventricular defect ($n = 1$) and a Ross–Konno procedure ($n = 2$). Actuarial freedom from reintervention for the hospital survivors was 81% (95%; CL 61–92%) at 6 months, 71% (95%; CL 47–87%) at 1 year and 59% (95%; CL 31–82%) at 2 years following surgery (Fig. 22-7). These studies demonstrate improved outcomes in the recent surgical era for single staged repairs, particularly in those patients with an isolated ventricular septal defect. Repair of complex intracardiac lesions remains a challenge.

The experience used a single staged approach for total repair in the premature and low birth weight infant with slightly higher mortality then older newborns, but overall acceptable outcomes. The rate of recoarctation is higher in the very low birth weight infants, and associated left heart lesions increase early mortality. Haas and colleagues from Ann Arbor, Michigan,[208] reviewed their experience with primary repair of the aortic coarctation with ventricular septal defect in 21 consecutive preterm (≤ 36 weeks) and/or low birth weight (< 3000 g) infants with interrupted aortic arch ($n = 10$), or aortic coarctation ($n = 11$) with a ventricular septal defect. The mean weight at operation was 2310 g (range, 1200–2900 g), including 12 patients at ≤ 2500 g and the gestational ages ranged from 30–41 weeks (mean, 36 weeks). Five patients with an interrupted arch and 2 patients with a coarctation also had severe subaortic stenosis, which was relieved by transatrial incision of the infundibular septum. The overall hospital mortality was 14% (3/21). Death was related to

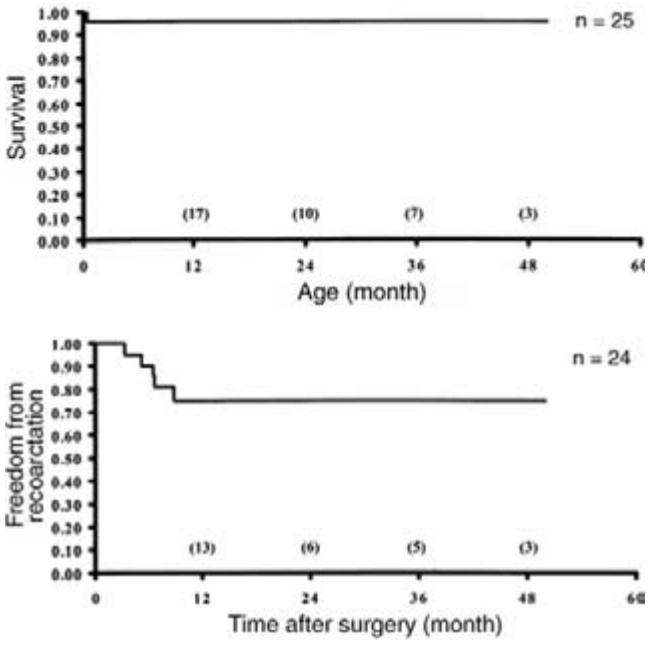


Fig. 22-7 **A**. Actuarial survival for all patients undergoing single stage repair of coarctation and ventricular septal defect. **B**. Freedom from recoarctation for hospital survivors. (Reprinted from Gaynor *et al.*,[207] Copyright (2000), with permission from Elsevier.)

low cardiac output in association with severe subaortic stenosis ($n = 2$) and sepsis ($n = 1$). Late mortality occurred in 3 patients, 2 of which were non cardiac. The mean follow-up was 33 months with 2 patients developing recurrent arch obstruction, successfully relieved by balloon angioplasty and surgical correction in 1 each. The survival at 30 days, and at 1 and 3 years was 86%, 76% and 70%, respectively. Similar results were reported by Bacha *et al*.[209] from a retrospective review of 18 consecutive neonates, < 2 kg who underwent repair of aortic coarctation between 1990 and 1999. Median weight was 1330 g, and median gestational age was 31 weeks. A ventricular septal defect was present in 5 patients, and Shone's complex in 4. Sixteen patients had resection and end-to-end anastomosis, and 2 had resection and subclavian flap. One patient died during hospitalization. Two patients died late postoperatively (5-year estimated survival 80%). Mean follow-up was 28 months. Eight patients (44%) had a residual or recurrent coarctation, 5 underwent balloon dilation, and 3 underwent reoperation. Freedom from reintervention for recoarctation was 60% at 5 years. Shone's complex or a hypoplastic arch was an independent risk factor for decreased survival ($P < 0.001$). Very low birth weight was a multivariate predictor for increased risk of recoarctation ($P = 0.01$).

In contrast to these studies, between 1984 and 1998 Isomatsu *et al*.[210] reviewed their institutional experience, in 79 patients < 3 months old with coarctation and ventricular septal defect who underwent a two stage repair. The first stage operation consisted of subclavian flap angioplasty and pulmonary banding. The median age at the initial operation was 28 days (range, 4–90 days), and median weight was 3.2 kg (range, 1.2–5.1 kg). A hypoplastic aortic arch was present in 27 patients, and coexisting anomalies were present in 13 patients. After a mean interval of 10 ± 9 months, a second stage repair was performed, with closure of the ventricular septal defect and pulmonary debanding. There were 2 hospital deaths and 4 late deaths. Mean follow-up was 9 ± 5 years (range, 2.0–18.3 years), and actuarial survival was 92% at 10 years (95% CL 86.6–98.3%). Age at first operation, body weight, hypoplastic arch, and coexisting anomalies had no significant influence on overall mortality. Freedom from recoarctation rate was 90% at 10 years (95% CL 83.7–97.2%). These authors suggested, to diminish mortality and recoarctation rate and to decrease the possibility of complications related to circulatory arrest and allogeneic blood transfusion, a two stage repair was still an effective technique. These data are similar to the multi-institutional survival of 97% reported by Quaegebeur *et al*.[200]

Finally, Ishino *et al.* from Japan[211] addressed the impact of surgical technique on early outcome without hypothermic circulatory arrest, using a single stage procedure with an isolated cerebral and myocardial perfusion and retrospectively compared this approach to the conventional two stage approach. Between 1991 and 1999, 24 infants, aged 4–137 days (median, 27 days) and weighing 1.7–4.3 kg (median, 3.0 kg), underwent repair either in one (group 1, $n = 11$) or two stages (group 2, $n = 13$). The mean isolated cerebral and myocardial perfusion time for group 1 was 13 min (range, 7–20 min), and the myocardial ischemic time did not differ between groups 1 and 2 (43 ± 4 vs. 42 ± 5 min, not significant). There were no hospital mortalities or neurological complications in either group, but 1 late death occurred in each group.

On balance these studies support single staged repair of the aortic arch obstruction and the intracardiac defects (particularly an isolated ventricular defect), through a median sternotomy, can be accomplished with low mortality in the newborn and infant. The mortality is slightly greater in the low birth weight and premature. Patients with complex intracardiac anatomy, multiple left heart lesions, the low birth weight infant or premature are at higher risk.

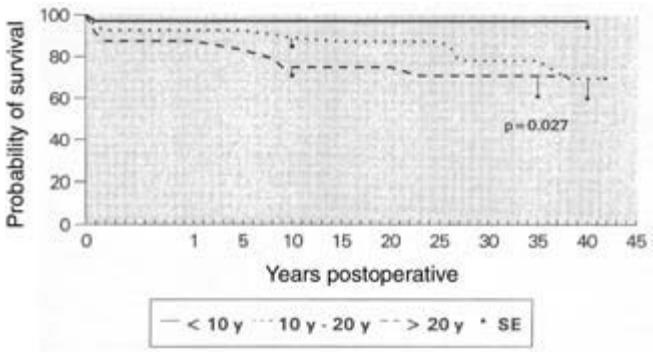
Aortic coarctation in the neonate with a small left ventricle

Obstruction of the left ventricular outflow tract may be associated with hypoplasia of the left heart, which may influence the options for treatment. Although the influence of the size of the left heart on the outcome for critical aortic stenosis has been described,[212] less is known about the spectrum of such hypoplasia seen with neonatal aortic coarctation. Tani and colleagues[213] described the spectrum and influence of hypoplasia of the left heart in neonatal coarctation; if described critical values for the adequacy of the left heart in neonates with critical aortic stenosis were applicable to neonates with coarctation, and, if any of the variables or associated abnormalities are risk factors for recoarctation. Studied were 63 neonates who underwent repair of coarctation, were from the initial echocardiogram, multiple measures of left heart structure were obtained and a score for adequacy, the so-called Rhodes score[212] for a biventricular repair calculated. The sizes were compared to previously reported minimal values, and then analyzed for their influence and associated anomalies on outcome. There were no deaths. There was a broad spectrum of sizes that did not correlate with the need for re-intervention. The calculated score for adequacy would have predicted survival in only 56% of the patients, and 73% of the neonates had at least one parameter measured in the left heart below previously reported minimal values. There was a broad spectrum of sizes for the left heart in neonates with aortic coarctation not predictive of outcome. Several additional studies have also addressed the effect of isolated hypoplastic arch in the neonate with a small left ventricle.[214] Alboliras *et al*.[214] report 8 infants with severe aortic coarctation and left ventricular hypoplasia, mean age 18 days (range, 1–48 days), and mean weight 3.5 kg (range, 2.7–4.3 kg). Associated diagnoses included mild aortic stenosis ($n = 4$), a ventricular septal defect ($n = 2$), and venous anomalies ($n = 2$). All had coarctation repair as a primary procedure (3 having concomitant intracardiac procedures); 7 required a subsequent operation. All are alive and well 1.1–6.7 years (mean 3.1 years) after the first surgery. Progressive increases were observed in aortic and mitral diameters, and in left ventricular dimensions, areas, and volumes when the preoperative and the most recent echocardiograms were compared. Despite severe left ventricular hypoplasia, a biventricular repair was possible in selected cases. Similarly, Serraf *et al*.[215] observed that the restoration of normal loading influences on the left ventricle, in the setting of multilevel left ventricular outflow tract obstruction and a duct dependent systemic circulation, can result in a biventricular repair in selected neonates. Twenty duct dependent neonates presented with this anomaly to the Marie-Lannelongue Hospital, Le Plessis-Robinson, France. All had aortic coarctation associated with multilevel left ventricular obstruction. Preoperative echocardiographic assessment noted a mean left ventricular end diastolic volume of 12.4 ± 3.0 mL/m^2 and mean Rhodes[212] score of –1.7 ± 0.8. Surgery consisted in relief of left ventricular outflow tract obstruction with coarctation repair, aortic commissurotomy in 1 and atrial

septal defect closure in 2 patients. There were 3 early and 2 late deaths. Failure of biventricular repair and left ventricular growth was obvious in patients with severe anatomic mitral stenosis. The other patients demonstrated growth of all left heart structures. At hospital discharge the left ventricular end diastolic volume was 19 ± 3 mL/m^2 (P = 0.0001) and the Rhodes score was –0.38 ± 1.01 (P = 0.0003). Actuarial survival and freedom from reoperation rates at 5 years were 72.5% and 46%, respectively. Finally, Tani *et al.*[216] also evaluated the influence of small left heart structures and the ability to achieve a biventricular repair in neonates with coarctation and aortic arch obstruction. All neonates in this study had a Rhodes score that would have predicted the need for a univentricular repair. All were duct dependent, but had antegrade ascending aortic flow and a small but nonstenotic aortic valve (< 30 mmHg gradient). Twenty such neonates aged 10 ± 9 days were identified with weights averaging 3.1 ± 0.6 kg. Left heart measurements obtained by preoperative echocardiography included an aortic annulus of 5.3 ± 0.3 mm, a mitral annulus of 8.4 ± 1.0 mm, transverse aortic arch of 3.4 ± 0.6 mm, and left ventricular volume of 25 ± 4 mL/M^2. All patients underwent coarctation repair by resection and an extended end-to-end anastomosis. Three patients underwent simultaneous pulmonary artery banding due to a large ventricular septal defect. There were no early or late deaths at a follow-up of 38 ± 16 months. Two patients required balloon aortoplasty due to recurrent coarctation (gradient > 20 mmHg) and in 1, resection of subaortic stenosis. Late follow-up in the remaining patients revealed 1 with moderate subaortic stenosis (gradient = 43 mmHg), 2 with mild aortic stenosis (gradient < 30 mmHg), and 2 with mild to moderate mitral stenosis. Sixteen patients (16/20, 80%) were free of symptoms and 4 (4/20, 20%) had mild residual symptoms. These studies document the biventricular physiology that can be achieved in neonates with small left heart structures and aortic arch obstruction with minimal mortality but varying late functional results. Standard echocardiographic measurements used to predict the need for a univentricular repair in critical aortic stenosis appear not valid for the neonate with aortic arch obstruction.

Coarctation in the older child

In the asymptomatic child with upper extremity hypertension, the timing of repair is elective in contrast to the emergent repair in the younger patient with heart failure. Elective repair in the asymptomatic child has been generally performed at 2–3 years of age, in the absence of severe upper extremity hypertension.[197–199,217–220] From the study by Beekman *et al.*[219] the need for reoperation after coarctation repair in infancy, was analyzed for 125 consecutive infants (< 12 months) who underwent repair of coarctation of the aorta by subclavian angioplasty or resection and end-to-end anastomosis. Sixty-three infants underwent repair by resection between 1960 and 1980, and 62 underwent subclavian angioplasty between 1977 and 1985. The mean age at operation with a subclavian flap angioplasty was 1.54 ± 0.93 months and for resection 2.70 ± 0.93 months (P = 0.02). There was no difference between groups in patient weights at repair, the proportion with complex anatomy or aortic arch hypoplasia. Follow-up duration for the subclavian flap group was 2.55 ± 0.51 years (range 0.3–8.2 years), and for the resection group 7.97 ± 3.61 years (range 0.6–21 years). Indication for reoperation was the presence of a coarctation gradient at rest of ≥ 40 mmHg and arm hypertension. Reoperation was required in 5 patients in the subclavian flap group and 12 patients in the resection group. The mean reoperation rate after subclavian flap repair was 0.0356 reoperations per patient-year, and after resection was 0.0342 reoperations per patient-year (P = 0.94). The risk of reoperation by the fifth postoperative year was found to be 16.3% after subclavian flap repair and 15.7% after resection. Similar observations were made by Brouwer *et al.*[220] from a retrospective study determining the actuarial survival after aortic coarctation repair > 25 years after surgery and the optimal age for elective aortic coarctation repair. From 1948 to 1966, 120 consecutive patients underwent aortic coarctation repair at a mean age of 15.5 ± 9.1 years. Resection and end-to-end anastomosis was performed in 103 patients (85.8%). Six patients died as a result of surgical problems, whereas late mortality in 15 patients was predominantly caused by cardiac causes. The mean follow-up period was 32 years (range 25–44.2 years). Ninety-two patients 96.8%) were in New York Heart Association class I. The probability of survival 44 years after operation was 73% (Fig. 22-8). Patients < 10 years at operation had the highest probability of survival at 97%. Multivariate analysis determined that age at operation was the only incremental risk factor for the occurrence of recoarctation, of late hypertension, and of premature death, suggesting that such sequelae could be avoided with elective repair at 1.5 years of age, when the probability of recoarctation will have decreased to < 3%, and the probability of upper body normotension and long-term survival would be optimized. This



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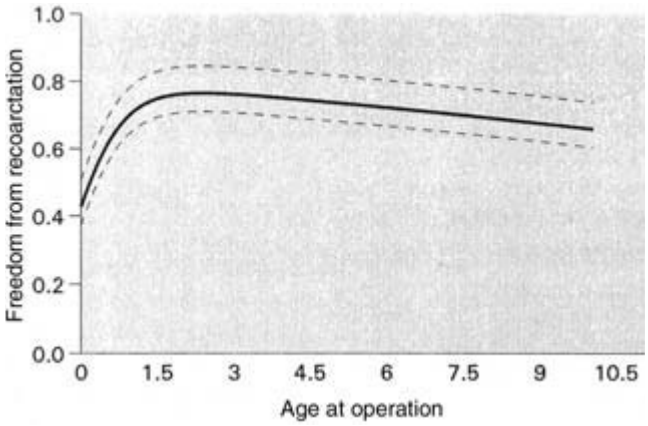


B

Fig. 22-8 **A**. Probability of survival after coarctation repair stratified into different age groups. SE, standard error. **B**. Composite nomogram showing freedom fro recoarctation, late hypertension, and premature death. Note that the optimal age for repair is *c.* 1.5 years of age. 70% CL, 70% confidence limits. (Reprinted from Brouwer *et al.*,[220] Copyright (1994) Mosby Inc., with permission from Elsevier.)

influence of age has been attributed to the early observations of Moss *et al*. [221] who demonstrated that the normal aorta attains 55% of its final adult diameter by 3 years of age. Since a hemodynamically significant aortic lesion requires a reduction in diameter of at least 50%, recoarctation following resection should be uncommon, even if no growth occurs at the anastomotic site. Finally, the risk of residual hypertension and early atherosclerotic cardiovascular disease is increased with late repair,[222] such that repair need not be delayed until late childhood or adolescence. In a long-term study by Liberthson *et al*.[223] following 234 patients, the prevalence of residual hypertension was only 6% in those repairs performed between 1 and 5 years of age, while 30–50% in patients repaired at an older age.

History and techniques of surgical repair (Fig. 22-9)

Blalock and Park [224] performed the first experimental coarctation repair in 1944 utilizing a turning down of the subclavian or carotid artery to bypass the lesion. Gross and Hufnagel [225] similarly experimented in the mid 1940s with aortic cross-clamping, resection of the lesion and an end-to-end anastomosis. The first human surgical repair occurred in 1945, reported by Craaford and Nylin from Sabbatsberg Hospital in Stockholm, Sweden,[226] applying an end-to-end technique.

The interposition graft was first reported by Calodney and Carson in 1950,[227] but was unsuccessful; Gross[228] in 1951 used an aortic homograft placed across the coarcted segment. For a time this was considered the treatment of choice for infant and neonatal repairs.[229,230] Morris and colleagues from Texas introduced prosthetic conduit material in 1960.[231] This approach remains useful in the treatment of the older patient with aneurysmal arch lesions, complex anatomy or those patients where an end-to-end anastomosis is not feasible.[232] Early results of end-to-end repair were not satisfactory with up to a 60% recurrence rate.[233–235] Vorsschute[236] reported in 1961 a technique termed "isthmuloplasty" which shortly evolved into the technique of patch aortoplasty, where an elliptical patch of prosthetic material (Dacron, Goretex™) was positioned across the coarcted area. This technique was thought to reduce the rate of recurrent obstruction,[237] and lessened exercise induced arm-to-leg gradients compared to patch repairs.[238,239] However, the occurrence of true aneurysms developing late after repair, opposite the side of the patch on-lay graft, has directed many centers to abandon this approach unless no other alternative was available.[240–244] In this regard, Parks and colleagues reported in 1995,[240] 39 patients repaired with a Dacron™ patch aortoplasty, between 1976 and 1987. The aorta ruptured in 10 patients; 6 died at a mean interval of 8.1 years (range 0.75–12.4) after repair. All 33 survivors were re-examined, with conventional magnetic resonance imaging in 26 patients, and magnetic resonance angiography in 18. Twenty patients (11 girls) had developed aneurysms, of which 9 were detected in patients studied by magnetic resonance. Ruptures occurred in 8 female patients, 3 of whom were pregnant. On follow-up, no aneurysms have been detected in those patients with negative magnetic resonance studies results. However, both Bertolini *et al*.[243] and Backer *et al*.[244] have recently suggested that the use of Goretex™ prosthetic material is not associated with such an event.

In 1966, Waldhausen and Nahrwold described the technique of subclavian flap aortoplasty in attempt to reduce the high rate of recurrent arch obstruction, which complicated contemporary repairs at the time.[245] Surgical details can be found in the review by Moulton *et al*.,[246] who described the advantages. An obvious disadvantage is the potential for reduced arm growth from interruption of the blood flow, which has been rarely reported.[247–251] There is a range of discrepancy in limb length from mild to rare reports of gangrene,[197,252,253] and aneurysms have been reported.[254,255] While early studies suggested a low incidence of recurrent arch obstruction,[256,257] more recent studies have refuted these observations.[217,219,198,258] A number of variations of the technique have been described,[259,260] the earliest the so-called "reverse flap" is where the subclavian artery is brought forward along the arch to address proximal lesions, such as arch hypoplasia (see above).

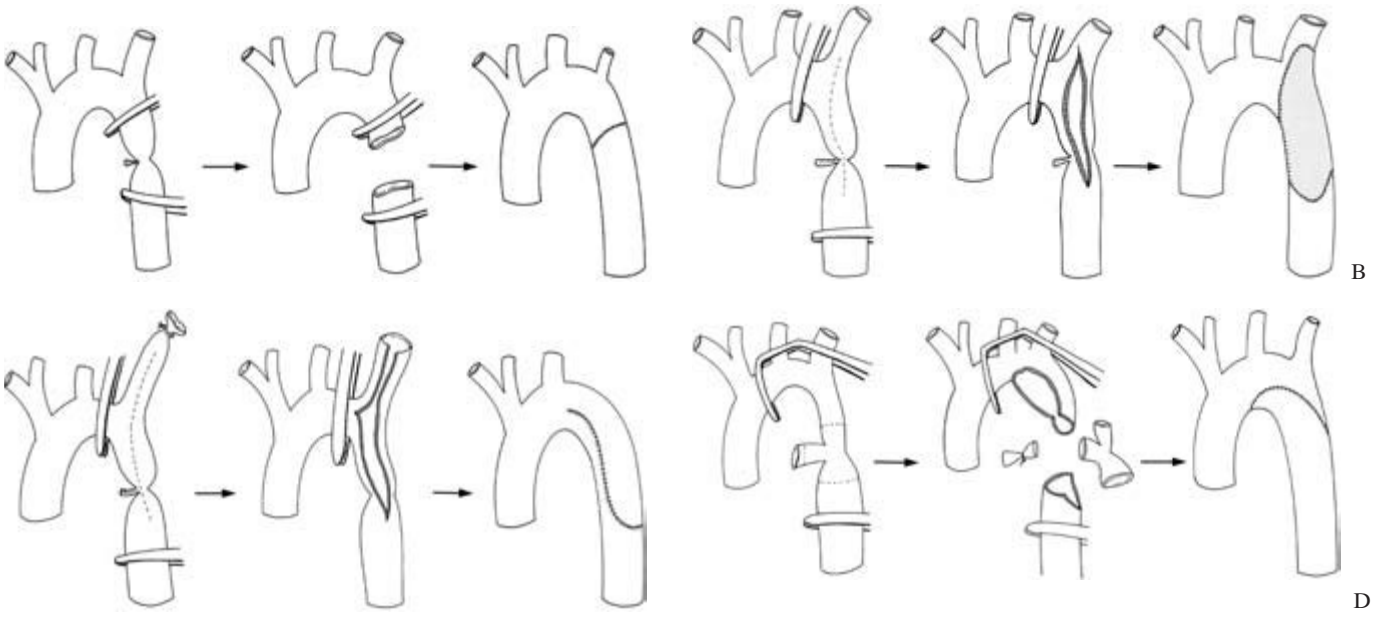


Fig. 22-9 Various surgical techniques for coarctation repairs. **A**. End–to-end repair. **B**. Patch repair. **C**. Subclavian flap arterioplasty. **D**. Resection with extended end-to-end repair.

Finally, there have been attempts to address the blood flow compromise from subclavian ligation, with either distal vessel reimplantation[261,262] or use of the internal thoracic artery to preserve blood flow to the arm.[263]

Lansman and colleagues[264] introduced the extended end-to end repair to address the occurrence of recurrent arch obstruction, particularly seen in neonates,[265] modifying the resection with end-to-end repair. This technique or one of its modifications[266–270] has been found very useful especially when there is associated tubular hypoplasia of the transverse arch or isthmus. Lacour-Gayet *et al*.[270] in 1990 reported 66 consecutive neonates with coarctation and severe hypoplasia of the transverse arch who underwent coarctation repair by resection of the coarctation and reconstruction of the arch. Mean age at operation was 14 ± 8 days, ranging from 2 to 30 days; and 63% of the newborn infants were < 2 weeks of age. The coarctation was isolated in 23%, associated with a ventricular septal defect in 39%, and associated with complex anomalies. The surgical technique comprised of a wide resection of the coarctation extending into the contiguous ductal tissue with reconstruction of the aortic arch, bringing the descending aorta into the concavity of the aortic arch. The early mortality (< 30 days) was 14% (9/66; 95% CL 5–22%), including 4 deaths occurring within the first month, at a concomitant or subsequent repair of an associated anomaly, and 6 late deaths, related to the associated lesions. The overall mortality rate was 23% (15/66; 95% CL 13–33%). The mean follow-up was 21 ± 10 months, (range, 6–66 months), and actuarial survival rates at 5 years are 72% ± 10% for the overall group; 87% ± 17% for simple coarctation; 88% ± 12% for coarctation and a ventricular septal defect; and 52% ± 18% for complex coarctation. The rate of recurrent coarctation was 12.5% (95% CL 2–23%), leading to 5 reoperations with no deaths. Freedom from reoperation was 89.5% ± 9% at 5 years. Similarly, Van Heurn *et al*.[271] reported a 15 year experience with a variety of arch reconstructive techniques, reviewing 151 infants younger < 3 months of age who underwent repair of coarctation between 1985 and 1990. In 25% and 33% of the patients there was hypoplasia of the isthmus and of the transverse arch, respectively. Surgical procedures included: subclavian flap angioplasty in 15 patients, resection with a traditional end-to-end anastomosis in 43, and resection with an extended end-to-end anastomosis into the arch in 77. In 30 patients, the extension was proximal to the origin of the left carotid artery (radically extended end-to-end anastomosis). Mortality (13 early and 12 late deaths) was related on multivariate analysis to the presence of an associated major heart defect, preoperative resuscitation, and direct postoperative gradient over the arch. The immediate postoperative gradient was significantly lower after both extended and radically extended end-to-end anastomosis if there was a hypoplastic isthmus, and after radically extended end-to-end anastomosis if there was transverse arch hypoplasia. Actuarial freedom from recoarctation at 4 years was 57% (CL 28–78%) after subclavian flap angioplasty, 77% (CL 60–87%) after end-to-end anastomosis, 83% (CL 66–92%) after extended end-to-end anastomosis and 96% (CL 77–100%) after radically extended end-to-end anastomosis. However, whether associated arch hypoplasia needs to be addressed in the newborn is not agreed upon. Machii and Becker[272] studied 15 coarctation specimens with a hypoplastic transverse arch. Eight patients < 1 month old and 7 were between 1 and 3 months. The diameter and length of the various segments of the aortic arch were measured. The number of elastin lamellae was determined histologically, collagen density was quantified with a microdensitophotometer and using immunohistochemistry alpha-actin-positive smooth muscle cells in the media of the ascending aorta and the hypoplastic transverse arch identified. In all patients, despite a hypoplastic transverse arch, the ascending and descending aorta grew. The number of elastin lamellae in the hypoplastic transverse arch when expressed as a ratio vs. diameter, this number was high ($P < 0.05$). Collagen density showed high absolute values in the descending aorta. In the older group, 4 of 7 showed no staining for alpha-actin in the hypoplastic transverse arch, whereas in those < 1 month of age, only 2 of 8 cases were negative. Thus, histologically, the hypoplastic transverse arch is characterized by a relatively high number of elastin lamellae, and fewer alpha-actin-positive cells in older specimens, which could indicate a diminished potential growth. However, several clinical studies have noted appropriate growth of the transverse arch after standard arch repair in this setting.[78,274–276] Siewers and colleagues[78] reported their experience with transverse aortic arch hypoplasia found in 33 (32%) of 102 infants undergoing coarctation repair by subclavian flap aortoplasty or classic resection and end-to-end anastomosis, and found excellent growth of the transverse arch after repair in all patients available for linear follow-up. They proposed extended arch repair should be reserved for the small group of infants with transverse aortic arch to ascending aorta diameter ratios of < 0.25. A prospective study was reported by Brouwer *et al*.[275] examining the fate of the hypoplastic aortic arch after resection of an aortic coarctation and end-to-end anastomosis. Between 1988, and 1990, 15 consecutive infants < 3 months of age were evaluated echocardiographically. Eight of these infants had a hypoplastic aortic arch with a mean *Z*-value of –7.14 ± 1.39. The other 7 infants had a "normal" aortic arch with a mean *Z*-value of –1.85 ± 1.08. All 15 infants underwent simple coarctation resection and end-to-end anastomosis. Six months after operation the mean *Z*-value increased significantly in those with a hypoplastic arch to –1.08 ± 0.69 ($P < 0.0001$) and in those with a "normal" aortic arch to 0.106 ± 0.99 ($P = 0.004$). No infant died (0%; CL 0–12%) and a recoarctation developed once (12.5%; CL 2–36%). Similar findings were presented by Jahangiri *et al*.[276] from a retrospective analysis of 185 consecutive patients who underwent subclavian flap angioplasty between 1974 and 1998. The patients included 125 neonates and 60 infants, with a median age of 18 days. Forty-one (22%) patients had aortic arch hypoplasia. The early surgical mortality was 3%, and recoarctation occurred in 11 (6%) patients at a median follow-up of 6.2 years (6.2 ± 4.6 years) including 4 of the 41 patients with arch hypoplasia. By multivariate analysis, risk factors for death were determined to be residual arch hypoplasia and low birth weight. The only risk factor for recoarctation was persistent arch hypoplasia after surgical treatment. However, angiographic imaging of the aorta showed that recoarctation was not due to a hypoplastic transverse arch, and it was probably at the site of ductal tissue. Survival at 5 and 10 years was 98% and 96%, respectively. Freedom from reoperation for recoarctation at 2 years was 95%, and at 5, 10, and 15 years, it was 92%. These authors concluded that subclavian flap repair remains an effective technique for repair of aortic coarctation with excellent results, low mortality and in the majority of patients, arch hypoplasia regresses after the procedure. The rationale for the more radical surgical approaches are (1) that retention of ductal tissue at the level of the coarctation, creates a substrate for the development of an obstructive shelf and a

recurrent lesion,[277] and (2) that the surgical correction must address the hypoplasia of the isthmus and distal arch.

Catheter-based therapies

In 1979, Thomas Sos and colleagues described the appearance of a post-mortem specimen with coarctation of the aorta after balloon dilation,[278] and in 1982, Lock *et al.*, performing balloon dilation on surgically excised coarctation of the aorta lesions, confirmed the feasibility of dilation. However, the dilation raised concerns of intimal and medial tears created in the arterial wall by the radial expansion of the balloon, resulting in aortic wall weakness, a substrate for subsequent aneurysm formation.[279] That same year, Singer *et al.* described a successful balloon dilation of a recurrent coarctation of the aorta after surgical repair in a critically ill neonate[280] and in 1983, Lababidi described a successful dilation of a native coarctation in an infant in cardiac failure.[281] Since then, numerous reports of balloon dilations of unoperated (or so-called native) coarctation of the aorta and recurrent coarctation of the aorta have appeared, detailing the efficacy of the procedure and complications, as a function of patient age, clinical status and associated cardiac lesions.[282–333] While such papers have demonstrated the feasibility of this approach, questions remain among many in the pediatric cardiovascular community as to the appropriateness of angioplasty in the unoperated lesion. In the setting of recurrent arch obstruction after initial attempted surgical repair, the procedure is less controversial.

Vascular injury after dilation

The initial studies performed by Lock *et al.* on excised human coarctations[279] and experimentally induced lesions in lambs[334] demonstrated that balloon angioplasty acts by tearing the vessel wall with resultant intimal and medial tears, extending over varying distances. Histological examination several weeks after dilation, however, revealed an intact and normal appearing intima. In some cases the media was thinned, with microscopic evidence of spreading of the medial elastic fibers. No aneurysm or atheromas were noted in specimens examined as late as 1 year after the procedure. Balloons with diameters 2–3 times the diameter of the lesion, inflated 4–8 atmospheres were employed.[279,334] In a similar study, Ho *et al.* examined coarctation of the aorta segments, dilated after surgical excision, using a balloon diameter similar to the diameter of the distal descending aorta. They confirmed the effectiveness of angioplasty in increasing the luminal diameter.[335] Intimal tears were again present in all specimens, transmedial tears in 86%, including 1 specimen where the tears reached the adventitial layer. Disorder of elastic fiber elements or cyst-like spaces in the media were described in 5 of the 7 dilated specimens (similar histologically to cystic medial necrosis as described by Isner *et al.*[148]) but there was no evidence that more extensive disruptions or tears occurred in those affected specimens.

In clinical applications, intimal and medial tears can be visualized angiographically after dilation where they present as irregularities within the aortic contour. Transesophageal echocardiography and intravascular ultrasound (IVUS) have also demonstrated intimal and medial flaps or tears, during and after the procedure, with a greater sensitivity than angiography.[336–340] Sohn *et al.* described IVUS findings following balloon angioplasty in 17 patients with coarctation of the aorta (12 coarctation of the aorta, 5 recurrent).[340] The size of the balloon used for dilation was two to three times the diameter of the coarcted segment but not exceeding by > 2 mm the diameter of the aorta proximal to the coarctation of the aorta. All lesions were successfully dilated as defined by an increase in aortic diameters of > 30% and residual peak systolic pressure gradients across the lesions of < 20 mmHg. A minor flap or dissection was defined as a thin, mobile membrane extending into the wall over not more than a quarter of the circumference of the aorta. All other more extensive lesions were classified as major dissections or tears. IVUS detected major dissections through the fibrous shelf into the medial layers of the aortic wall with intimal tears in 10 of the 12 patients with native coarctation of the aorta. The remaining 2 patients had minor flaps. Of the 5 patients with recurrent coarctations, 4 had major dissections and 1 had no evidence of an intimal tear. Intimal tears were generally seen at a right angle or on the wall opposite to the preexisting scar in lesion. Angiography detected dissections in only 6 of the native coarctations and 2 of the 5 recurrent lesions. Follow-up IVUS was performed in 7 of those 17 patients (6 with major dissections and 1 with no lesion) at a follow-up catheterization 20 ± 7 months after the dilation and showed persistent major dissections in 2 patients and a decrease to minor flaps in 2 patients. The remaining 3 patients showed only scarring without intimal flaps. Angiography was abnormal in only 1 of those patients. In 4 patients, there was angiographic and ultrasonic evidence of healing and remodeling of the vessel and no aneurysms were detected. This study confirmed that even significant tears can heal partly or completely.

As the healing process may not restore a normal vessel wall,[334] it may become structurally weakened, but whether this is a significant problem in the long term has not been detailed. That ruptures, dissections and late aneurysm occur under certain circumstances after balloon dilation of coarctation of the aorta and recurrent coarctations underscore this issue.[288,294,300,307,314,333,341–343,343A] Nevertheless, despite preexisting cystic medial necrosis as described by Isner and colleagues,[148] Ho *et al.* failed to demonstrate more extensive lesions after dilation in affected cases.[335] Furthermore, surgical experience with long-term follow-up after repaired arch dissections would suggest that this is a rare problem.

As a result of histological healing and normalization of the blood flow patterns after a successful angioplasty, remodeling of the aortic contour can occur. Rao *et al.* have demonstrated this process, from angiograms obtained 6–30 months after dilation.[344] Weber *et al.* also illustrated this process from magnetic resonance imaging studies performed 18 and 36 months after successful balloon dilation in patients with discrete coarctation of the aorta and an otherwise normally developed aorta).[345] Similarly, the quantitative angiographic analysis by Suarez de Lezo *et al.*[328] also suggests a tendency for arch realignment, as does data from Beekman *et al.*[286] documenting the diameter of the dilated segment to isthmus diameter ratio approaching unity in follow-up studies.

The healing process can however be excessive and lead to restenosis. Brandt *et al.* performed histological examination of surgically resected lesions following balloon angioplasty.[346] Of 11 patients with initially successful balloon dilations in the setting of native lesions, 3 patients presented with recurrent stenosis > 6 months after the dilation. Study of the surgically resected segments in those cases showed occlusive neofibroelastic proliferation. In neonates and young infants however,

restenosis following balloon angioplasty is more likely the result of persistent active ductal tissue and/or the presence of associated arch hypoplasia (see below).[36,295,320,347]

Balloon angioplasty for native coarctation

The first clinical applications of balloon coarctation of the aorta angioplasty addressed situations in which surgery had been to that time disappointing, unoperated coarctations in ill neonates and infants, and recurrent lesions after surgical repair.[280,281,293,302,305,326,327] Although these reports universally showed that the procedure was feasible, relatively safe and in most cases immediately effective in reducing the gradient and enlarging the aorta, results were disappointing in neonates and infants with unoperated lesions due to frequent restenosis.[293,305] The persistence of active ductal tissue in the neonatal coarctation of the aorta was thought, as in the surgical repair, to explain this high rate of restenosis.[36,295,320,347] It would also appear that rheologic factors affected outcomes, particularly when transverse arch or isthmal hypoplasia was associated.[294,318,348] In 1984, Cooper *et al.* and Lababidi *et al.* reported on balloon dilation of unoperated discrete coarctation in older children.[287,303] Results were encouraging, as the procedure was successful in all with no recurrence, 1–8 months after the angioplasty. Two concerns arose from those preliminary reports: could we accept this as a treatment in neonates and young infants, knowing that restenosis rates were high after dilation, and was it safe to dilate the aorta knowing that the vessel wall was altered?[349]

Subsequent reports on restenosis rates in neonates and infants and complications including femoral artery damage, blood loss during the procedure,[317,320] and aneurysm formation,[288,333,346] further divided opinion. Rao and colleagues took the position that balloon dilation was the procedure of choice in ill neonates and infants as well as in older children.[317,350,351] In their study of 19 neonates and infants with unoperated coarctation, aged 3 days to 12 months (median, 2.5 months), pressure gradients across the lesion decreased from 39 ± 12 mmHg to 11 ± 7 mmHg with a significant increase in coarctation diameters. No patient required immediate surgery. Recurrent lesions, defined as a gradient > 20 mmHg, were present in 5 of 16 patients followed 6–15 months after dilation, 4 of the 5 being neonates at the time of dilation.[317] This approach was further supported by Fontes *et al.* describing results of balloon angioplasty on 33 patients, aged 28 days to 49 years (mean 10 years), with unoperated coarctation. The procedure was immediately successful in all. On repeat catheterization performed in 13 of these patients, a mean of 12 months after the procedure, restenosis occurred in 1 (who was a neonate at time of dilation) and a fusiform dilation of the arch in another.[295] While young age and isthmal hypoplasia were recognized by Rao *et al.* as risk factors for recurrent coarctation,[318] the authors argued that in their hands, this was a relatively safe procedure, allowed significant symptomatic improvement in the ill neonate and infant and allowed postponement of a more "definitive" treatment until an older age, if required. The opposite conclusion was drawn by Redington *et al.* who experienced early restenosis in 5 of 7 neonates despite successful acute results. Together with other authors they raised again the question of the long-term safety for the older children.[320,330,332,352,353] Unfortunately, for several years, the literature remained unclear and incomplete regarding the definition of what exactly constituted an aneurysm, and consistent hemodynamic and anatomic definitions of a recurrent lesion.[354] Today, larger clinical studies are available with follow-up reaching 5–10 years after dilation.[294,307,314] Although such studies excluded neonates or infants with severe isthmal hypoplasia, all age groups were included (neonates, infants and older children).

Immediate results

Immediate hemodynamic results were favorable in all large studies, with a reduction in arm-to-leg pressure gradients < 20 mmHg, when expressed as a mean for the entire group as well as for each age grouping.[294,307,314] Post-dilation gradients of < 20 mmHg were obtained in 78–91% of the patients, with similar percentages in the different age groups.[294,307] This was recently confirmed by McCrindle *et al.* reporting on the acute results of 422 balloon dilations of native coarctations, performed in 25 institutions between 1982 and 1995.[306] Patients' ages ranged from 2 days to 63 years with a median of 4.2 years. Mean systolic gradient before dilation was 42 ± 18 mmHg. Suboptimal results as defined above, were noted in 19% of procedures. Significant independent risk factors for an early suboptimal outcome included a higher systolic gradient before angioplasty, earlier procedure date and older patient age.[306] Ovaert and colleagues [355] reported the clinical impact of balloon angioplasty for native coarctation of the aorta and determined predictors of outcome. Hemodynamic, angiographic and follow-up data on 69 children who underwent balloon angioplasty of native coarctation between 1988 and 1996 were reviewed. Stretch, recoil and gain of the coarctations circumference and area were calculated and related to outcomes. Initial systolic gradients (31 ± 12 mmHg) fell by –74 ± 27% ($P < 0.001$), with an increase in mean coarctation diameters of 128 ± 128% in the left anterior oblique, and 124 ± 87% in the lateral views ($P < 0.001$). Two deaths occurred, one at the time of the procedure and one 23 months later, both as a result of an associated cardiomyopathy. Seven patients had residual gradients of > 20 mmHg. One patient developed an aneurysm, stable in follow-up, and 4 patients had mild dilation at the site of the angioplasty. Freedom from reintervention was 90% at 1 year and 87% at 5 years with follow-up ranging to 8.5 years (Fig. 22-10). Factors significantly

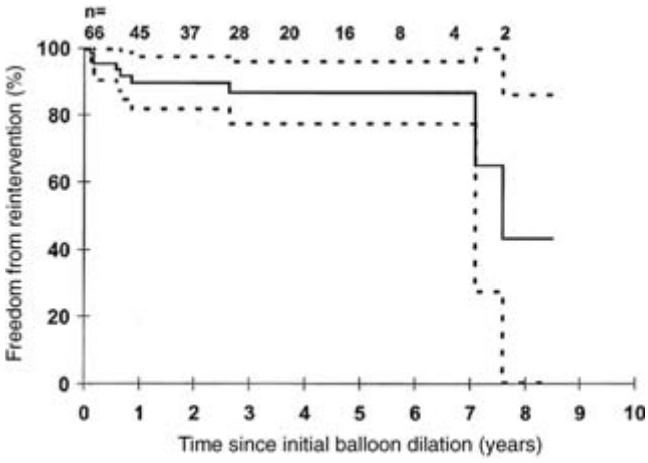


Fig. 22-10 Kaplan–Meier plot of freedom from reintervention after initial transcatheter balloon angioplasty**.** Dashed lines, 95% confidence intervals. (Reprinted from Ovaert *et al.*,[355] Copyright (2000), with permission from The American College of Cardiology Foundation.)

associated with decreased time to reintervention included a higher gradient before, a smaller percentage change in gradient after dilation, a small transverse arch and a greater stretch and gain but not recoil.

Restenosis

Restenosis, defined as the reappearance of a pressure gradient > 20 mmHg, despite a successful initial result, has been noted in all studies. Mendelsohn *et al*. described an overall 13% incidence of restenosis, reaching 60% in infants < 12 months of age, compared to 7.3% in the older child.[307] Fletcher *et al*. observed an incidence of 23% restenosis after successful dilation, reaching 77% in neonates, 30% between 1 and 6 months, but < 20% in older patients.[294] Rao *et al*. described an overall recurrent coarctation rate, including immediate failure and late restenosis, of 27%, reaching 83% in the neonates < 1 month, 39% in infants between 1 month and 1 year and 8% in older children.[314]

Young age (< 1 year), isthmal hypoplasia (less than two-thirds of the ascending aorta proximal to the origin of the right innominate artery) and a small diameter coarctation segment < 3.5 mm before or < 6 mm after angioplasty were confirmed to be significant risk factors for early or late failure.[294,314,318] In a recent retrospective echocardiographic study of the aortic arch before unoperated coarctation angioplasty, Kaine *et al.* noted that the diameter *Z*-value of the aortic isthmus was a strong predictor of outcome after balloon dilation. An isthmus value ≤ –2.16 predicted an early failure with a 91% sensitivity and 85% specificity. Ninety per cent of patients with a *Z*-value > –1, remained free of recoarctation at late follow-up. When corrected for the aortic isthmus *Z*-value, age at angioplasty and associated cardiac defects had no significant effect on angioplasty outcome.[348]

Aneurysm formation

When follow-up screening for aneurysms was performed, using chest radiographs, magnetic resonance imaging or angiography, an incidence as low as 5% of early or late aneurysms has been described.[307,314] This is significantly lower than some earlier reports describing aneurysm formation in up to 43% of cases.[286,288,295,303,309,312,328,346] Technical factors such as longer balloons or prolonged inflation times (> 30 s), may have contributed to these events. Discrepancies are also partly related to the absence of a consistent definition of an aneurysm and on occasion the absence of high-resolution angiography before and after procedure. While various definitions exist for the presence of an aneurysm, most investigators would agree that it constitutes a wall contour deformation, whose diameter is 1.5 times the aorta at the level of the diaphragm.[255,286,324,356,356A] The importance of high quality angiography before and after dilation was stressed by Rao *et al.* as the appearance of the ductal bump (or fifth aortic arch) can complicate assessment if obscured on the angiogram before dilation, but outlined after the procedure.[316] Several authors have reported good outcomes after surgical repair of aneurysms that occurred after balloon angioplasty.[288,307,310,314,330,346] Minich *et al.* compared surgical results after unsuccessful angioplasty or angioplasty complicated by aneurysm formation with surgery on lesions not previously dilated, and found no increased risk of complications including spinal cord injuries in either group.[357] These authors concluded that surgical repair was safe after failed balloon angioplasty of unoperated coarctation.

Other complications

No acute mortality related directly to the procedure has been noted in recent large studies,[294,307,314] although they have been described in the past, often related to vessel perforation.[293,300] Severe neurological complications have been reported in < 2% of the procedures and most often related to thromboembolic episodes[294,307,358] and anticoagulation is recommended during the procedure to avoid such events. Femoral artery occlusion, another serious complication, has been described in 10–16% of the cases, reaching the highest percentages in neonates and small infants.[294,307,314,359,360] Such vascular complications have, over the past decade, decreased in frequency with the development of lower profile balloons, use of systemic anticoagulation and judicious catheter techniques.[361] Paradoxical hypertension, well described after surgical coarctation repair, has only rarely (and generally only of mild degree) been described after balloon angioplasty.[314] This may be due to lessened activation of the rennin–angiotensin system, aortic arch manipulation and pain.[362–364] Determinations of plasma catecholamine concentrations have shown that neurosympathetic activation is less after balloon angioplasty when compared to surgical repair.[362,365,366]

Neonates and infants

In the neonate and in the first months of life, restenosis after balloon dilation is increased and dilation should be considered as palliation rather than definitive therapy.[294,307,314] This restenosis rate gradually decreases during the first year of life.[294] Femoral artery trauma and occlusion remain an additional concern in this age group, even if low profile balloons are used. Although often reversible with heparin or thrombolytic therapy, it can result in irreversible occlusion of the femoral artery making access for further catheterizations difficult, and potentially resulting in growth impairment of the ipsilateral leg. Two-dimensional and Doppler echocardiography and magnetic resonance imaging have been shown to be reliable noninvasive methodologies for detection of stenosis or occlusion of the iliofemoral vessels.[360,361,367] Such studies have noted iliofemoral stenosis or occlusions in cases where clinical examination had not defined femoral artery thrombosis due to a well-developed collateral circulation, suggesting that the incidence of vessel compromise may be underestimated.[360,361] However, there appears to be a reduction in the rate of vessel trauma from retrograde catheterizations over the last decade,[361] owing to improved catheter design, attention to technique, and post-catheterization management.

Arch restenosis and femoral artery complications have directed many authors to abandon balloon dilation of unoperated coarctations in neonates and infants, making exceptions for severely ill neonates or infants in which surgery is considered too high risk.[307,360,368,369] Other authors continue to advocate balloon dilation as the treatment of choice in neonates and infants, arguing that if restenosis occurs, repeat balloon dilation or surgery can always be performed at a later date distant from this "critical" period of instability.[294,370] Transductal or transumbilical approaches have been advocated as alternatives to transfemoral approaches in newborns to avoid femoral artery complications,[371–373] but have not achieved universal application.

Attempted comparisons between balloon angioplasty and surgery have often resulted in more controversy and disagree-

ments then developing common ground to rationally apply one or another treatment algorithm, depending upon circumstance.[301,368,369,374] The inconsistencies of available data make impossible objective comparisons in neonates and infants. Such studies span different time periods, different age groups, different morphological subsets and technical aspects of surgery. In addition, definitions of success, restenosis, aneurysm and indications for reintervention vary amongst studies.[368] Johnson *et al*. compared their surgical results from 37 neonates and infants and data available in the surgical literature, with that on balloon angioplasty in the same age group. They noted similar low mortality rates between the two procedures but significantly higher restenosis rates after balloon dilation.[301] However, the time periods during which the procedures were undertaken were not concurrent, and the data on balloon dilation included the technical learning curve of the balloon procedure. In addition, comparison of complications other than mortality and restenosis was not addressed in this paper. Rao *et al.* analyzed data from 29 neonates < 3 months of age, of whom 14 had surgery and 15 balloon angioplasty, during the same time period. Initial clinical data, presentation and associated defects were similar. Early and late mortality (1 early and 3 late deaths in both groups) and recurrent coarctation rates (46% in the surgical group, 50% in the angioplasty group) were not statistically different between the groups. Hospital stay and duration of mechanical ventilation was significantly longer in the surgical group. Significant complications including acute renal failure, central nervous system events, cardiac arrest, tension pneumothorax, septicemia and paradoxical hypertension occurred in 57% of the surgically treated patients. Significant complications, including femoral artery trauma and blood loss requiring transfusion, occurred in 26% of the patients of the angioplasty group. In view of these results, these authors suggested balloon angioplasty was an acceptable alternative in neonates and infants < 3 months of age.[375] It is of note, however, that in most recent surgical reports, restenosis rates are much lower than those reported by Rao and colleagues.[376–379]

What is clear is that no single or ideal treatment algorithm exists for coarctation in the neonate and infant. The morphology of the arch, condition of the child and local institutional results for both procedures in reference to mortality and restenosis should be taken into account in the decision process. Since 1985, at the Hospital for Sick Children, Toronto, a surgical treatment algorithm has been in place for children < 6 months of age. During this period, 9 children < 6 months of age, have undergone balloon dilation due to their clinical status and perceived surgical risks. Neonates have not undergone balloon dilation due to the concern of arterial trauma and the temporary nature of this approach.

The older child

Balloon dilation has been more widely applied in the older child. It has, overall, been a safe procedure, with good early results and restenosis rates between 7% and 12% from recent large studies.[294,307,314,314A] The main concern remains over the possibility of weakening of the aortic wall and the potential or reality of aneurysm formation. Studies with follow-up up to 90 months and systematic screening by chest radiographs, angiography or magnetic resonance imaging, report an incidence of 5% for the presence (or development) of an aneurysm.[307,314] Magnetic resonance imaging has proven to be an excellent non-invasive method for morphological study of the aortic arch and is recommended for all patients following balloon angioplasty.[308] Even if current reported rates of aneurysm formation remain low, there remains concern about long-term outcomes, including impact upon the risk of dissection,[380,381] arterial wall structural integrity in the face of the potential of late development of systemic hypertension, and in situations such as pregnancy, when histological changes in the arterial wall occur,[382,383] mandates close follow-up as for the surgically treated patient.

Between 1985 and 1990, Shaddy *et al.* prospectively randomized 36 patients with discrete isolated coarctation, aged 3–10 years, to either angioplasty or surgery.[324] Immediate hemodynamic results on pressure gradients were similar in both groups. Aneurysm formation was 20% in the angioplasty group vs. none after surgery. All aneurysms were stable over time and none required surgery. Restenosis was also higher in the angioplasty group although it did not reach statistical significance. An isthmus diameter < 65% of the aorta at the level of the diaphragm was thought a risk factor for restenosis after both surgery and angioplasty. The incidence of complications between groups was similar. Hospital stays and total costs were significantly lower in the angioplasty group. The authors concluded that balloon angioplasty was an acceptable alternative to surgery but close follow-up was mandatory.[324]

The recorded results after balloon angioplasty together with its attendant low morbidity and absent risk of spinal cord damage have made balloon dilation of unoperated coarctation an attractive alternative to surgery in children after the age of 6 months. While the risk appears to be low, we must remain cautious regarding development and possible progression of aneurysms. Additional issues such as the effect of angioplasty on the late development of hypertension and its consequences have yet to be addressed.

The adult

As in older children, results of balloon dilation of unoperated coarctation in adults have been encouraging.[284,291,292,310,328,329,336,384,385] Immediate satisfactory results (pressure gradients < 20 mmHg after dilation) were noted in all series in > 74% of the patients.[291,292,310,329] However, McCrindle *et al.* in their analysis of 422 balloon dilations for unoperated coarctation on patients aged 2 days to 63 years (median age 4.2 years), found increasing age to be a risk factor for a suboptimal outcome (as defined above).[306] The authors suggested that long-standing obstruction may be associated with increased fibrotic change in the aorta, and as a consequence less amenable to dilation.[306] However, upon repeat catheterization, performed 4–48 months after angioplasty, Fawzy *et al.* found recurrent obstructions in none of the patients who had an initially successful procedure.[292] Of the patients who had an unsuccessful initial procedure (3 of 22) all had increasing obstruction at restudy. Similarly, Tyagi *et al.* found restenosis in only 3 of 35 patients (8%), 9–15 months (mean 13 months) after the balloon angioplasty.[329] Schräder *et al.* reported a mean 4-year follow-up after dilation on 29 unoperated lesions in patients 14–54 years of age (median 25 years).[386] The mean peak systolic pressure gradient decreased from 62 ± 18 mmHg to 21 ± 13 mmHg immediately after dilation and was 14 ± 13 mmHg at follow-up. Twenty-three patients had a residual gradient of < 20 mmHg and in 2 between 20 mmHg and 30 mmHg. Arterial blood pressure was normal in

23 (79%). A dorsal aneurysm with a diameter of 5 cm developed in 1 patient within the first year, and subsequently the patient underwent an uneventful surgical repair. A "small bulge" (< 50% of the aortic diameter) at the dilation site was seen in 2 patients, and remained unchanged over a 3- to 9-year follow-up. Three additional patients had angiographic evidence of intimal tears at the time of dilation, and 1 patient a dissection distal to the dilated segment, all treated conservatively, and no further arch dissection in 3–6 years of follow-up. Current available reports describe an incidence of aneurysm formation between 5% and 11.5%[291,292,329,386] in the adult. No follow-up longer than 5 years is however currently available. Recently, Walhout *et al.*[387] examined potential differences in the indication and outcomes of balloon angioplasty for coarctation in children and adults. Balloon dilation for coarctation of the aorta was performed in 85 patients who were classified according to age and native coarctation/recoarctation. Groups A (patients aged < 16 years, $n = 32$) and B (patients aged ≥ 16 years, $n = 17$) included patients with native coarctations. Follow-up included two-dimensional Doppler echocardiography and additional angiography or magnetic resonance imaging. Gradient reductions in groups were compared by use of the independent-samples *t*-test. Immediate success was equal in both groups. Pressure gradients decreased 23 mmHg in group A, and 31 mmHg in group B. Pressure gradient drops, compared between groups A and B, showed a significant difference ($P = 0.001$). The length of hospital stay ranged from 12 to 48 h. The period of follow-up ranged from 6 months to 12 years (mean 4.9 years), and Kaplan–Meier curves of groups A and B were not different, as determined by means of log-rank analysis. Reintervention survival was 100% for the adult group, and 78% for the pediatric aged group (Fig. 22-11). No aneurysm formation was encountered. Koerselman *et al.*[388] reported recently on a cohort of adult patients with coarctation of the aorta to evaluate the immediate and mid-term follow-up results of balloon angioplasty of native coarctation in (mainly young) adults. Coarctation of the aorta was diagnosed by means of ultrasound or angiography, and defined as a stenosis with a pressure gradient ≥ 20 mmHg. Nineteen consecutive adults (12 males, 7 females; aged 14–67 years, median 29 years) were treated from 1995 to 1999. Mean pressure gradient decreased from 49 ± 21 to 4.8 ± 8.2 mmHg ($P < 0.0001$). One patient showed a suboptimal result with a residual pressure gradient of 28 mmHg. In 1 other patient a stent was placed on request of the referring physician. Follow-up was 100% and ranged from 3 to 47 months (mean 20 ± 13 months). At 1-year follow-up mean systolic blood pressure was reduced from 159 ± 19.5 to 132 ± 18 mmHg ($n = 18$; $P < 0.0001$), and mean ankle-arm pressure index improved from 0.73 ± 0.09 to 0.96 ± 0.05 ($n = 18$; $P < 0.0001$). Antihypertensive medication could either be reduced or stopped in 7 patients (54%). With ultrasound, angiography or MRI, no patients had signs of aneurysm formation or worsening restenosis during follow-up. Long-term results were reported by Paddon *et al.*[389] after dilation of aortic coarctation in 17 symptomatic adults. Sixteen patients, with a mean age of 28 years (range, 15–60 years), were reviewed at a mean interval after angioplasty of 7.3 years (range 1.5–11 years). At follow-up, 16 patients were alive and well, 1 additional patient having undergone surgical repair and excision of the coarctation segment following dilation. Mean arm systolic blood pressure for the group decreased from 174 mmHg before dilation to 130 mmHg at follow-up ($P = 0.0001$), with the mean gradient falling significantly from 51 to 18 mmHg ($P = 0.001$). The average number of antihypertensive drugs required per patient decreased from 0.56 to 0.31 ($P = 0.234$). No significant residual stenoses or restenoses were seen on MRI, while small but clinically insignificant residual pressure gradients were recorded in all patients using Doppler echocardiography. Complications included 1 transient ischemic attack at 5 days, 1 external iliac dissection requiring stent insertion, and a further patient who developed a false aneurysm close to the coarctation site at 12 months, which subsequently required surgical excision.

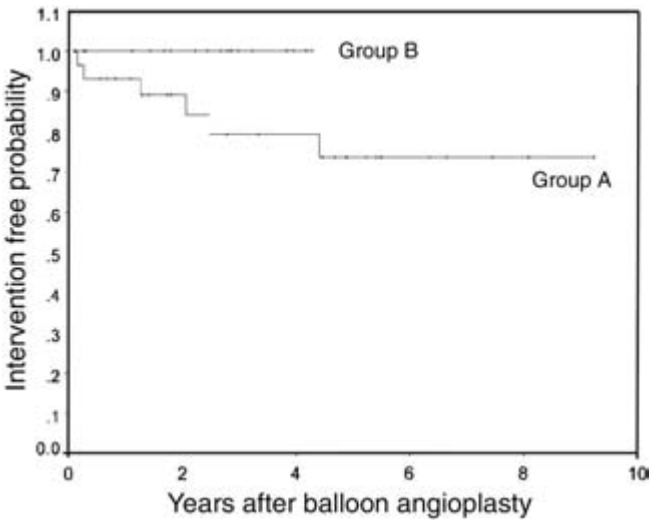


Fig. 22-11 Reintervention-free survival after balloon angioplasty for native coarctation of the aorta in children and adults. No reintervention took place in group B, the adult group. Lower line, child population, group A; in this group, the ratio of 78% at 2.5 years remained intervention-free throughout the 9-year follow-up period. (Reprinted from Walhout *et al.*,[387] Copyright (2002) Mosby Inc., with permission from Elsevier.)

Finally, Shim *et al.*[390] undertook a retrospective review of hospital charges in children > 1 year old with native coarctation of the aorta who underwent balloon angioplasty, primary surgical repair, or elective surgical repair after unsuccessful balloon angioplasty. Hospital charges were less overall in the balloon angioplasty group, although the failure rate was higher. Using a treatment strategy of primary balloon dilation in all patients with a 31% failure rate (their institutional data) the hospital costs would be $10 627 per patient, and would be advantageous up to a balloon failure rate of 81%, before primary surgery becomes cost effective (Fig. 22-12).

Management of residual or recurrent coarctation after balloon angioplasty

Indications for reintervention after balloon dilation are the same as for unoperated coarctation; hypertension with a significant (≥ 20 mmHg) gradient between upper and lower limbs.[300,313,357,391] Several reports have commented upon the feasibility and effectiveness of repeat balloon dilation of restenosis or residual persistent coarctation after balloon therapy in neonates, infants and older children.[294,300,307,313,314,316,333] In a recent report, Rao *et al.* referred 4 of 16 patients with persistent coarctation or restenosis following balloon angioplasty for surgery, 2 due to long segment

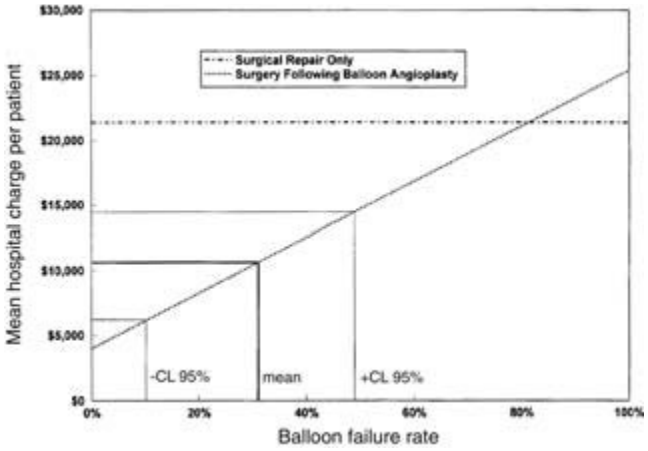


Fig. 22-12 Sensitivity analysis revealing the hospital charge for a treatment strategy of primary balloon dilation of coarctation of the aorta. In this treatment strategy, the hospital charge for balloon angioplasty equals the hospital charge plus the hospital charge for surgery in that proportion with a failed angioplasty. Thus, a balloon dilation is always effective, the hospital charge is only that cost for the balloon dilation alone. Conversely, if balloon dilation was never effective, the hospital charge would be that cost of the balloon dilation plus the surgical cost. The observed red failure rate in this study was 31%, resulting in a mean hospital charge of $10 627, and the treatment strategy is no longer advantageous to primary surgical repair (i.e. the hospital charges with either strategy are equal when the balloon dilation failure rate is 81%). (Reprinted from Shim *et al*.,[390] Copyright (1997), with permission from Exerpta Medica, Inc.)

tubular narrowing, and 2 others "early" in their experience. The remaining 12 underwent repeat dilation, which reduced the peak to peak systolic gradient from 38 ± 11 mmHg to 10 ± 6 mmHg. The diameters of the balloons used were slightly larger than at the initial dilation, but remained more than the diameter of the aorta at diaphragm. Peak arm-to-leg pressure differences, 26 ± 15 months after repeated dilation, remained essentially unchanged (11 ± 6 mmHg).[391]

In a report of 11 children having had failed balloon dilation for unoperated coarctation, Brandt *et al.* raised a frequent concern voiced by many surgeons.[346] These authors noticed reduced collateral flow following angioplasty despite development of restenosis in 3 of the 11 patients, and suggested that as a result, the risk of spinal cord injury after surgery could be increased. Minich *et al.* reported in 1992, 11 children who underwent surgery after unsuccessful angioplasty.[357] No paraplegia or mortality occurred and the authors considered surgery to be safe and effective in this setting. Other reports similarly have also not observed spinal cord injuries when surgery was performed for persistent or recurrent lesions after dilation.[294,300,307,314] The apparent risk of repeat balloon dilation in this setting is probably no greater than operation for recurrent coarctation.

A distinction should be made between a residual or recurrent coarctation, as the underlying morphological lesion may affect outcome. Recurrent coarctation is likely due to excessive and ultimately obstructive healing after primary balloon dilation and perhaps more amenable to a repeat procedure.[346] Persistent or residual stenosis is related to several factors, including a technically poor procedure (small balloon, inaccurate arch measurements, etc.), histological factors (stretching ductal tissue, elastic vessel recoil), or arch anatomy, and should be considered before attempting a repeat procedure. It is also reasonable to assume that risk factors for unsuccessful primary balloon dilation, such as isthmal or transverse arch hypoplasia, will also affect a repeat dilation.

Balloon dilation of recurrent coarctation following surgical repair

Since the first clinical report of successful balloon dilation of recurrent coarctation following surgical repair,[280] this treatment option has been widely applied. Surgical repair for persistent or recurrent coarctation after attempted primary surgical repair is technically difficult, associated with a high recurrence rate, significant mortality (10–20%), and morbidity.[331,392,393] The latter is often related to neurological complications, including spinal cord damage, pulmonary complications, infection and bleeding.[217,331,393–396] Although the first animal models failed to successfully dilate the surgically created lesions,[279,397] sub-sequent clinical studies[289,297,302,303,305,311,323,325,331,332,332A] revealed that balloon dilation resulted in both effective and sustained reductions in arm-to-leg gradients and has become an attractive alternative to surgical therapy.

The largest studies have shown immediate success (gradient < 20 mmHg) in 65–100% of patients.[283,289,296,298,306,311,319,332,398] Hemodynamic results were similar regardless of the previous surgical technique (end-to-end anastomosis, subclavian flap aortoplasty or patch aortoplasty).[289,296,298] Recurrent stenosis, despite initial success has been noted as high as 30% in 1 series during a follow-up of 2 months to 7 years.[283] This latter study showed aortic arch hypoplasia to be a strong predictor of a poor hemodynamic outcome.[283] In a recent review of 90 patients who underwent balloon dilation after attempted primary surgical repair at the Hospital for Sick Children, Toronto, optimal results, defined as a post-procedure gradient < 20 mmHg, were obtained acutely in 87% of the patients.[399] At long-term follow-up to 12 years, 53 of 74 patients (72%) with an initial optimal result remained free of reintervention. The presence of arch hypoplasia, defined as a transverse arch *Z*-value < –2 was the strongest predictor of a poor long-term outcome. Fifty-three per cent of patients with transverse arch hypoplasia had a suboptimal long-term result requiring intervention, while only 29% of patients without transverse hypoplasia had an unsuccessful long-term result ($P = 0.04$) (Fig. 22-13). Repeat balloon dilation offered effective treatment in some of the residual or recurrent stenosis in several published series.[283,289,298,398]

Although the periadventitial surgical scar tissue was thought for several years to be protective against extensive vessel damage,[297,302] large dissections and fatal aortic ruptures have been described.[296,341,346] The same technical precautions as for balloon dilation of unoperated lesions are recommended,[400] although some authors have deliberately opted for slightly larger balloons.[298] Procedure related mortality has varied from none to 2.5%.[289,296,298,399] Aneurysm formation has been described in none to up to 14%, and emphasizes again the need for close and long-term follow-up.[283,289,298,323,398] Other complications have included femoral artery trauma 17%), neurological damage (2%), and "post-coarctectomy" syndrome (2%).[283,289,296,298,311,398] No neurological damage involving the spinal cord has been described explained by the brief period of interruption to aortic flow.[296]

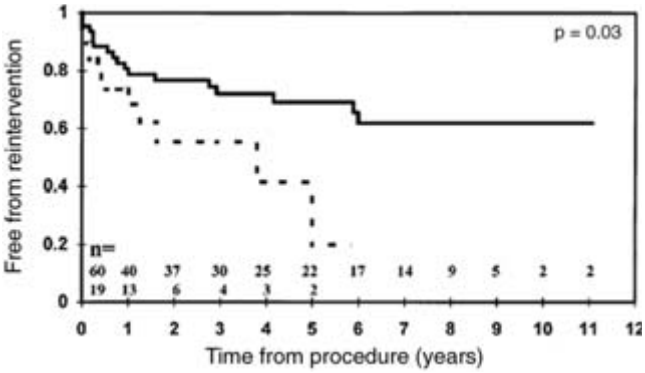


Fig. 22-13 Kaplan–Meier estimates of freedom from reintervention for patients with and without transverse arch hypoplasia after initial dilation. Solid line, patients without aortic arch hypoplasia; dashed line, those with transverse arch hypoplasia. (Reprinted from Yetman *et al*.[399], Copyright (1997), with permission from The American College of Cardiology Foundation.)

The effectiveness and safety of the procedure has made balloon dilation an attractive alternative to surgery, and should be considered as the initial treatment option.[396] As such, it has lowered the threshold for reintervention in patients with recurrent coarctation. Although most authors recommend reintervention for resting gradients > 20 mmHg, some authors have opted to intervene for gradients > 15 mmHg,[289] compared to gradients > 40 mmHg recommended by some, at times where surgery was the only treatment option.[392] This lower threshold could potentially help to preserve long-term left ventricular performance and reduce the long-term complications of hypertension.[289,401–403]

Endovascular stenting and coarctation of the aorta

Over the last decade, endovascular stents have become an integral component of treatment algorithms for patients with congenital heart lesions.[404–407,407A–C] These devices were designed to oppose the recoil of elastic vascular stenoses after failed primary balloon angioplasty, providing vessel wall support. Additionally, they provide a framework or scaffold for endothelial cell growth, reducing thrombosis risk.[408] Several experimental studies and early clinical reports have demonstrated the feasibility and immediate effectiveness of the balloon expandable stent placement in the patient with coarctation and recurrent coarctation.[406,409–412] Stent placement may address some limitations attendant to balloon dilation, with recurrent stenosis due to vessel recoil, long tubular narrowings or aneurysm formation, becoming less clinically important issues.[409]

The use of a rigid stent in the growing child raises the possibility of an acquired stenosis from the fixed diameter of the implant. To address this question Morrow *et al.* implanted stents in the aorta of growing swine and demonstrated the feasibility of reexpansion without significant injury to the neointima, the media or adventitia.[413] In an animal study, Mendelsohn *et al.* described aortic rupture after stent redilation in 2 of 7 animals. This occurred near or at the surgical suture line used to create the lesion. How this relates to use in the unoperated lesion is unclear, but does raise a word of caution.[414] Of similar concern was the potential occlusion of important branch vessels arising from the aorta. Patency of side branches from coronary and pulmonary arteries, even after prolonged stent placement, has, however, been established.[415] Although current reports are encouraging, the experience in children is still limited.[409,412,416] In the fully grown patient, stent placement is particularly attractive, since further intervention is unlikely to be needed with fully expanded devices (up to 25 mm).

Outcomes after primary stent implantation

Early results after stent implantation for both native and recurrent coarctation are generally good[416A-423] with near complete resolution of gradients in many cases. Marshall *et al.* reported a series of 33 patients from Boston with a reduction of systolic gradient from 25 to 5 mmHg.[416A] Likewise Magee *et al.* from Guy's Hospital, London reported 17 patients with a reduction of gradient from 26 to 5 mmHg.[417] In our own early experience at University Health Network, The Toronto General Hospital, reported by Harrison *et al.*, we saw a gradient reduction from 46 to 3 mmHg.[418] These results define improved resolution of stenosis compared to balloon dilatation alone. Although deaths appear to be very infrequent, complications do occur, in particular stent migration and vascular complications at the site of arterial cannulation. Aneurysm formation is an uncommon complication although follow-up with detailed imaging of the stented area is often incomplete in the published series. From the available data it would appear that aneurysms occur in < 5% of patients after this procedure. Alcibar *et al*.[420] reported results after primary stent implantation for coarctation and recoarctation of the aorta in 14 patients (mean age 20 ± 12 years) with coarctation of the aorta (11 native and 3 postoperative); 2 patients had associated malformations. The morphology varied: 10 having a diaphragm-like obstruction (1 with moderate arch hypoplasia); 2 a distorted coarctation and 2 acquired complete aortic obstruction. Five patients were hypertensive and 1 presented with cardiogenic shock and severe arrhythmias which did not respond to intensive medical therapy. The procedure was effective in all cases with the coarctation diameter increasing from 4 ± 2 to 15 ± 2 mm ($P < 0.0001$) and systolic pressure gradient decreasing from 43 ± 19 to 2 ± 2 mmHg ($P < 0.0001$). At 19 ± 8 months follow-up, all patients sustained clinical improvement. One patient with complete aortic obstruction while experiencing a dramatic improvement, died from a sudden cardiac event 22 months after the procedure. Angiographic follow-up in 7 patients, 1 year after implantation, noted no recoarctation with secondary vessels patent, and absence of restenosis.

Blood pressure after stent implantation

In the series by Magee *et al*.[417] 14 patients were hypertensive before the stent implantation. At follow-up, only 2 remained hypertensive, although 8 continued to require antihypertensive medications. Thanopoulos *et al*.[419] reported 17 patients from Athens, Greece and found that after a mean follow-up of 33 months, 15 were normotensive, the remaining 2 requiring only low dose propranolol for hypertension.

Effects of stenting on vessel wall compliance

There are relatively few data available regarding the effects of surgical and catheter procedures for coarctation on compliance of the aortic wall and pulse wave propagation. It has been a

concern that the non-compliant stented segment would increase the risk of long-term hypertension by interfering with normal aortic compliance. Pihkala *et al*.[424] at the Hospital for Sick Children in Toronto performed an experimental study in pigs with aortic stenting and implantation of ultrasonic crystals into the aortic wall above and below the stent. Various indices of aortic compliance were measured, including stiffness index beta and elastic modulus of aortic compliance. At 3 months follow-up, there was no difference between the stented and the control groups in terms of these various indices of compliance. There was also no difference in plasma renin and serum aldosterone levels. The follow-up period in this study was, however, quite short and further studies are required, nevertheless, this study would appear to offer cautious reassurance.

The current practice at the Hospital for Sick Children (depending on anatomical suitability) is to perform surgical repair on children with native coarctation requiring intervention < 6 months of age and primary balloon dilatation on children requiring intervention > 6 months of age to mid-adolescence. After this (i.e. when the patient is approaching adult size, around 50 kg) primary stent implantation is performed. At the University Health Network, The Toronto General Hospital, primary stent implantation is performed in all adult patients with an anatomically suitable lesion. The first stent implantation for coarctation occurred in November 1994. Since that time, 55 patients (32 male) have undergone the procedure with a median age at implantation of 32 years (range 14–70 years). In 37 cases, the intervention was for native coarctation and in 18 for recurrent coarctation. Mean upper limb systolic blood pressure before stenting was 160 mmHg and diastolic pressure 86 mmHg. Forty patients had a systolic hypertension (> 140 mmHg) before the procedure. The systolic coarctation gradient was reduced from 44 ± 21 mmHg to 2 ± 5 mmHg, and in 39 patients, the gradient was completely abolished by the procedure. Only 1 patient had a suboptimal result in terms of stenosis relief, with a residual gradient of 20 mmHg, the patient returning for re-dilatation with a high pressure balloon, with reduction of the gradient to 2 mmHg.

Procedural complications

There were no deaths, and 1 patient had distal migration of the stent during insertion. A second stent was inserted across the coarctation site and both stents stabilized across the coarctation segment in series. In another patient the balloon ruptured during deployment and became trapped in the partially deployed stent. The stent and balloon were withdrawn to the iliac artery where the balloon was removed and replaced with a second balloon for deployment. Although satisfactorily deployed, the iliac artery subsequently occluded at the site of the stent, requiring surgical removal and repair of the iliac artery. A further patient had proximal migration of the stent during deployment. In this case, the aortic arch tapered to a discrete coarctation just beyond the left subclavian artery. The stent was positioned to cover the hypoplastic distal arch, therefore crossing the left subclavian artery, but to avoid the left common carotid. However, during the inflation the stent migrated, so as to cover the left common carotid as well as the subclavian artery. The stent was fully deployed in this position and there was only a 3 mmHg residual coarctation gradient. The patient has remained well and asymptomatic since the procedure. One patient developed focal femoral artery stenosis following the procedure producing claudication and requiring surgical repair of the femoral artery. There were no other significant vascular complications.

Effect on blood pressure

Follow-up blood pressure data were available for 49 patients with a mean follow-up of 20 months. Mean systolic blood pressure at follow-up was 127 mmHg and mean diastolic pressure 75 mmHg. Seven of 49 patients continued to have systolic hypertension and 14 required antihypertensive drugs (mean 0.6 antihypertensive drugs per patient throughout the entire population).

Follow-up studies

Cardiac catheterization was performed in 24 patients at a mean of 19 months after the initial procedure. The mean gradient was 3 mmHg, and no significant aneurysms were seen, although 3 patients had 2–3 mm arterial wall irregularities. Whether this represents the substrate for aneurysm formation remains uncertain.

Finally, allowing expansion of long segment narrowings, stents may become extremely useful in patients with diffuse obstructive aortitis, as seen in Takayasu's disease,[425,426] where balloon dilation has been less successful with the formation of aneurysms.[427,428]

Prognosis and outcomes

A normal life after successful repair of coarctation of the aorta in childhood is to be anticipated as is normal growth and development. There should be little restriction on physical activities, generally, in those normotensive children, with resting arm-to-leg gradients < 10 mmHg, and no hypertension during exercise and normal sporting activities (in the absence of isometric exercise and contact sports) are encouraged.[429]

After repair however, the long-term outcomes are modified by a number of clinical and hemodynamic issues[1] (Table 22-3). Repair during infancy is often associated with residual or recurrent arch obstruction.[197–200,202,217–220,286,294,307,309] In this regard, residual coarctation refers to a persistent arch obstruction noted immediately after intervention. This may be due to an inadequate arch reconstruction, or associated hypoplasia of the isthmus or transverse arch. There is, however, evidence that the transverse arch may grow after repair in infancy.[78] In the

Table 22-3 Clinical and hemodynamic conditions that may affect long-term outcomes after coarctation repair[1]

Residual or recurrent arch obstruction
Rest or exercise hypertension
Left ventricular hypertrophy
Coronary artery disease
Aortic aneurysm
Aortic dissection
Intracranial hemorrhage
Reduced left arm growth/subclavian steal
Endocarditis/endarteritis
Associated intracardiac lesions

Siewers *et al*. study,[78] transverse aortic arch hypoplasia was found in 33 (32%) of 102 infants undergoing coarctation repair by subclavian flap aortoplasty or classic resection and end-to-end anastomosis, and in follow-up excellent growth of the transverse arch after repair in all patients available for linear follow-up was observed.

A recurrent coarctation implies the evolution of an arch obstruction after successful repair. This frequently occurs as a result of poor growth at the suture line repair site. This is particularly true if the repair is performed before 3 years of age, when the aortic diameter is < 50% of its adult size.[217,218] The incidence of residual or recurrent coarctation following surgical repair in early infancy varies between 15% and 30%.[199,200,202] In a study by Beekman *et al*.,[219] addressing the influence of surgical technique on the need for reoperation after coarctation repair in infancy, follow-up data were analyzed for 125 consecutive infants (< 12 months) who underwent repair by a subclavian angioplasty, or resection and end-to-end anastomosis technique. Sixty-three infants underwent repair by resection and 62 by subclavian angioplasty, at a mean age at operation for infants with subclavian flap angioplasty of 1.54 ± 0.93 months and for infants with resection 2.70 ± 0.93 months. There was no difference between the groups in weights at initial repair or the proportion of patients with complex anatomy or aortic arch hypoplasia. Follow-up duration for the subclavian flap group was 2.55 ± 0.51 years (range 0.3–8.2), and for the resection group was 7.97 ± 3.61 years (range 0.6–21). Indication for reoperation was the presence of a coarctation gradient at rest of ≥ 40 mmHg and arm hypertension. Reoperation was required in 5 patients in the subclavian flap group and 12 patients in the resection group. The mean reoperation rate after subclavian flap repair was 0.0356 reoperations per patient-year, and after resection was 0.0342 reoperations per patient-year ($P = 0.94$). To determine an individual's risk of requiring reoperation from these group measures, a reoperation risk model was developed. The risk of reoperation by the fifth postoperative year was found to be 16.3% after subclavian flap repair and 15.7% after resection. Recently, several surgical studies have suggested that using an extended end-to-end resection may reduce significantly this recurrence rate.[203,244,266] In the Sandhu study,[203] arch obstruction was repaired using resection and primary anastomosis in 60 patients, with 7 early postoperative deaths (11.7%; 70% confidence limit 8–16.6%). The 53 survivors were followed for a mean of 23 months (range, 1–78), for a total of 1219 patient-months. Recurrent arch obstruction ≥ 20 mmHg has occurred in 2 of 53 patients (3.8%; 70% CL 1.9–7.5%); both underwent successful balloon angioplasty. Similar data from balloon angioplasty series detail similar results when that procedure is performed in infancy.[286–294]

Late cardiovascular complications after operative repair included systemic hypertension, premature coronary artery disease, aortic valve abnormalities, aortic aneurysm, and recoarctation. Indeed, it is well recognized that patients with repaired coarctation of the aorta have premature morbidity and mortality. Several long-term studies have noted that the mean age of patients who died (35–38 years of age) underwent repair in late childhood or beyond.[430–433] A the recent study by Toro-Salazar *et al*.[432] reported the outcome in 274 subjects ≥ 50 years after coarctation repair with operative repair of coarctation performed between 1948 and 1976. Twenty patients (7%) died in the immediate postoperative period. Of the 254 survivors, 2 were lost to follow-up, 45 (18%) died at a mean age of 34 years, and 207 (81%) were alive ≥ 50 years after the original operation. Coronary artery disease and perioperative deaths at the time of a second cardiac operation accounted for 17 of the 45 late deaths (Fig. 22-14). Predictors of survival were age at operation and blood pressure at the first postoperative visit. Of the 207 long-term survivors, 92 (48%) participated in a clinical cardiovascular evaluation. Thirty-two had systemic hypertension that was predicted by age at operation, blood pressure at the first postoperative visit, and paradoxical hypertension at operative repair. New cardiovascular abnormalities detected at follow-up evaluation included evidence of a previous myocardial infarction, cardiomyopathy, atrial fibrillation, moderate to severe left ventricular outflow tract obstruction, moderate aortic valve regurgitation, recoarctation, and ascending aortic dilation. Thus, long-term survival was noted as being significantly affected by age at operation, with the lowest mortality rates observed in patients who underwent surgery between 1 and 5 years of age. More than one-third of the survivors developed significant late cardiovascular abnormalities. Many (but not all) of these adverse outcomes are the consequences of mechanical problems at the repair site, in particular recurrent coarctation. In a recent review of 11 studies which assessed 718 asymptomatic patients who had undergone patch aortoplasty, a recurrence of a significant obstructive lesion was noted in up to 50% of survivors of neonatal repair and an overall recurrence rate of 5%.[244]

Maron *et al*.[222] noted that the long-term prognosis of those patients undergoing coarctation repair was also adversely affected by the presence of systemic hypertension associated with an increase in premature atherosclerosis and coronary events. Indeed, up to one-third of all late deaths occur from acute myocardial infarction.[220,430] Such elevation in blood pressure, both systolic and diastolic, may occur at rest, and appears most frequently in those repaired late in childhood, with a risk

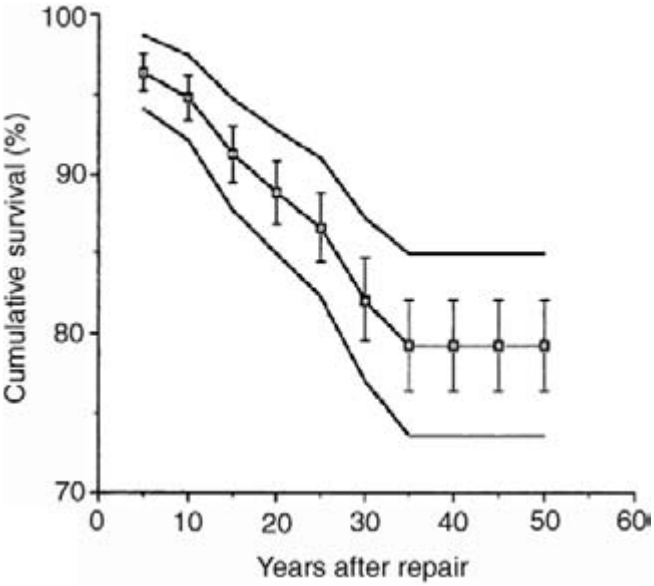


Fig. 22-14 The overall late cumulative survival curve for the 252 operative survivors of coarctation of the aorta repair at the University of Minnesota. All patients underwent surgery between 1948 and 1976. Mean ± SE and 95% confidence intervals are shown. (Reprinted from Toro-Salazar *et al*.,[432] Copyright (2002), with permission from Excerpta Medica.)

as high as 10%.[220] Up to 66% of all patients repaired may have resting hypertension 20–30 years after repair,[220,430,431] although the mean age of repair in those series was 10–20 years of age. In the study by Presbitero et. al.,[431] 226 patients underwent repair before and after the age of 20 years, and 30% and 60% were hypertensive by 20 years follow-up, respectively. In the 571 patients studied by Cohen *et al.*[430] late hypertension occurred in 7% of the infant repairs contrasting 33% repaired after 14 years of age. Brouwer speculated that the optimal age of repair was 18 months as this showed the best results with respect to recurrence, normal blood pressure and life expectancy.[220] Recently, O'Sullivan *et al.*[434] reported the prevalence of hypertension in a cohort of patients using the current surgical strategy of repair in early childhood. Casual and 24-h blood pressure were measured in 119 children and compared with data from 1034 normal controls. The arch repair and left ventricular parameters were assessed using Doppler echocardiography. Median ages at surgery were 0.2 years (interquartile range 0.04–2.0) and 12.0 years (9.0–14.5), respectively. Patients were classified as having "no" ($n = 70$) or "mild" ($n = 49$) arch obstruction. Casual systolic blood pressure was > 95th centile in 28% overall and in 21% of the no arch obstruction group. Mean 24-h systolic blood pressure was > 95th centile in 30% overall and in 19% of the no obstruction group. This unique study of a large cohort of patients treated for coarctation in early childhood showed a disappointingly high prevalence of hypertension was already apparent in children aged 7–16 years in the absence of significant arch obstruction.

The etiology of this late post-repair hypertension, in patients without a residual resting gradient may in part be related to morphological and functional changes in the arch vasculature proximal to the original lesion.[272,435] Sehested *et al.*[436] examined 8 human coarctation specimens pharmacodynamically. In 4 of these, and in 12 additional patients, the aorta above and below the coarctation was studied morphologically and compared with 8 control aortas. *In vitro* stimulation with potassium, noradrenaline, and prostaglandin F_2 in the postcoarctation aortic ring preparations showed a significantly greater contractility than precoarctation rings ($P < 0.05$). Volumetric analysis showed significantly more collagen ($P < 0.01$) and less smooth muscle mass ($P < 0.01$) in the aorta above than below the coarctation. No significant differences were found between sections from the arch and distal to the arterial duct in the normal aortas. The authors concluded that the precoarctation aortic wall was more rigid than the postcoarctation wall, and may influence baroreceptors in the upper vascular bed in such a way as to tolerate a higher pressure. This could explain the preoperative proximal hypertension, the paradoxical hypertension and the frequent lack of normalization of blood pressure postoperatively. From animal studies, it has been identified that there is abnormal intimal and medial hypertrophy in the proximal aortic arch > 1 year after relief of experimental coarctation.[437] Such morphological alterations would be expected to provide the structural basis for the functional abnormalities seen in vascular[438] or baroreceptor reflex activity.[439] Using high resolution ultrasound, Gardiner *et al.*[440] studied the right brachial arteries of 25 normotensive young adults who had undergone successful repair of coarctation in childhood (mean age at repair, 62 months; range, 0–167 months, including 8 patients operated on in infancy; mean age at study, 19 years; range, 14–27 years) and 50 age- and sex-matched control subjects. The degree of reactive hyperemia produced after distal cuff occlusion and release, and the changes in arterial diameter in response to reactive hyperemia (with increased flow causing endothelium-dependent dilation) and to glyceryltrinitrate (an endothelium-independent dilator) were assessed. The response of the right femoral artery to glyceryltrinitrate was also measured in 12 coarctation subjects and 12 control subjects. Studies were performed 13.7 years (range, 7–21 years) after surgery. Reactive hyperemia was significantly lower in coarctation subjects, as were endothelium-dependent dilation and glyceryltrinitrate response, reflecting an abnormal dilatory capacity in both the resistance and conduit arteries. In contrast, glyceryltrinitrate-induced dilation in the femoral arteries was similar to that in control subjects. On multivariate analysis, glyceryltrinitrate response and systolic blood pressure at peak exercise were inversely correlated ($r = -0.52$, $P = 0.04$). Vascular responses were not related to the age at repair. Despite such abnormal vascular responses, overall exercise performance appeared within normal limits, particularly in those children repaired young as noted by the study by Balderston *et al.*[441] In this study, 31 children with postoperative coarctation of the aorta underwent maximal graded bicycle ergometry using an electronically braked ergometer and the James protocol; and 18 also underwent expiratory gas measurement using a mass spectrometer. The mean age at operation was 41 months and the mean age at evaluation was 134 months (mean follow-up interval 93 months). The maximal voluntary peak heart rate was 194.6% of predicted value, indicating excellent effort, mean power was 111% of predicted value and, when measured, maximal oxygen consumption was 89% of predicted value with an anaerobic threshold at 63 ± 3.5% of exercise time. The observed work variables were not different from values in the control group and were not affected by the type of repair. The mean peak systolic blood pressure was 152 ± 7.6 mmHg vs. 147 ± 5.7 mmHg in the control group (P = NS). Patients who had associated intracardiac lesions had significantly lower maximal oxygen consumption (85 ± 3% vs. 98 ± 4% of predicted value).

Systolic hypertension may also occur during dynamic exercise,[403,442–445] in patients with and without resting hypertension, no or minimal resting gradients and no clinical evidence of a recurrent arch obstruction, during bicycle or treadmill exercise studies. In the study from Toronto, Pelech *et al.*[403] studied blood pressure response to exercise in 15 children, aged 5–15 years, before and at periods up to 6 months following coarctectomy. Preoperatively, 11 of 15 children had systolic hypertension at rest and 12 of 15 after exercise. After surgery, only 1 child had mild systolic hypertension at rest, whereas exercise-induced hypertension persisted in 33% of patients (all > 10 years of age). Exercise plasma renin activity was elevated preoperatively but normalized following surgery, and no significant difference was seen in resting or exercise plasma catecholamine levels measured before and after surgery. Over the follow-up period of 6 months, echocardiographic evidence of left ventricular hypertrophy regressed in the younger patients but not in the older patients with exercise-induced hypertension. Although alterations in vascular reactivity may play a role as noted above, the development of exercise induced upper limb hypertension is usually associated with the development of or an increase in a gradient between the arm and leg. This may in part be a reflection of an increased flow across the relatively non-distensible area of the repair. Guenthard[446,447] demonstrated that these hypertensive responses to exercise were not related to anatomical lesions but to an interaction between an enhanced sympa-

thetic nervous system and structural–functional abnormalities in the precoarctation vessels. In this regard, Kavey *et al*.[448] studied 10 patients after surgical repair of coarctation, with a resting arm-to-leg gradient of ≤ 18 mmHg, by treadmill exercise before and after beta blockade with atenolol. Mean age was 5.5 years at repair and 18 years of age at study. At baseline, systolic blood pressures at the end of exercise ranged from 201 to 270 mmHg (mean 229 mmHg), and arm-to-leg gradients ranged from 30 to 143 mmHg (mean 84 mmHg). Follow-up treadmill exercise studies were performed after beta blockade. Upper extremity systolic pressures at the end of exercise were normalized in 9 of the patients. Maximal systolic blood pressure recorded at the end of exercise ranged from 163 to 223 mmHg (mean 196 mmHg, $P \leq 0.005$). Arm-to-leg gradients at the end of exercise also decreased significantly to a mean of 51 mmHg ($P < 0.05$). No patient had symptoms on atenolol and exercise endurance times were unchanged.

It has also been observed that children after coarctation repair have abnormal left ventricular mass and function.[401,449] The Leandro *et al*. study [401] addressed the relation between ambulatory blood pressure measurements and alterations in left ventricular performance in 20 patients with normotension at rest after successful repair of aortic coarctation. Exercise testing, ambulatory blood pressure monitoring and two-dimensional echocardiographic studies in 13 boys and 7 girls (mean age 14.2 ± 2.31 and 14.7 ± 3 years, respectively) who had no evidence of recoarctation were compared with the findings in 20 matched control subjects. No difference was found in systolic blood pressure at rest or peak exercise between patients and control subjects. Male patients developed a significant arm-to-leg gradient at peak exercise. Systolic ambulatory blood pressure was higher throughout the day in the male group. In the female group, systolic blood pressure was higher only during sleep. No difference was found in diastolic blood pressure or heart rate. The transverse aortic arch was smaller and the left ventricular mass greater in all patients. The relation of wall stress to rate-corrected velocity of shortening was 2 SD above normal in 8 of the 20 patients, suggesting that some have enhanced contractility. The E/A ratio on the atrial echocardiogram was significantly reduced in the patient group. Similarly, Moskowitz *et al*.[449] investigated whether left ventricular structural or functional abnormalities persisted in children on long-term follow-up after successful correction of coarctation of the aorta, using two-dimensional echocardiography in 11 subjects and 22 age-matched control subjects. These authors found that despite group similarities in age, body size, and systolic blood pressure, greater fractional shortening ($P = 0.0001$), indexed peak shortening velocity ($P < 0.001$), and greater left ventricular mass index ($P < 0.05$) were seen in the coarctation group in the face of lower left ventricular wall stress ($P = 0.0001$). Left ventricular mass index correlated with the resting arm-to-leg gradient, which ranged from –4 to +10 mmHg. The coarctation group had decreased early filling ($P < 0.006$) with compensatory increased late diastolic filling ($P < 0.05$). Diastolic filling abnormalities were prominent in the older coarctation subjects and were related to both systolic blood pressure ($P < 0.001$) and left ventricular mass index ($P < 0.01$). Thus, despite apparently successful repair of coarctation of the aorta, persistent alterations in both systolic and diastolic left ventricular function and mass are present in children at long-term follow-up.

An aneurysm at the site of the repair may develop, the incidence of which is highest amongst those patients repaired with a prosthetic patch (Dacron^{TM}),[356,450–454] although noted in all types of coarctation repairs,[255] and responsible for 7% of deaths.[430] The occurrence is 9% late after repair, with a 36% mortality rate if left untreated. Resection of the coarctation shelf or the use of Dacron^{TM} may contribute to the wall thinning. In an attempt to identify the predictors of aneurysmal formation after surgical correction of aortic coarctation, von Kodolitsch *et al*.[453] studied 25 aortic aneurysms requiring corrective surgery 152 ± 78 months after the initial repair, eight were located in the ascending aorta (type A) and 17 at the site of the previous repair (local type). Seventy-four patients, without progression of the aortic diameter within 189 ± 71 months after coarctation repair were used for categorical data analysis in an attempt to identify the predictors of aneurysm formation after surgery. Advanced age at coarctation repair ($P < 0.004$) and patch graft technique ($P < 0.0005$) independently predicted local aneurysmal formation. Type A aneurysm was associated with the presence of a bicuspid aortic valve ($P < 0.02$), advanced age at coarctation repair ($P < 0.044$) and a high preoperative peak systolic pressure gradient of 74 ± 21 mmHg ($P < 0.041$) using univarate analysis. Conversely, multivariate analysis confirmed only the presence of a bicuspid aortic valve ($P < 0.015$) as an independent predictor of type A aneurysm. Receiver operating characteristic curve analysis revealed that 72% of patients with an aneurysm after surgery had an operation at age 13.5 years or more, whereas 69% with no aneurysm after surgery had an operation at a younger age (Fig. 22-15). In the prospective study by Bromberg *et al*.[356] an aneurysm was found in 24% of such patients 1–19 years after patch aortoplasty. These lesions may occur after balloon dilation as well, and have been the reason some cardiologists are reluctant to perform these procedures. The risk of aneurysms after balloon dilation for coarctation of the aorta varies widely in the litera-

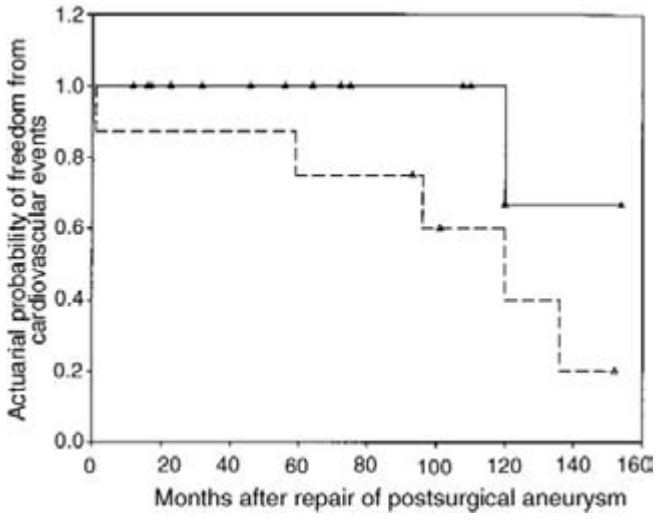


Fig. 22-15 Actuarial probability of event-free survival of patients with postsurgical aneurysms after repair of aortic coarctation. There is a trend toward a higher probability of cardiovascular events in type A aneurysms (dashed line, triangles, censored cases) than in local aneurysms (solid line, triangles, censored cases) ($P < 0.08$). The mean event-free survival time was 104 months (95% confidence interval 70–137). (Reprinted from von Kodolitsch *et al*.,[453] Copyright (2002), with permission from The American College of Cardiology Foundation.)

ture, but in larger follow-up studies ranges from 2 to 5%.[294,307,355] A bicuspid aortic valve is found in up to 85% of coarctation patents and in the long term is responsible for necessitating valve replacement.

Other factors may affect long-term outcomes after coarctation repair and include diminished left arm growth or subclavian steal syndrome, aortic dissection and intracranial hemorrhage. Procedures, which sacrifice the left subclavian artery, may alter long-term functional capacity of the left arm. Van Son *et al*.[455] studied the long-term effect of two surgical techniques for repair of coarctation of the aorta in infancy, resection and end-to-end anastomosis and subclavian flap angioplasty on the blood supply of the upper left limb, quantified by Doppler spectrum analysis of blood flow velocities in the left brachial artery at rest and during postocclusive reactive hyperemia. Twenty-three patients participated in this study: 9 patients after subclavian flap angioplasty (median age, 8 years), 14 patients after resection and end-to-end anastomosis (median age, 8 years), and 10 control subjects (median age, 9.5 years). At rest, a highly significant decrease of blood flow velocities in the left brachial artery was measured in all patients in the subclavian flap angioplasty group compared with those in the resection and end-to-end anastomosis and control groups, as documented by various Doppler spectrum parameters. During reactive hyperemia, a moderate capacity of physiologic augmentation of blood flow velocities was observed in 5 patients of the subclavian flap angioplasty group. This capacity was marginal in 2 patients with complaints of claudication in the left upper limb during strenuous exercise, which can be related to the number of branches of the left subclavian artery ligated during operation. Such patients may experience arm claudication during exercise, diminished arm growth and experience a subclavian steal syndrome with neurological consequences if the vertebral artery remains intact.[197,454,456] Aortic dissection can occur at the coarctation repair site with or without the presence of an aortic aneurysm. Factors which may predispose to such an event include: cystic medial necrosis of the aortic wall, persistent systemic hypertension, atherosclerosis, an associated bicuspid aortic valve, and is particularly common in those patients with Turner's syndrome. Cerebrovascular accidents are a cause of death in 7% of patients, either due to hypertension or cerebral vascular anomalies.[430,431] Anomalies in the Circle of Willis are common in patients with aortic coarctation (10%), and if associated with a berry aneurysm, may result in an intracranial hemorrhage. Such cerebrovascular accidents have been identified as an important cause of late morbidity and mortality following arch repair.[222,457]

Bacterial endocarditis or endarteritis is the cause of significant morbidity in the patient with a repaired arch lesion. Endocarditis may occur on a bicuspid aortic valve, or any other associated cardiac lesion. Endarteritis occurs typically at or just distal to the site of the coarctation repair in areas of turbulence and intimal thickening, and in some patients may result in the formation of an aneurysm.

All references can be found at the end of the book. See pp. 712–23 for Chapter 22.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

23

Robert M. Freedom and Shi-Joon Yoo

Interruption of the Aortic Arch

Interruption of the aortic arch is an uncommon cardiovascular anomaly characterized by complete lack of anatomic continuity between the transverse aortic arch or isthmus and the descending thoracic aorta (Fig. 23-1).[1–4] This condition usually produces symptoms in the neonate coincident with constriction and/or closure of the arterial duct, although patients surviving to adulthood have been reported. Symptoms reflect a disordered circulation to that portion of the body supplied by the arterial duct before its functional closure.[4–10] Interruption of the aortic arch should be distinguished anatomically from atresia of the aortic arch where continuity between these segments is achieved by an imperforate, fibrous strand of various length (although the hemodynamic and physiological effects may be identical) (Fig. 23-1).[2,3,9]

Incidence

This is an uncommon anomaly rarely occurring in isolation.[1–11] There are no data at this time suggesting a difference in fetal prevalence when compared to live born prevalence. The New England Regional Infant Cardiac Program identified 21 infants with interrupted aortic arch from 1968 to 1974 from a total cohort of 2251 infants with heart disease.[12] These 21 infants accounted for 0.9% of all congenital heart disease seen in New England and represented a frequency of 0.019 per 1000 live births. Data from the Baltimore–Washington Infant Study addressing the prevalence of congenital heart disease at live birth identified 31 patients with interruption of the aortic arch among 4390 patients surveyed in the 1981–89 study period.[13] The Prospective Bohemia Survival Study identified 19 babies at birth with interruption of the aortic arch.[14] These accounted for 0.38% of congenital heart defects encountered in this survey and the prevalence was 0.02 per 1000 live births. The Pediatric Cardiac Care Consortium found a prevalence of 0.066 per 1000 live births for interruption of the aortic arch.[15]

Gobel and colleagues summarized those rare familial instances of interruption of the aortic arch in siblings, noting that the few reported cases have been type B.[16] This sibship also had an aberrant right subclavian artery and conotruncal abnormalities, the latter suggesting a relationship to neural crest abnormalities. Other familial incidences have also been recorded.[17] This condition is usually not familial, but there is a well-known association between interruption of the aortic arch and the DiGeorge syndrome (DGS), this syndrome characterized by maldevelopment of the third and fourth pharyngeal pouches (i.e. the thymus and parathyroid glands) resulting in various combinations of conotruncal heart defects that include type B interruption of the aortic arch,[18–35] T-cell immunodeficiency, hypocalcemia, and facial abnormalities. The great majority of DGS cases are associated with hemizygous deletions at the chromosome 22q11 locus. To establish the involvement of the 22q11 locus in the etiology of IAA type B, independently from the typical DGS phenotype, Lewin *et al.* evaluated 73 patients with conotruncal heart defects using fluorescence *in situ* hybridization (FISH) analysis with probes from the 22q11 DGS locus.[34] From this group, 7 patients were deleted (including 4 of the 11 patients with IAA type B). FISH analysis was extended to a total of 22 patients with IAA type B and 11 of these (50%) were deleted. FISH and Southern blot analyses using additional markers within the DiGeorge chromosomal region were performed on patients found not to be deleted in the initial FISH screening. No small deletions or rearrangements were detected. In their patient population, a single, specific genetic defect was the basis for one half of the IAA type B cases. These data suggest that IAA type B is one of the most etiologically homogeneous congenital heart defect. A 22q11 deletion in IAA type B may or may not be associated with the typical DGS phenotype. They conclude that, IAA type B, *per se*, should be an indication for 22q11 deletion testing. Marino and his colleagues performed a chromosome analysis in 27 children with various types of interruption of the aortic arch. Deletion 22q11 was prevalent in patients with simple IAA type B, and was absent in patients with IAA type A and in those with associated additional major cardiac defects. They conclude that anomalies of the infundibular septum should be considered a characteristic aspect of children with interruption of the aortic arch and deletion 22q11. One of the more consistent markers of monosomy 22q11 is cervical origin of the subclavian artery.[34A]

Of 119 patients with interruption of the aortic arch seen at the Toronto Hospital for Sick Children, noncardiac abnormalities were noted in 66 patients, and included DiGeorge syndrome in 24 patients, dysmorphic features in 20, renal abnormalities in 7, encephalopathy in 3, liver abnormalities in 3, cleft palate in 2, polydactyly in 2, tracheo-esophageal fistula in 2, Meckel's diverticulum in 2, Pierre Robin syndrome in 1, bilateral talipes equinavarus in 1, Down syndrome in 1, skeletal abnormalities in 1, and cardiofacial syndrome in 1 patient.[36]

Types of interruption of the aortic arch

The initial classification for interruption of the aortic arch was proposed by Celoria and Patten, and was based on the site of the interruption: distal to the left subclavian artery; between the left common carotid artery and the left subclavian artery; and

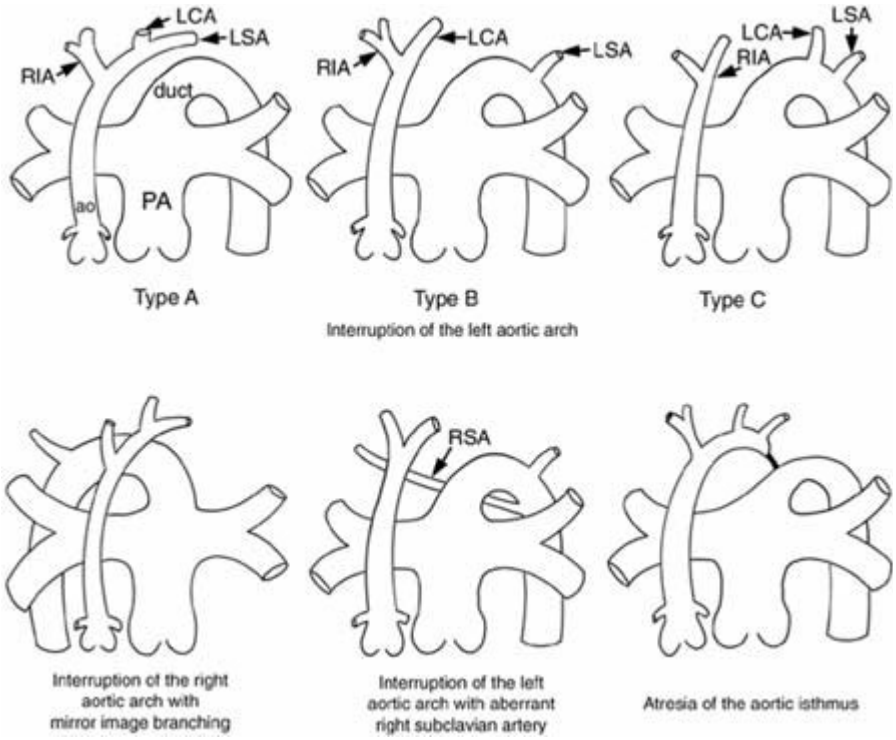


Fig. 23-1 Types of interruption of the aortic arch. Interruption of the left aortic arch (upper panel) is classified into three types; type A, interruption distal to the origin of the left subclavian artery (LSA); type B, interruption between the origins of the left common carotid (LCA) and left subclavian arteries; type C, interruption between the origins of the innominate (RIA) and left common carotid arteries. Interruption can occur in association with right aotic arch (bottom, left). It can also occur with an aberrant right (RSA) or left subclavian artery, interruption being between the subclavian arterial origins (bottom, middle). Atretic aortic arch (bottom, right) is a different entity. In contrast to an interrupted aortic arch, there is continuity between the segments achieved by a fibrous cord of variable length. The lumen courses downward or backward with or without a short segment of blind tract before giving rise to the last branch.

between the innominate artery and the left common carotid artery (Fig. 23-1, Table 23–1).[1]

The last site of interruption is by far the least common. However, the classification of Celoria and Patten did not take into consideration those patients with interruption and a right-sided aortic arch, nor did it mention the aberrant subclavian artery. A few patients with interruption of the aortic arch have been reported to be associated with a persistent fifth arch,[37–42] although in two of these reports, the nature of the fifth aortic arch was not appreciated, and the connection was called an aortopulmonary fistulous tract or communication.[37,42]

Morphogenesis of interruption of the aortic arch

Interruption of the aortic arch reflects those intracardiac malformations producing reduced blood flow to the fourth aortic arches.[2,3,6–9,43–57] Those conditions are diverse and include ventricular septal defect with posterior displacement of the infundibular septum and subaortic stenosis; truncus arteriosus; aorticopulmonary window; complete transposition of the great arteries; double-outlet right ventricle of the Taussig–Bing type, hypoplastic left heart syndrome and certain forms of double-inlet ventricle.[2–9,44–50,54–92]

Less common associations include aortic atresia with either an aortopulmonary window, patent arterial duct, or a fifth aortic arch as the source of blood to the ascending aorta; atrioventricular discordance; aortic origin of the right pulmonary artery, aortopulmonary window and interruption; double-inlet ventricle and other forms of "single" ventricle.[37–42] There are also those unusual instances where interruption of the aortic arch has been identified in the patient with either severe pulmonary stenosis or tetralogy of Fallot.[78–80] The finding of bilateral outflow tract obstruction contradicts the usual theories of morphogenesis.[2,51–53] Ductal origin of the subclavian artery has been identified in the patient with interruption of the aortic arch.[81] This implies therefore bilateral arterial ducts. Anomalous origin of the left anterior descending coronary artery from the pulmonary trunk has been recorded in a patient with type B interruption.[82] The relationship between the DiGeorge syndrome and interruption of the aortic arch has been explored.[18–35] Van Mierop and Kutsche suggest that the DiGeorge syndrome and interruption of the aortic arch are due to an abnormal developmental process involving the neural crest.[30,53]

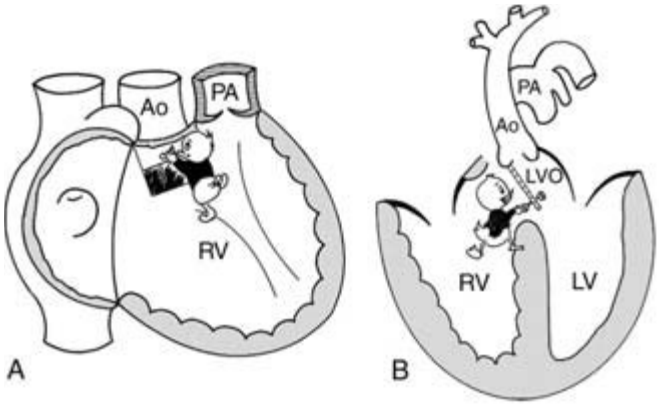
The ventricular septal defect and left ventricular outflow tract obstruction

In patients with a biventricular heart and normal segmental anatomy, a ventricular septal defect is almost always present, excluding those patients with interruption and an aorticopulmonary septal defect or those rare patients with interruption in isolation.[2,3,5–9,44–50,54–72] While the ventricular septal defect may occupy any position within the ventricular septum, its morphology most commonly compromises flow to the ascending aorta during fetal life. That defect which so characterizes interruption of the aortic arch is the posterior displacement of the infundibular septum which occurs above the ventricular septal defect and below the aortic valve so as to encroach upon the

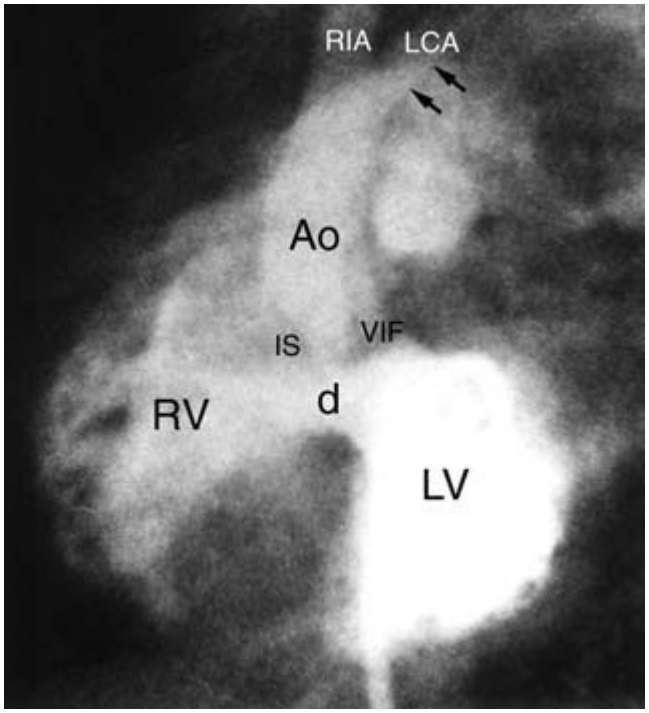
Table 23-1 Types of interruption of the aortic arc

Type A	Distal to left subclavian artery
Type B	Between left common carotid artery and left subclavian artery
Type C	Between innominate artery and left common carotid artery

left ventricular outflow tract (Fig. 23-2). The malalignment occurs as if the door of the infundibular septum is opened toward the left ventricular outflow tract. The so-called hinge of the door is along the ventriculoinfundibular fold when viewed from the right ventricle and along the aortic valve annulus when viewed from the left ventricle. We and others have seen the doubly committed subarterial ventricular septal defect in the patient with interruption of the aortic arch.[2,5–9] In addition, a perimembranous confluent defect with aortic overriding and partial closure by tricuspid tissue is not uncommon in any large cohort of these patients. Tissue tags derived from the tricuspid valve and responsible for narrowing the ventricular septal defect may further compromise the left ventricular outflow tract already reduced in size because of the aortic override. Al-Marsafawy and colleagues provided an important review of those mechanisms producing left ventricular outflow tract obstruction in hearts with interruption of the aortic arch and concordant atrioventricular and ventriculoarterial connections.[56] The left ventricular outflow tract obstruction may be quite mild or very severe, so severe in some patients that conventional biventricular repair is seemingly precluded. The mechanisms responsible for left ventricular outflow tract obstruction are more complicated than malalignment of the infundibular septum in isolation. In those patients with a discordant ventriculoarterial connection with a "single" ventricle malformation, it is often the size of the VSD that limits systemic blood flow.[93–99]



A



B

Fig. 23-2 Interrupted aortic arch with a posterior malalignment type of ventricular septal defect with subaortic narrowing. **A**. Mechanism of subaortic obstruction with posterior malalignment of the infundibular septum. The infundibular septum (trap door) is pushed backward and the left ventricular outflow tract (LVO) is narrowed. **B**. Angiogram showing the ventricular septal defect (d) and posteriorly deviated infundibular septum (IS). There is persistent left ventriculoinfundibular fold (VIF) or anterolateral muscle of Moulaert. The aortic arch is interrupted (arrows) after the origin of the left common carotid artery (LCA). Ao, aorta; LV, left ventricle; PA, pulmonary artery; RIA; right innominate artery; RV, right ventricle.

The mechanisms responsible for left ventricular outflow tract obstruction in interruption of aortic arch include, among others:

- posterior displacement of infundibular septum
- anterolateral muscle bundle of Moulaert
- aortic valve stenosis
- hypoplasia of aortic valve annulus
- tissue tags.

Interruption of the aortic arch and bronchial compression

While bronchial compression may reflect a very much enlarged left atrium, there are uncommon causes of airway obstruction specifically associated with interruption of the aortic arch including bilateral arterial ducts or interruption with right-sided descending thoracic aorta.[100,101]

Outcome analysis

Little information is available on fetal diagnosis of interruption of the aortic arch, although there is a substantial literature on prenatal diagnosis of coarctation of the aorta.[102] Of the six fetuses recognized by Hornberger to have interruption of the aortic arch, three pregnancies were terminated, and the remaining three died postnatally. Of the 19 children identified in the Bohemia study,[14] the mean survival to 6 months of age was 26.32%. Indeed all those who died did so by the age of 6 months, and the highest mortality was in the first week of life when 42.11% of the children had died, and by the end of the first month of age, an additional 21% had died. At this time, the survival curve stabilized at 36.84%. However, there was ongoing attrition and between 1 and 6 months of age, the mean survival curve decreased to 26.32% and remained at this level to the age of 15 years.

A substantial literature on surgical intervention for interrupted aortic arch has accumulated, but most have concerned a case report or small series.[93–115] In 1988, Sell and his colleagues reported on the surgical experience with 63 patients with an interruption of the aortic arch and associated cardiac anomalies from 1974 to 1987 [116] (Fig. 23-3). The 30-day, and the 1-, 5-, and 10-year survival rates were 61%, 52%, 48%, and 47%, respectively, for the entire cohort. The surgical results improved during the course of the experience, and in 1986, the probability of death within 2 weeks of repair was only 6%. Of the 33 patients undergoing repair of the interruption and a ventricular septal

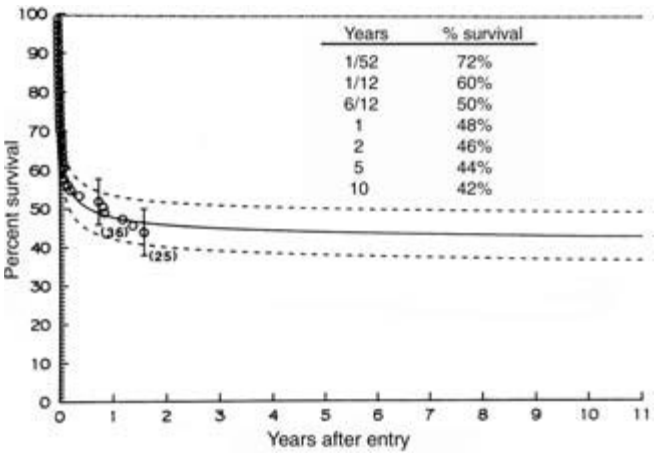


Fig. 23-3 Time-related survival of patients ($n = 71$) with interrupted aortic arch, including all deaths seen between 1974 and 1987. Time zero, time of entry; open circles, individual deaths, actuarially positioned; solid line, parametrically determined survival; dashed lines, enclose 70% confidence limits. (Reprinted from Sell *et al.*,[116] Copyright (1988) Mosby Inc., with permission from Elsevier Inc.)

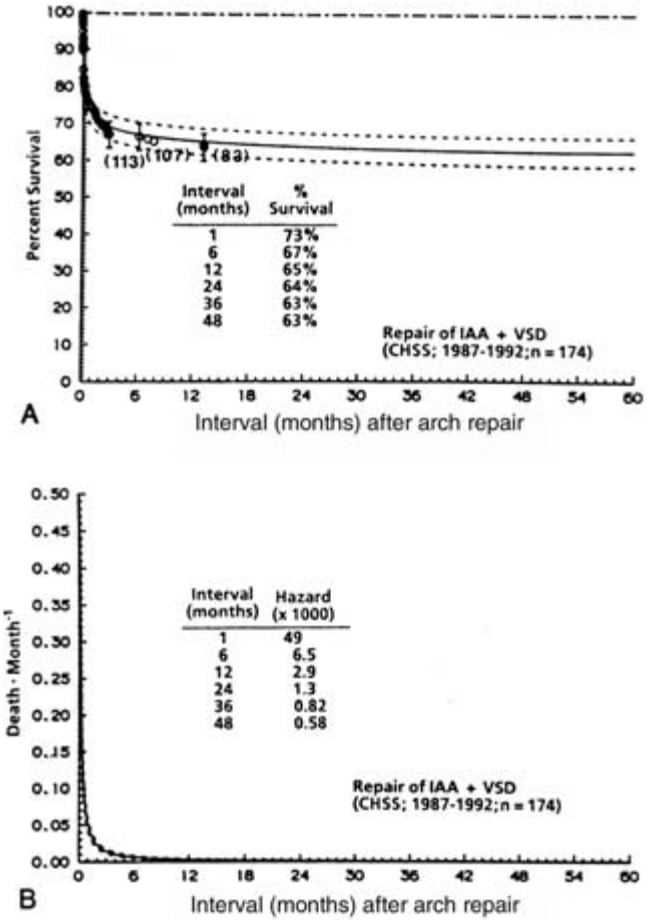


Fig. 23-4 A. Survival after the original arch repair (at time zero). The numbers indicate the numer of patients remaining at risk at the time of the estimate. The solid line is the parametric estimate of survival, and the dashed lines enclose the 70% confidence limits. The dashed-dot-dashed line represents the survival of an age-gender-matched general population (US life tables). B. Hazard function for death. (Reprinted from Jonas *et al.*,[70] Copyright (1994) Mosby Inc., with permission from Elsevier Inc.)

defect, left ventricular outflow tract obstruction developed in 8 patients and 7 of the 8 required reoperation to address the obstruction, with no deaths.[116] Time-related freedom from this complication was 97%, 78%, and 58% at 1 month, 1 year, and 3 years, respectively. Recurrent or persistent aortic arch obstruction was found in 15 patients and occurred more frequently in those who underwent a direct anastomosis than after a tube graft interposition.

Jonas and his colleagues reported in 1994 the findings from the Congenital Heart Surgeons Study.[70] This multi-institutional study enrolled 183 neonates with interruption of the aortic arch and ventricular septal defect between 1987 and 1992. Nine died before surgical intervention. The survival for the remaining 172 patients was 73%, 65%, 63%, and 63% at 1 month, and 1, 3, and 4 years after repair, respectively (Fig. 23-4). The risk factors for death were low birth weight, younger age at repair, type B interruption, outlet and trabecular ventricular septal defects, smaller size of the ventricular septal defect, and subaortic narrowing. Procedural risk factors for death after repair were: (1) repair without concomitant procedures in patients with other important levels of obstruction in the left heart–aorta complex; (2) a Damus–Kaye–Stansel anastomosis; (3) subaortic myotomy/myomectomy in the face of subaortic narrowing. These data are derived from experience in some patients dating back 15 years, and it is likely that some of these procedural risk factors have been neutralized.

The Pediatric Cardiac Care Consortium identified 300 patients with interruption of the aortic arch operated upon between 1984 and 1994.[89,117] Of these 208 were considered to have simple interruption, namely a ventricular septal defect and an arterial duct. In the 92 with complex interruption, a common arterial trunk was found in 36; tricuspid atresia in 8; transposition in 8, mitral atresia in 6, other forms of "single" ventricle in 6, aortopulmonary window in 6, and double outlet right ventricle in 5. The other 17 had a wide spectrum of complex associated malformations. The type of interruption was type A in 111(37%), 62% type B, and type C in 1%. An aberrant right subclavian artery was identified in 9 with type A interruption (8%) and in 39 of those with type B (20%) interruption. The interruption occurred in a right aortic arch in 10 neonates. The overall surgical mortality included 105 deaths in the 300 patients (35%). For those with simple transposition treated either by primary repair or with staging with a pulmonary artery band and later debanding and VSD closure, the mortality was 63 of 208 (30%). Forty-two deaths (46%) occurred in the complex group. As in the experience of other centers, mortality was higher in those with more complex anatomy and among their 36 patients with a common arterial trunk, 24 (67%) died postoperatively. In addition over the time course of the survey, the operative mortality remained constant. For those with simple interruption, two surgical protocols were used: primary repair with a mortality of 37% and the two-stage approach, with a mortality of 46%. In the consideration of reducing operative mortality, the introduction of prostin therapy allowed these babies to be stabilized before operative intervention, and this medical maneuver certainly led to improved perioperative care.[118–120] In addition, the evolution from invasive to non-invasive imaging for diagnosis was a benefit for these often desperately ill babies.[6,8,9,121–130]

Karl and his colleagues from the Royal Children's Hospital in Melbourne reported on the outcome of 30 infants with interruption of the aortic arch who underwent a biventricular repair.[115] Of these 30 there were two operative deaths, and three late deaths. Left ventricular outflow tract obstruction was not a risk factor for hospital or late deaths in these patients (Fig. 23-5). The development of subaortic stenosis and recurrent coarctation were encountered late in several patients, but these results were excellent. Apfel and colleagues of the Babies Hospital in New York City reported in 1998 the results of primary repair of 19 babies with interruption of the aortic arch and ventricular septal defect between 1986 and 1996.[131] There was no attempt to relieve the subaortic obstruction, no matter how severe it appeared. No operative deaths were encountered and all the patients were alive at 1 year. However, seven patients went on to require surgical relief of the subaortic stenosis, with two deaths.

Serraf and his colleagues reported in 1996 the results of surgical intervention in 82 consecutive patients with interrupted aortic arch seen between 1985 and 1995.[132] Three died before any repair could be carried out and 79 underwent surgical repair. The median age at operation was 9 days, ranging from 1 day to 6 years. Most were in severe heart failure, and 31.5% were either anuric or oliguric. Forty-three required aggressive preoperative resuscitation. Preoperative brain ultrasound performed routinely since 1987 revealed intracerebral bleeding in 6 patients. Type A interruption was found in 37 patients; 41 patients had type B, and one had type C interruption. Interrupted aortic arch was associated with a single VSD in 35 cases; 24 patients had associated complex defects; and 30 had significant subaortic stenosis. An aortopulmonary window was identified in 4 patients, common arterial trunk in 8; transposition of the great arteries in 5, double-outlet in 1; "single" ventricle in 1; and multiple VSDs in 2. Sixty-four patients underwent single-stage repair and 15 underwent multistage repair. A variety of surgical techniques were used to address the subaortic stenosis. Immediate surgical mortality was 18.9% with an overall mortality of 31%. Since 1990, the operative mortality improved to 12%. Survival at 5 years for the entire cohort was 73.5% and for complex forms, 70%. For those patients with subaortic stenosis survival at 5 years was 60%. In this series, twenty-three patients underwent 26 reoperations, for recoarctation, bronchial compression, s-stage repair, conduit replacement resection of subaortic stenosis, and a few miscellaneous operations.[132]

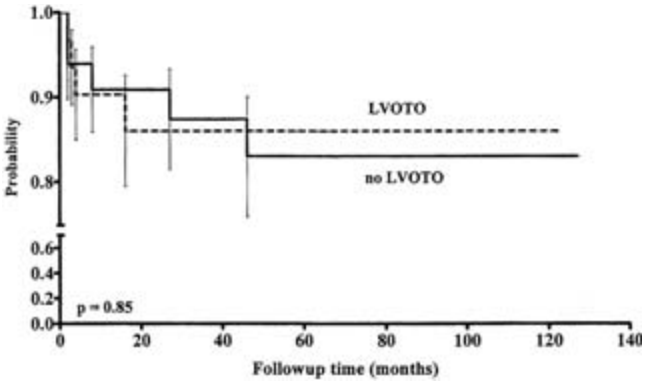


Fig. 23-5 Data from the Royal Children's Hospital in Melbourne show that left ventricular outflow tract obstruction (LVOTO) does not influence survival. Standard error is shown for each group. (Reprinted from Fulton *et al.*,[137] Copyright (1999), with permission from The Society of Thoracic Surgeons.)

The issue of subaortic stenosis cannot be separated from interruption of the aortic arch as in so many of the patients the very nature of the ventricular septal defect promotes left ventricular outflow tract obstruction.[2,3,6–10,44–49,54–57,63–66,69–72,92,93,95,104,106,109–111,116,117,132–136] Fulton and his colleagues have asked whether left ventricular outflow tract obstruction influences outcome of interrupted aortic arch repair.[137] Perhaps the question should be re-phrased: does surgical relief of left ventricular outflow tract obstruction influence outcome of interrupted aortic arch repair? The data provided by Fulton and his colleagues answer the second question.[137] This group had experience with 72 patients with interrupted aortic arch and some form of left ventricular outflow tract obstruction was identified in 36 patients. Left ventricular outflow tract obstruction was highly associated with type B interruption of the aortic arch and an aberrant right subclavian artery. In 29 of these the left ventricular outflow tract obstruction was subaortic and valvar in 7. The left ventricular outflow tract obstruction was severe enough in 15 as to require surgical intervention at the time of the repair. In the entire series of 72 patients there were 2 hospital deaths, and 7 late deaths. Left ventricular outflow tract obstruction was not a significant risk factor for hospital or late death. Actuarial survival for the entire cohort was 84.8% at 12 years. There was 87% 10-year survival for patients with left ventricular outflow tract obstruction compared with 83% for those without left ventricular outflow tract obstruction. It is difficult to reconcile this experience with that of Apfel and colleagues cited earlier.[131] Furthermore, in some centers where the subaortic obstruction is judged to be severe, a Norwood approach is advocated.[138] In this regard, Erez and colleagues have reported a modest series of patients who underwent successful biventricular repair after initial Norwood operation for interrupted aortic arch with severe left ventricular outflow tract obstruction.[139] Others have advocated a Norwood–Rastelli approach for complex systemic outflow tract obstruction and aortic arch interruption.[140] Obviously, at this time there is not unanimity of opinion as to whether or not subaortic obstruction needs to be addressed surgically at the time of repair and what methodology should be used. It will be interesting to assess in follow-up the effect of the everting suture technique as a maneuver to treat left ventricular outflow tract obstruction.[135,136]

We have reviewed the outcome of all consecutive patients (n = 119) with interruption of the aortic arch presenting from 1975 to 1999 to the Toronto Hospital for Sick Children.[36] The site of the aortic arch interruption was as follows: between the left subclavian artery and the ductus arteriosus in 30 patients (25%), between the left subclavian artery and the left common carotid artery in 84 patients (71%), and between the left common carotid artery and the right common carotid artery in only 5 patients (4%). All patients had an associated patent ductus arteriosus. A ventricular septal defect (VSD) (n = 117) was present in 107 patients (92%). The type of VSD (n = 80) was as follows: 20 patients (25%) had a perimembranous VSD, 31 patients (39%) had a perimembranous VSD with posterior deviation of the infundibular septum, 16 patients (20%) had a muscular outlet VSD, 6 patients (8%) had a muscular VSD, 4 patients (5%) had a membranous VSD and 1 patient (1%) had an atrioventriuclar septal defect defect. Subaortic stenosis was

noted in 51 patients (43%), a hypoplastic or stenotic aortic valve annulus in 16 patients (13%) and a hypoplastic left ventricle in 3 patients (3%). The presence of a hypoplastic aorta was noted in 8 patients (7%). In total 60 patients (50%) had an obstructive lesion or hypoplasia within the left heart complex. In three consecutive birth cohorts (1975–84, 1985–93 and 1994–99) there was an increase in one-stage repair for biventricular hearts: 68%, 75%, 100% (Fig. 23-6). The overall survival after repair was disappointing with 50% at age 1 month, 35% at 1 year, and 34% at 5 years. We have seen improvement with repair of uncomplicated IAA in those who had repair since 1993 (5 year survival, 93%). Freedom from re-intervention for arch obstruction was 69% at 5 years (Fig. 23-7).

Finally, the reality for the development or worsening of late left ventricular outflow tract obstruction and recurrent or persistent obstruction of the aortic arch are issues that will require continued surveillance.[131,141,141A,141B] There may be a consequence for the late development of aortic regurgitation as well. An occasional patient may develop airway obstruction.[142–144] When one records the blood pressure in these operated patients it is important to remember the laterality of the aortic arch, if the origin of the subclavian arteries was normal; if the right subclavian artery was isolated, etc.[145,146]

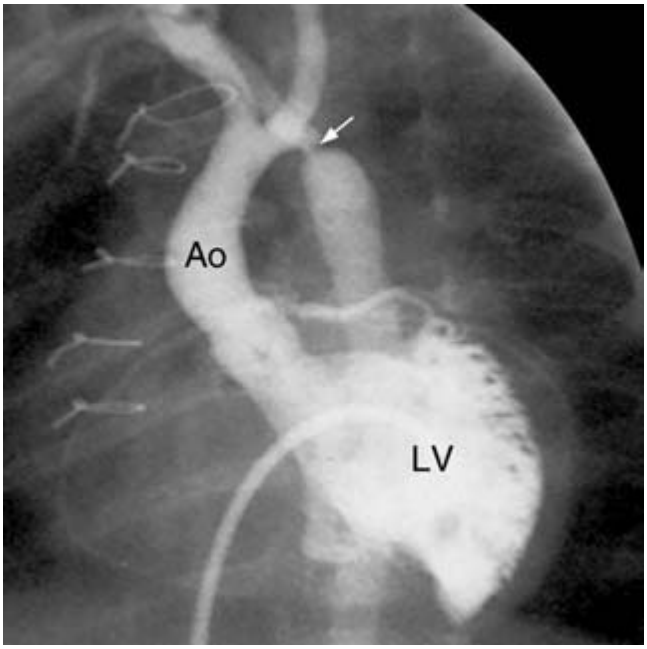


Fig. 23-7 Stenosis (arrow) of the aortic arch after reconstruction of the interrupted aortic arch. The posterior wall of the left ventricle (LV) shows mild form of myocardial noncompaction. Ao, ascending aorta.

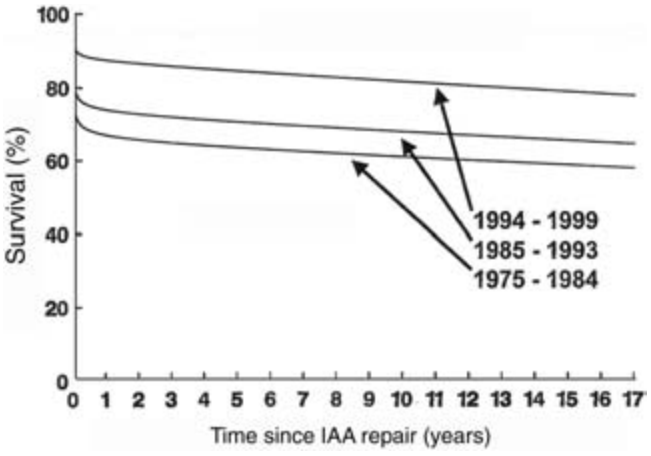


Fig. 23-6 Data from the Toronto Hospital for Sick Children shows improving results with repair of interrupted aortic arch (IAA) with time.

In summary:

- Repair of interrupted aortic arch and the associated anomalies continue to be a challenge.
- Surgical results for repair of interrupted aortic arch and ventricular septal defect continue to improve.
- Microdeletion q2211 is well defined in patients with type B interruption of the aortic arch. This may contribute to long-term cognitive, speech and behaviour problems.
- Moderately severe subaortic obstruction may not affect early surgical mortality or outcome.
- Caudal displacement of the infundibular septum may contribute to late subaortic obstruction and the necessity for reoperation.
- Extremely severe preoperative subaortic stenosis and interrupted aortic arch has been successfully treated with a Norwood-Rastelli approach.[140] Whether this approach is better than subaortic resection is uncertain at this time.
- These patients require life-long surveillance, particularly with scrutiny of the subaortic area and reconstituted aortic arch.

All references can be found at the end of the book. See pp. 723–7 for Chapter 23.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

24A

Robert M. Freedom, Shi-Joon Yoo, John G. Coles, and Igor Konstantinov

Total Anomalous Pulmonary Venous Connections

Classic bilaterally total anomalous pulmonary venous connections are characterized by connection of the pulmonary veins from both lungs to form a confluence behind the left atrium, and the venous channel from this confluence connecting with either a systemic vein or to the right atrium, or to both.[1–23] Rarely, the termination of all the pulmonary veins in the left atrium may be anomalous because of persistence of the so-called common pulmonary vein. It has been suggested that total anomalous pulmonary venous connection reflects failure of development of the common pulmonary vein, as suggested both by Lucas and Delisle, their respective colleagues, and others.[3–13] With failure of development of the common pulmonary vein and its incorporation into the left atrium, an anastomosis almost always results and enlarges between the pulmonary venous plexus of the lung buds and the systemic veins. The persistence of these embryonal connections at the supracardiac, cardiac, or infracardiac and thus usually subdiaphragmatic level permits classification of total anomalous pulmonary venous connections by their respective site or sites of connection (Figs 24A-1, 24A-2).[3–13]

Data from Paster and colleagues revealed that in their series of total anomalous pulmonary venous connections, the site of connection was to the left innominate vein in 37%; coronary sinus, 16%; infracardiac including portal system and ductus venosus, 15%; right superior vena cava, 14%; right atrium, 11%; and mixed, 7%.[17] Using Darling's classification of the mixed type of total anomalous pulmonary venous connection, part of the pulmonary venous connects at one level and part to another.[18] Arciprete and colleagues reported 3 cases having all the pulmonary veins connected to both the coronary sinus and the left vertical vein.[19] They indicated that arbitrary classification of total anomalous pulmonary venous connection into cardiac, supracardiac, infracardiac, and mixed types does not lend itself to description of such lesions and may obscure their clinical importance. They emphasized that a more detailed and precise definition of the multiple channels and sites of connections is necessary for accurate surgical repair when these less common variants of anomalous connection are encountered.

Jenkins and her colleagues have investigated whether mortality in patients with bilaterally total anomalous pulmonary venous connections could be predicted from preoperative individual pulmonary vein size.[24] Using echocardiographic measurements, their data framed in a Cox proportional hazards model revealed that the small sum of individual pulmonary vein diameters, small confluence size, and presence of heterotaxy syndrome were each significant univariate predictors of survival. Patients in their study with the heterotaxy syndrome had significantly smaller pulmonary veins than those without heterotaxy. However, both by stratified analysis and by multivariate modeling, the strong association between individual pulmonary vein size and survival was independent of the presence or absence of heterotaxy. Normal measurements of the pulmonary veins have been published elsewhere.[25]

Mechanism(s) of obstruction in total anomalous pulmonary venous connections

Many papers have discussed elsewhere those mechanisms responsible for obstruction in total anomalous pulmonary venous connections.[4–18,20–23,26–55] These observations about the mechanisms of obstruction are summarized in Table 24A-1.

In those patients with confounding cardiac malformation that reduce pulmonary blood flow, the clinical recognition of severe pulmonary venous obstruction may be masked.[56–65] Some years ago we demonstrated the role of a prostaglandin challenge to unmask the severe pulmonary venous obstruction.[66] All-too-frequently, if this association was not recognized preoperatively, the surgical construction of a systemic-to-pulmonary arterial anastomosis would unmask the culprit; namely, the obstructed pulmonary venous connections. This combination of problems occurs primarily, but not exclusively, in those patients with visceroatrial heterotaxy.[67–70] The left ventricle was considered hypoplastic in many patients with the obstructed form of total anomalous pulmonary venous connections, and this hypoplasia was considered responsible for postoperative deaths. However, volumetric analysis showed that most left ventricular volumes were within the normal range, although sometimes at the lower limits of normality.[70–73]

Atresia of the common pulmonary vein

Common pulmonary vein atresia is a rare condition characterized by a formation of confluence of pulmonary veins behind, but not communicating with the heart or a systemic vein.[74–85] Survival for even a short time is likely mediated by small connections between bronchial and pulmonary veins. Dilated pulmonary lymphatics producing pulmonary lymphangiectasia are conspicuous in this condition.[4,5,81] Babies with atresia of the common pulmonary vein have the severest form of obstructed bilateral total anomalous pulmonary venous connections, usually presenting with intense pulmonary edema and intense hypoxemia shortly after birth. This condition has been recognized by cross-sectional echocardiography as by angiography. Surgery has been successful in an occasional patient with atresia

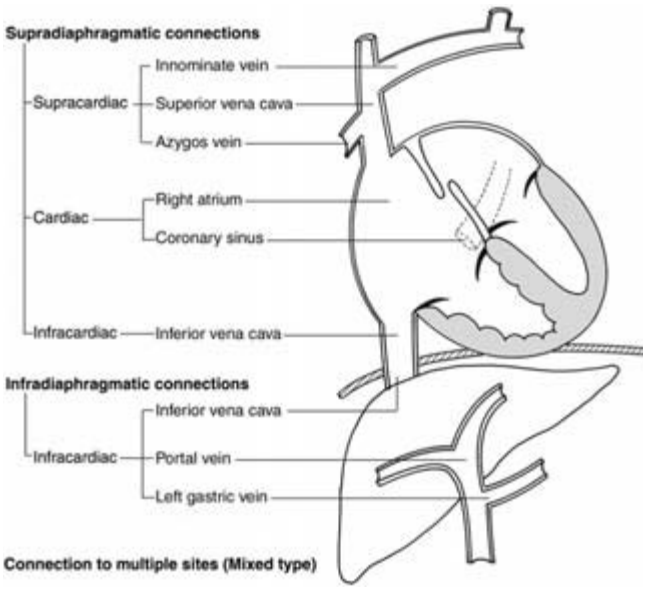


Fig. 24A-1 Classification of anomalous pulmonary venous connection according to the site of abnormal connection(s).

of the common pulmonary vein. Extracorporeal membrane oxygenation has been used to support these patients before and following surgery to allow "healing" of the lungs.[83]

Incidence

Of the 2251 infants with congenital heart disease enrolled in the New England Regional Infant Cardiac Program, 63 infants with isolated total anomalous pulmonary venous connections were identified, making this the 12th most common lesion.[86] The prevalence in this study of isolated total anomalous pulmonary venous connections was 0.058 per 1000 live births. Fyler mentions as well that total anomalous pulmonary venous connections were considered a secondary diagnosis in another 24 instances, occurring in 18 with asplenia or polysplenia. Data from the Baltimore–Washington Infant Study provided a prevalence of 0.083 per 1000 live births, and a very similar prevalence of 0.087 per 1000 live births was identified in the Alberta Heritage Pediatric Cardiology Program.[87,88] The prospective Bohemia Survival Study identified 40 children with total anomalous pulmonary venous return from 815 569 children born between 1980 and 1990, for a prevalence of 0.05 per 1000 live births. These 40 patients accounted for 0.80% of all heart malformations.[89]

This is not for the most part a familial disorder, although total anomalous pulmonary venous connections have occasionally been identified in siblings and may occur in particular syndromes.[90,91] Recently a kindred from Utah and Idaho was described in which 14 individuals have total anomalous pulmonary venous connections of various anatomic types.[92] The gene for this familial form of total anomalous pulmonary venous connection was mapped to chromosome 4p13-q12. Bleyl and colleagues have found a vascular endothelial growth factor receptor which maps to the same region and this has been identified as the candidate gene for familial and perhaps the sporadic form of total anomalous pulmonary venous connection.[93]

McCrindle and his colleagues set out to determine whether Aboriginal Canadians from Manitoba and Ontario have an increased incidence of isolated total anomalous pulmonary venous drainage and to compare results obtained from two different data sources and time periods.[94] A nonconcurrent cohort study was undertaken. Incidence rates and relative risk from "traditional" data sources (cases from medical records data; births from Census, Vital Statistics and Native Registry data for Manitoba and Ontario) from 1972 to 1984 were derived and compared with those from computerized hospital abstract data from Manitoba for 1987–91. Using traditional data sources an incidence of 0.282/1000 live births was noted in Aboriginals vs. 0.062 in non-Aboriginals for a relative risk of 4.6 (95% CI = 2.7–7.7). For Manitoba only the relative risk was 5.8 (95% CI = 2.6–12.8). Using computerized administrative data from Manitoba the relative risk was 5.8 (95% CI = 1.3–25.8). These data suggest there is an increased incidence of isolated total anomalous pulmonary venous connection in Aboriginal peoples from Manitoba and Ontario.

Associated cardiac malformations

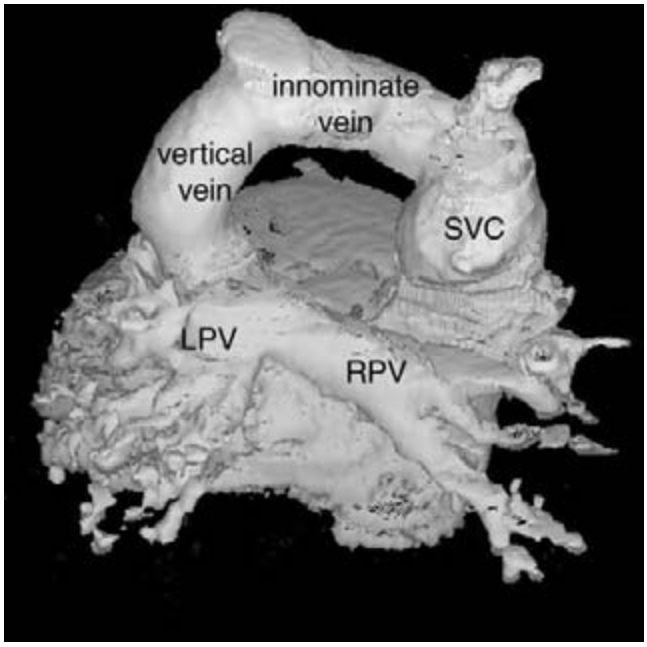
Total anomalous pulmonary venous connections can be found with a wide variety of cardiac malformations, and are especially common in patients with visceroatrial heterotaxy. Other malformations including tetralogy of Fallot, tetralogy with absent pulmonary valve, interruption of aortic arch, coactation of aorta, "single" ventricle, complete and corrected transposition of the great vessels, ventricular septal defect, complete atrioventricular septal defect, double-outlet ventricle, hypoplastic left heart syndrome, common arterial trunk, scimitar syndrome, etc., have all been seen in association with total anomalous pulmonary venous connections.[8,13,14,26,30,41,45,57,59,70,95–101]

Outcome analysis

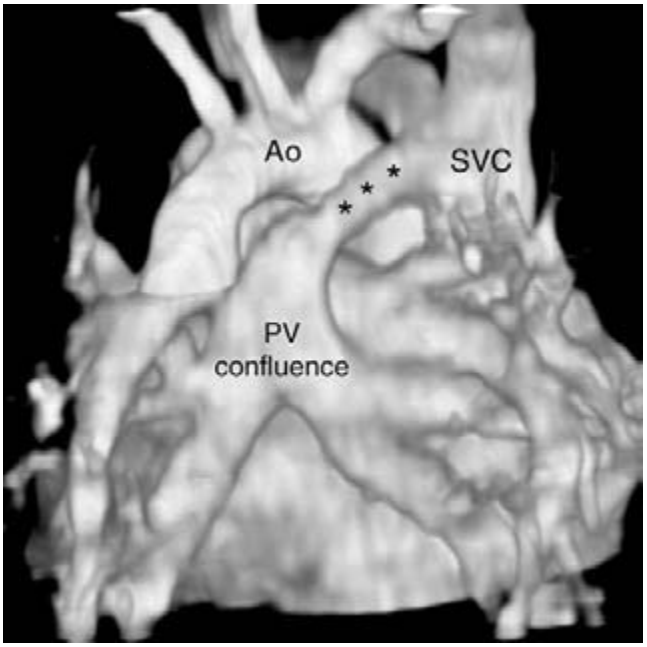
There is some information on the fetal recognition of total anomalous pulmonary venous connections.[102–105] The diagnosis is based on an abnormal four-chamber image showing an enlarged right atrium and right ventricle.[102,104] These findings are germane to those fetuses with unobstructed forms of total anomalous pulmonary venous connections. Such right heart enlargement occurs considerably later in gestation in those fetuses with severe obstruction.[102,104] There is virtually no information about outcome of fetuses with total anomalous

Table 24A-1 Mechanisms of obstruction in total anomalous pulmonary venous connections

Stenosis of the individual pulmonary veins
Stenosis at the abnormal connection
Intrinsic stenosis of the conveying channel such as vertical vein (Fig. 24A-3)
Extrinsic compression of the conveying channel
Compression the vertical vein between the bronchus and pulmonary artery in supracardiac type, so-called anatomical vice position (Fig. 24A-4)
Small esophageal hiatus in infracardiac type
Drainage into the liver, a solid parenchymal organ, with infracardiac connection to the portal vein–ductus venosus complex



A



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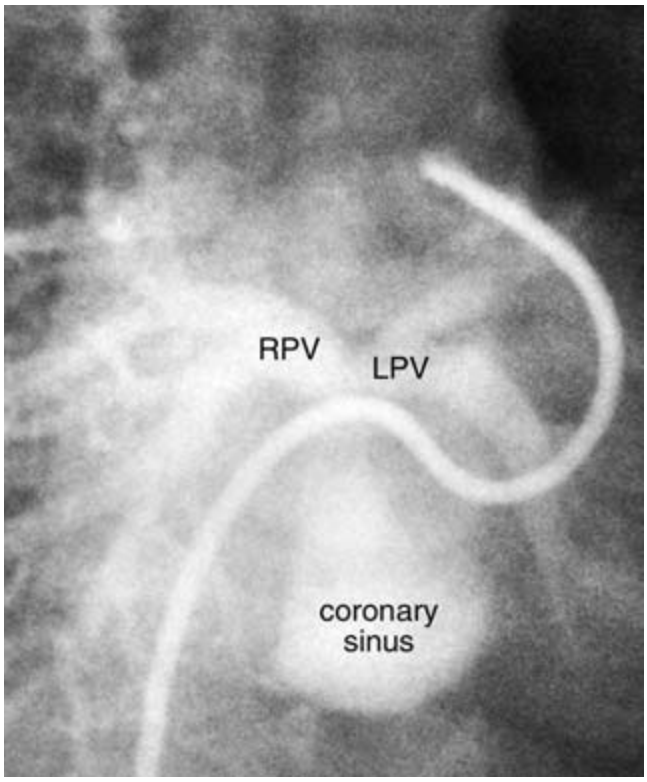

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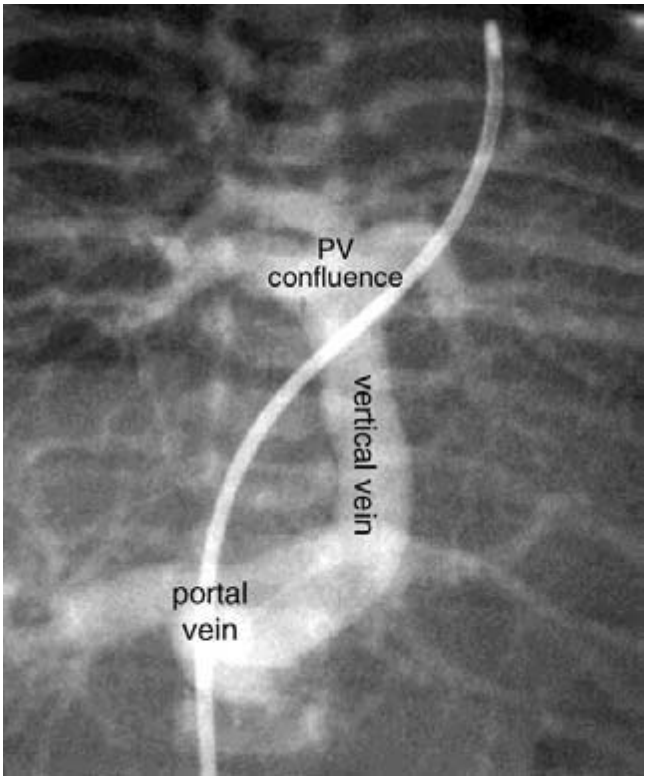


D

Fig. 24A-2 Examples of total anomalous pulmonary venous connections. **A**. CT angiogram seen from behind shows anomalous connection to the innominate vein.(Courtesy of Dr Yang Min Kim, The Sejong Heart Institute, Korea.) **B**. MR angiogram seen from behind shows anomalous connection to the superior vena cava (SVC). The vertical vein connecting the pulmonary venous (PV) confluence shows long segment narrowing (asterisks). **C**. X-ray angiogram shows anomalous connection to the coronary sinus (CS). **D**. X-ray angiogram shows anomalous connection to the portal vein. Ao, aorta; LPV, left pulmonary vein; PV, pulmonary vein; RPV, right pulmonary vein.

pulmonary venous connections in isolation. The majority of patients with obstructed total anomalous pulmonary venous connections present in early infancy, but an occasional patient will present in the adult.[106] Similarly while most patients with nonobstructed total anomalous pulmonary venous connections present in early infancy or childhood, an occasional patient will survive without diagnosis until adulthood.[107]

As in many other aspects of the diagnosis and management of congenital heart malformations, diagnosis has evolved from angiography[16,26,48] to cross-sectional echocardiography and

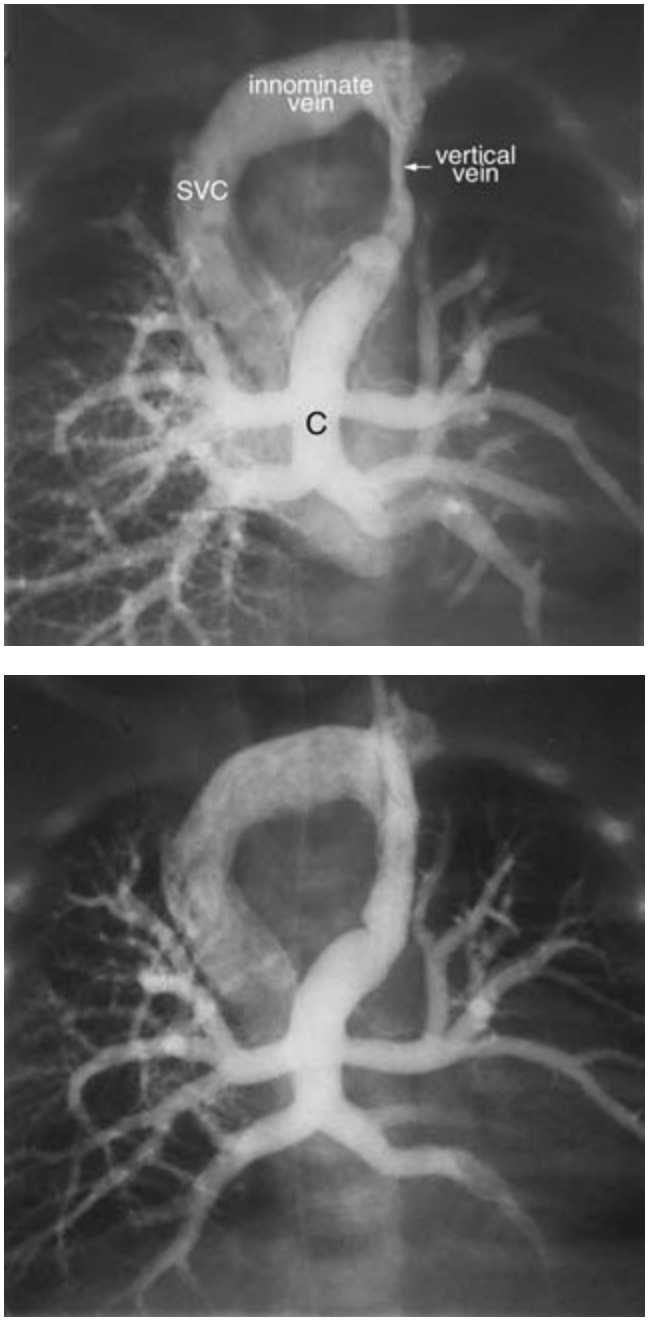


Fig. 24A-3 Total anomalous pulmonary venous connection to the innominate vein. **A**. Injection into the common pulmonary vein shows intrinsic narrowing of the distal part of the vertical vein. **B**. Stent dilatation of the vertical vein was performed for temporary improvement of the pulmonary venous drainage before the surgery. C, confluence of the pulmonary veins; SVC, superior vena cava.

color Doppler interrogation of individual pulmonary veins[108–120] (Figs 24A-2 to 24A-4). One should be reminded that hypotension from compression of the pulmonary venous confluence can result from passage of the probe when performing a transesophageal study.[118] There is also increasing experience with contrast-enhanced MR angiography in the evaluation of pulmonary veins.[120A,120B]

Clabby and her colleagues have summarized the surgical results for many series starting with publication dates in 1966 and concluding in 1993.[121] Surgical mortalities ranged from 85% in the 1960s to mortalities of < 5% in some series.[121] The Pediatric Cardiac Care Consortium reported on its experience with 437 primary operations for total anomalous pulmonary venous connections amongst 27678 operations performed between 1985 and 1993. The connection was supracardiac in 40%, cardiac in 17%, infracardiac in 22%, mixed in 10% and in 11% the site of connection was unknown. The mortality by type of connection was 14.2%, 11.6%, 32.6%, 15.8% and 31%, respectively. For patients with total anomalous pulmonary venous connections in isolation, the operative mortality was 16%. In most centers, surgical results for isolated total anomalous pulmonary venous connections have demonstrated continuing improvement. The use of extracorporeal membrane oxygenation has led to increased salvage of the sickest of these neonates, usually those with the severest forms of obstruction.[122–129] There are many variations in the anatomy of the mixed type of total anomalous pulmonary venous connections, and surgical repair of these patients remains a challenge.[130–137] The Great Ormond Street Hospital for Sick Children has reported its experience with the surgical management of mixed total anomalous pulmonary venous connections.[130] Between January 1, 1971, and December 31, 1994, 232 patients with total pulmonary venous drainage underwent surgical correction. Twenty of these patients (8.6%) had mixed type total pulmonary venous drainage. The ages at operation ranged from 1 day to 46 months, with a median of 2.3 months. Severe pulmonary venous obstruction was present in 3 patients, all of whom underwent emergency operation. Three patients (15%), all of whom had preoperative pulmonary venous obstruction, died after operation. There were 2 late deaths, 1 of pulmonary vein stenosis and the other of probable pulmonary hypertension. The actuarial survival at 10 years was

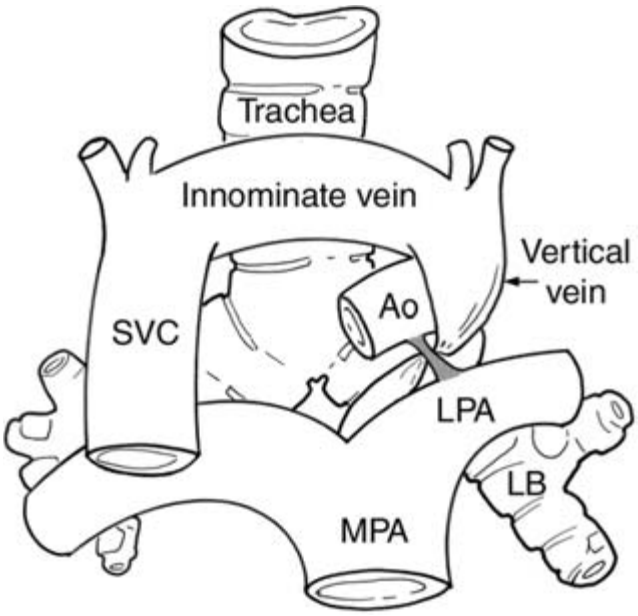


Fig. 24A-4 Anatomical vice location of the vertical vein in total anomalous venous connection to the innominate vein. The vertical vein passes through a narrow space formed by the left pulmonary artery (LPA) anteriorly, ligamentum or patent ductus arteriosus (shaded) medially, and the left main bronchus (LB) posteriorly. MPA, main pulmonary artery; SVC, superior vena cava.

Table 24A-2 Anatomic types and distribution of patients with total anomalous pulmonary venous connections[99]

TAPVC type	Simple	Complex	Total patients (%)
Infracardiac	41	15	56 (33)
Cardiac	26	7	33 (19)
Mixed	10	6	16 (9)
Supracardiac	49	16	65 (38)
Total	126	44	170

73% for all patients; patients who survived the initial operation had a 10-year survival of 87%.

Continuing with data from the Pediatric Cardiac Care Consortium, the operative mortality for patients with total anomalous pulmonary venous connections and other significant associated cardiac malformations excluding asplenia was 31%; and for those patients with total anomalous pulmonary venous connections and asplenia, the mortality was 54.5.[121] We and others have reported on the poor outcome of repair of patients with single ventricle pathology and total anomalous pulmonary venous connections.[67–70,99] This particular combination is commonly but not exclusively seen in patients with asplenia/right atrial isomerism. Sadiq and his colleagues reported only a 38% long-term survival in patients with right atrial isomerism and total anomalous pulmonary venous connections requiring palliation with a systemic-to-pulmonary artery shunt.[67] For those babies requiring intervention in the first month of life, long-term survival decreased to 13%, findings very similar to those published by Hashmi and his colleagues from the Toronto Hospital for Sick Children.[68] Gaynor and his colleagues have reported on the long-term outcome of 73 infants with single ventricle and total anomalous pulmonary venous connections treated between 1984 and 1997.[69] Overall survival was 45% at 6 months of age, 37% at 1 year of age, and 19% at 5 years. Twelve patients died before surgery. Of the 61 patients undergoing surgery, survival was 54% at 6 months of age, 44% at one year of age, and 23% at 5 years. The heterotaxy syndrome was present in 52 patients (71.2%). For the entire cohort, survival was worse for those with obstructed total anomalous pulmonary venous connections than for those without obstruction ($P = 0.02$).

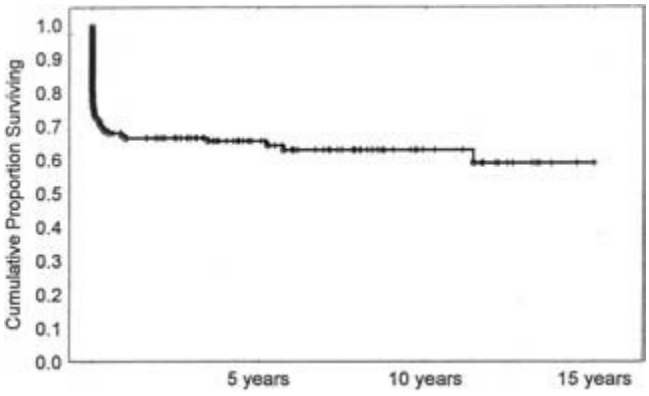
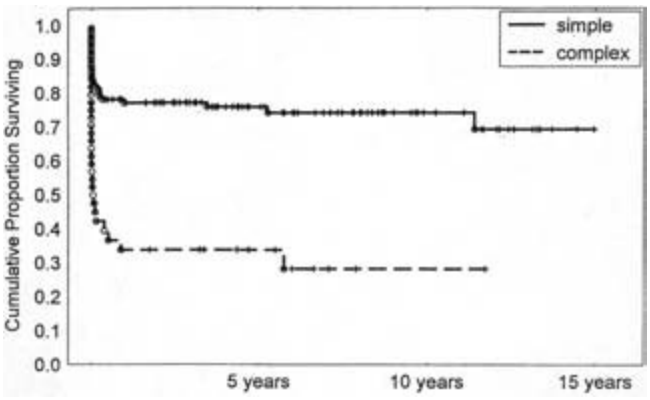


Fig. 24A-5 Actuarial survival of the 170 patients who underwent repair of total anomalous connection. (Reprinted from Caldarone *et al.*,[99] Copyright (1998), with permission from The Society of Thoracic Surgeons.)



Fig, 24A-6 Stratified actuarial survival of the patients with simple and those with complex type of total anomalous pulmonary venous connection. The impact of complex associated anomalies is readily apparent. (Reprinted from Caldarone *et al.*,[99] Copyright (1998), with permission from The Society of Thoracic Surgeons.)

Calderone and his colleagues from the Toronto Hospital for Sick Children addressed the impact of coexisting cardiac anomalies on the surgical management of total anomalous pulmonary venous connections.[99] Our group reviewed 170 consecutive patients with total anomalous pulmonary venous connections undergoing repair from 1982 to 1996. Of these 170 patients, 126 were considered "simple" and 44 "complex." The ratio of males to females was 1.7 to 1. The median age at operative repair was 20.5 days and the median patient weight 3.5 kg. The anatomic types and distribution of patients is shown in Table 24A-2. Operative mortality for simple cases decreased from 26% to 8%, while mortality for complex cases remained constant at 52%.

Age, size, and the presence of atrial isomerism were univariate predictors of mortality. Multivariable analysis identified only univentricular heart and associated cardiac lesions as predictors of operative mortality.[99] The actuarial survival for the entire cohort of 170 patients is shown in Fig. 24A-5, and when stratified by simple vs. complex in Fig. 24A-6. The difference in survival for patients with total anomalous pulmonary venous connections and a biventricular heart when compared to a univentricular heart is striking (Fig. 24A-7).

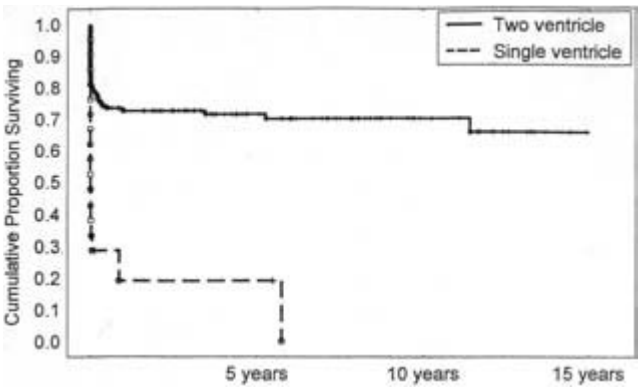


Fig. 24A-7 Stratified actuarial survival for the patients with biventricular heart and those with univentricular heart. (Reprinted from Caldarone *et al.*,[99] Copyright (1998), with permission from The Society of Thoracic Surgeons.)

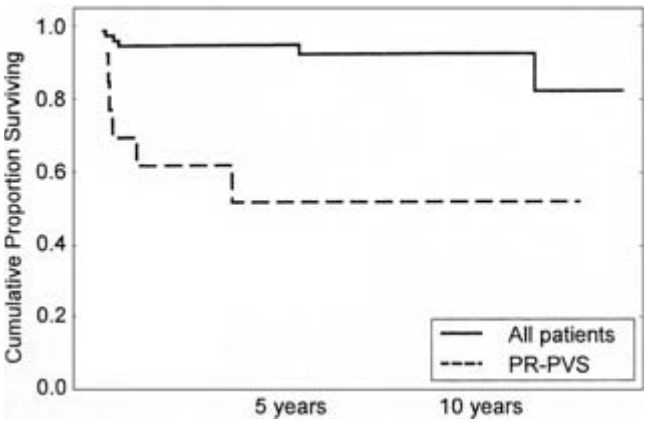


Fig. 24A-8 Survival after repair of total anomalous pulmonary venous connection with early (< 30 days) mortality excluded for patients with and without subsequent postrepair pulmonary vein stenosis ($P < 0.001$). PR-PVS, postrepair pulmonary veins stenosis. (Reprinted from Caldarone *et al.*,[156] Copyright (1998), with permission from The Society of Thoracic Surgeons.)

Despite improving results in the surgical management of total anomalous pulmonary venous return,[121,138–150] there continues to be relentless pulmonary vein stenosis after repair.[151–157] Of the 170 consecutive patients identified from this institution undergoing repair for total anomalous pulmonary venous connections we identified 13 with postrepair pulmonary vein stenosis (Figs 24A-8, 24A-9).[156] This complication was most common in those with infracardiac or mixed drainage. Four patients had unilateral pulmonary vein stenosis and 9 had bilateral obstruction. Seventeen reoperations were performed in the 13 patients. All four patients with unilateral stenosis survived, including the two who progressed to nearly complete unilateral pulmonary vein occlusion. Six of the nine with bilateral obstruction died, but two of the three survivors were repaired with a novel technique which created a sutureless neoatrium (Fig. 24A-10).[156,158,159] A substantial number of reports have commented on the poor outcome of patients with postoperative bilateral pulmonary venous obstruction, although there has been an occasional success.[151–159] In our experience and in the experience of others, the use of catheter-positioned endovascular stents has not provided sustained relief of the obstruction.[156] The histopathology of the pulmonary veins can be very abnormal in some patients with total anomalous pulmonary venous connections.[160] Yamaki and his colleagues have shown that the mean thickness of the media of small pulmonary arteries and veins was 12.7 and 7.6 microns, respectively, in the total anomalous pulmonary venous connection cases, both values being significantly larger than those for normal and ventricular septal defect with pulmonary hypertension cases.[161] The medial thickness in the arteries and veins was greater in the cases of pulmonary venous obstruction than in those without such obstruction. The medial thickness of small pulmonary arteries in total anomalous pulmonary venous connection cases correlated with increased pulmonary arterial pressure. When the patients with the same pulmonary arterial pressure levels were compared, the medial thickness was always greater in those who had total anomalous pulmonary venous connection than in those who had ventricular septal defect. The medial thickness of pulmonary veins was also highly correlated with increased pulmonary arterial pressure in total anomalous pulmonary venous connection. The severity of the intimal lesions was milder in those who had total anomalous pulmonary venous connection than in those

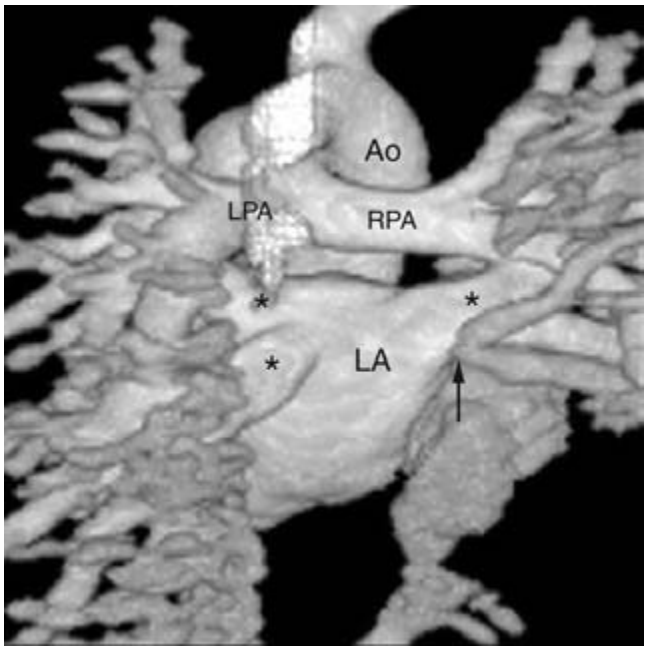


Fig. 24A-9 Pulmonary vein stenosis after surgical repair of the mixed type of total anomalous venous connection. Contrast-enhanced MR angiogram shows that the right lower pulmonary vein (arrow) is completely occluded. Other pulmonary veins (asterisks) are unobstructed. Ao, aorta; LPA, left pulmonary artery; RPA, right pulmonary artery.

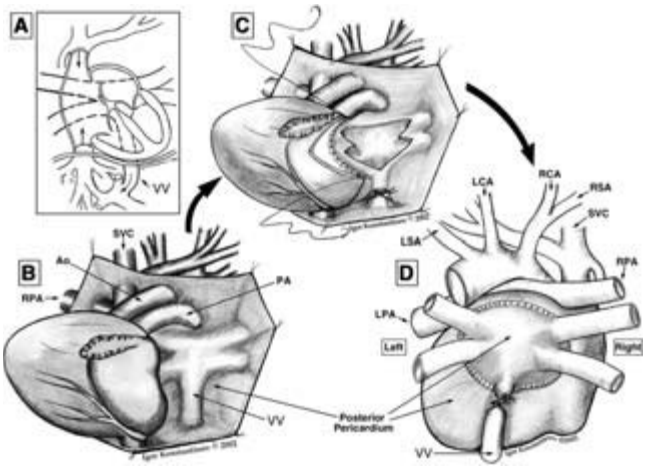


Fig. 24A-10 *In-situ* pericardial repair of the total anomalous pulmonary venous connection (TAPVC). **A**. Pathology of infracardiac TAPVC. **B**. Heart tilted rightward and the pulmonary venous confluence exposed. **C**. Vertical vein (VV) ligated, the pulmonary venous confluence opened and the atrium sutured to the posterior pericardium around the opening in the venous confluence. **D**. View from behind showing the suture line connecting the atrium directly to posterior pericardium. Ao, aorta; LCA, left carotid artery; LPA, left pulmonary artery; LSA, left subclavian artery; RCA, right carotid artery; RPA, right pulmonary artery; RSA, right subclavian artery; SVC, superior vena cava.

who had ventricular septal defect, suggesting the protective role of the thickened pulmonary arterial media against development of intimal lesions. Intimal fibrous thickening of pulmonary veins was not seen in the cases of ventricular septal defect, but it was present in 45% of the total anomalous pulmonary venous connection cases. Lymphangiectasia was characteristically present in 62% of the total anomalous pulmonary venous connection cases. Interstitial emphysema was often a complication of lymphangiectasia, and it led to postoperative death. In the follow-up of operated patients with total anomalous pulmonary venous connections, chest radiography, pulmonary perfusion scans and color Doppler assessment of the individual pulmonary veins are important investigations.[115–117] When the chest radiograph demonstrates unilateral pulmonary edema, not infrequently, the "wet" side has normal pulmonary venous flow. Redistribution of flow occurs in response to the contralateral pulmonary venous obstruction. This would be confirmed by a pulmonary perfusion scan which shows the majority of flow to the "wet" side and by Doppler imaging which would demonstrate abnormal flow patterns characteristic of obstruction in the contralateral pulmonary veins. Postoperative pulmonary artery wedge angiography or selective injection into the pulmonary veins will also demonstrate the site and mechanism of obstruction.[26,48,153,162–164] We find that contrast-enhanced MR angiography is extremely useful in defining the postoperative anatomy of the pulmonary veins.[120A,120B] The hemodynamic significance of stenosis can also be evaluated by using phase-contrast MRI.

Arrhythmias, usually supraventricular, have been amply recorded in asymptomatic patients after anatomically successful repair of total anomalous pulmonary venous connections, and rarely complete heart block results. Because patients with supraventricular ventricular rhythm disturbances are often asymptomatic, it is best that periodic ambulatory electrocardiograms be recorded.[165] We have not observed this postoperatively, but some patients with the infradiaphragmatic form of total anomalous pulmonary venous connections may have a gastrointestinal hemorrhage.[166,167]

Our own results have not been as favorable as some we have noted. We have reviewed the outcomes of 340 children with isolated total anomalous pulmonary venous drainage (TAPVD) born between January 1943 and February 1997, and evaluated at a single institution at a median age of 18 days at presentation (range, birth to 12.2 years).[168] TAPVD was supracardiac in 44%, cardiac 20%, infracardiac 25%, mixed 9% and unknown in 2%. Before 1960, patients presented at a significantly older age and were less likely to have infracardiac TAPVD, suggesting significant pre-hospital mortality for this group. Repair was performed in 288 patients (85%) at a median age of 2 months (range, 1 day to 14.1 years); the remaining patients died without or before surgery. The proportion of patients without repair according to birth cohort was 56% before 1950, 1950–59 39%, 1960–69 20%, 1970–79 10%, 1980–89 10% and 1990–97 2%. The median age at repair decreased significantly for birth cohorts: 9.7 years before 1950, 1950–59 1.2 years, 1960–69 0.31 years, 1970–79 0.25 years, 1980–89 0.06 years and 1990–97 0.07 years. Pulmonary vein obstruction (PVO) was present before surgery in 43% with supracardiac TAPVD, 23% in cardiac, 91% in infracardiac and 62% with mixed drainage. Kaplan–Meier survival estimates after repair were 74% at 1 week, 67% at 6 months, 63% at 5 years and 59% at 20 years. Since 1970 there has been no significant improvement in survival after repair, with survival since 1990 ($n = 52$) of 94% at 1 week, 85% at 6 months and 75% at 5 years. After controlling for date of repair, significant independent factors associated with mortality included younger age at repair and infracardiac and cardiac connections. The presence of pulmonary venous obstruction (PVO) before repair was associated with the greatest adjusted risk of mortality.

We have reviewed our more recent experience with the repair of total anomalous pulmonary venous return and have compared the results of a conventional repair with *in-situ* pericardial repair of total anomalous pulmonary venous obstruction. Since January, 1995, 77 patients underwent repair of total anomalous pulmonary venous connection (TAPVC) at the Hospital for Sick Children, Toronto. Among these 77 patients, 19 underwent *in-situ* pericardial repair, either as a primary operation instead of a conventional repair ($n = 13$), or as a secondary operation to treat recurrent bilateral pulmonary venous obstruction (PVO) following previous repair of TAPVC ($n = 6$). Among this subset of 19 patients undergoing pericardial repair, 13 patients had a biventricular heart, and 6 patients, a univentricular AV connection complicated by TAPVC.

TAPVC in biventricular heart: survival results

There was 1 death among 13 patients with TAPVC in the setting of a biventricular heart. This includes 8 patients considered at high risk for recurrent obstruction following conventional repair, on the basis of an unusually hypoplastic pulmonary venous confluence and/or pulmonary veins, or cases in which the anomalous pulmonary veins connected to the cavo-atrial junction, and 5 patients with recurrent PVO following repair of TAPVC. One of 13 (7.69%) patients with biventricular TAPVC did not survive as a result of pulmonary parenchymal disease secondary to advanced Scimitar syndrome.

Recurrent PVO following repair of TAPVC: hemodynamic results

In-situ pericardial repair of recurrent PVO following repair of biventricular TAPVD has yielded uniformally good results with follow-up exceeding 5 years in some patients. Hemodynamic studies in this subgroup have revealed normalization of pulmonary arterial pressures and dramatic improvement or normalization of pulmonary venous flow patterns based on spectral Doppler echocardiographic assessment. Postrepair phase-contrast cine MR studies have typically revealed abolition of the stenotic flow patterns characterized by elevated peak diastolic velocity and blending of the systolic and diastolic peaks (i.e. loss of phasicity). (In our paper, we do not have pre-repair data. That means we are not able to say that stenotic flow pattern was abolished.) Comparison of PV flow patterns following *in-situ* repair with that after conventional repair of TAPVC using cine MR revealed significantly lower peak systolic flow velocities with decreased systolic/diastolic flow ratio in the "*in-situ*" group, possibly related to incorporation of the pericardium to the left atrial wall. This could result in diminished compliance of the functional left atrium.[168A]

TAPVC in complex univentricular AV connection

Encouraging initial experience in patients with recurrent PVO following biventricular TAPVC repair motivated the use of this technique at the time of primary operation to repair TAPVC in association with univentricular AV connection – historically an

invariably lethal entity. Among 6 patients with a complex right ($n = 5$) or left ($n = 1$) isomerism in association with obstructed TAPVC in whom "preemptive" *in-situ* pericardial repair was elected, there were 3 deaths, one of whom had evidence of recurrent PVO at the time of death.

Congenital pulmonary venous obstruction

In-situ pericardial repair was used to repair PVO occurring in the context of isolated congenital pulmonary vein stenosis ($n = 2$), PVO in association with ASD ($n = 1$), VSD ($n = 1$), and at the time of cardiac transplantation for hypoplastic left heart syndrome ($n = 2$). Results: there were 3 deaths among 6 patients with congenital PVO (50%). Autopsy-confirmed, recurrent, as opposed to residual, PVO, was present at the time of death in 1 of the 3 non-survivors.

Indications for *in-situ* pericardial repair

In-situ pericardial repair to augment pulmonary venous flow pathways appears to be worth while regardless of the anatomical substrate producing pulmonary venous obstruction, and has well-documented utility in the management of recurrent PVO following biventricular repair of TAPVC. Accrual of further experience is required to determine the efficacy of this approach in the entity of congenital pulmonary vein stenosis, occurring in isolation or with associated intracardiac defects. The preemptive use of this procedure in the challenging morphological subset of patients with univentricular AV connection complicated by actual or potential PVO likewise requires further evaluation.

One of the issues that has not been completely resolved is whether the vertical vein in patients with bilateral total anomalous pulmonary venous connections to the left brachiocephalic vein should be invariably ligated at the time of the repair. Some have stated that in those neonates who are very unstable after repair with severe pulmonary hypertension a vertical vein left patent may be advantageous.[169–174] The analogy to a small defect of the oval foramen in this situation is obvious, both permitting a right-to-left shunt.[171] Others have indicated that an unligated vertical vein can promote a substantial left-to-right shunt.[172] Both issues deserve consideration because the situations are different. In those patients where residual vertical vein patency results in an important left-to-right shunt, transcatheter closure using any of a variety of devices may avoid the requirement for surgical intervention.[175–179] We have had the opportunity to close in the catheter laboratory a descending vertical vein that remained patent some years after repair of total anomalous pulmonary venous connection to the portal vein. Residual patency of the descending vein in this situation is admittedly uncommon. Thus it is clear that complete involution of the vertical vein (ascending or descending) cannot be taken for granted.

The following statements summarize the situation for patients with total anomalous pulmonary venous connections.

- Total anomalous pulmonary venous connections can take one of several forms and can be isolated or associated with more complex cardiac anomalies.
- Surgical results for patients with total anomalous pulmonary venous connections in isolation continue to improve.
- Surgical results have been disappointing in patients with complex lesions, especially those with right isomerism and obstructed bilateral total anomalous pulmonary venous connections.
- Patients with mixed type of total anomalous pulmonary venous connections continue to be a challenge.
- Postoperative pulmonary venous obstruction especially when involving all four pulmonary veins continues to be a surgical challenge and results of revision have for the most part not been satisfactory.
- More experience with the so-called sutureless technique may salvage some of these patients.[158,158]
- There is ongoing discussion as to the merits of ligating the vertical vein in patients with supracardiac connections to the left brachiocephalic vein.
- The majority of children undergoing isolated total anomalous pulmonary venous connection repair can expect an excellent long-term functional outcome. Factors present before operation, such as pulmonary venous obstruction and associated anomalies, can influence overall health and school performance in the long term.[180]

All references can be found at the end of the book. See pp. 727–31 for Chapter 24A.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

24B

Robert M. Freedom and Shi-Joon Yoo

The Scimitar Syndrome or Hypogenetic Right Lung Complex

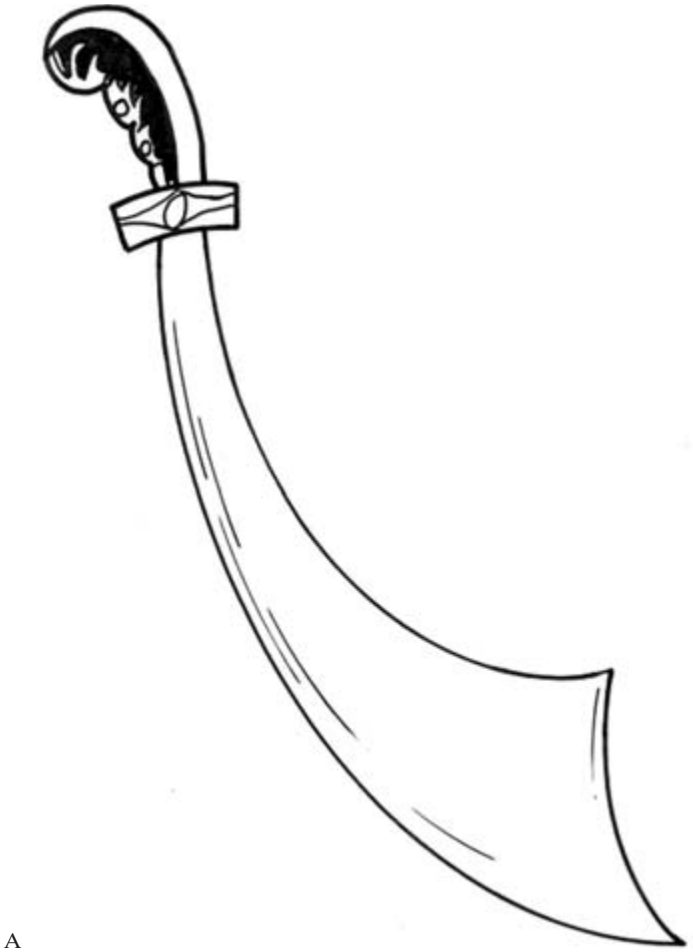
A scimitar is a short Turkish sword, and this term has come to designate a finding of a curved vascular shadow that descends towards the right hemidiaphragm, and which is produced by an anomalous right pulmonary vein that drains the right lung (Fig. 24B-1).[1] First described by Cooper and Chassinat in 1836 but not using the terms "scimitar" or "sign"according to Mulligan,[2–5] it was 75 years later when Park further characterized the constellation of abnormalities associated with defective development of the right lung, anomalous development of the right pulmonary artery and vein, and dislocation of the heart simulating dextrocardia.[6] Halasz and his colleagues[7] and then Neill and her colleagues at Johns Hopkins fully characterized the syndrome now known as the "scimitar" syndrome,[8] although Cirillo credits to Halasz and his colleagues the first use of the word "scimitar" in this context.[5] The scimitar syndrome is characterised by dextrocardia, hypoplasia of the right pulmonary artery, underdevelopment of the right lung, abnormal connection of the right pulmonary veins to the inferior vena caval–right atrial junction (giving the scimitar appearance on the frontal chest radiograph), and anomalous systemic arterial supply to the right lung, often its basal segments (Figs 24B-1, 24B-2). It is likely that Dotter and his colleagues were the first to diagnose this condition during life with cardiac catheterization and angiography.[9]

Abnormalities of lung lobation and bronchial branching are common to this syndrome.[7,9A,9B] The right lung often consists of two lobes or only one lobe. Both bronchi are commonly long, suggesting that the right upper lobe is missing. As the right upper lobar bronchus arises distally from the right main bronchus, the bronchial anatomy may resemble a right-isomeric type of bronchial branching.[9A,9B] Many cases have been described to be associated with pulmonary sequestration. However, it should clearly be understood that most of these cases are the cases of anomalous systemic arterial supply to a part of the right lung without true sequestration from the bronchial connection.[7,9B]

It is usually the right pulmonary artery that is underdeveloped in this syndrome, but occasionally, the left lung may be underdeveloped.[7–28] In cataloging those anomalies affecting the right pulmonary artery in the hypogenetic right lung syndrome, the degree of hypoplasia may be very mild, or extremely severe. Indeed, congenital absence of the right pulmonary artery has also been described in this syndrome.[29–31] We have documented pulmonary artery stenosis in the already hypoplastic right pulmonary artery.[10] Pulmonary arterial stenoses in the contralateral lung have also been observed.[32] Not infrequently in patients with the scimitar syndrome, the connection of the pulmonary veins with the inferior caval vein may be stenosed, and in one such reported case, the confluence of anomalous veins connected primarily with the left atrium.[33,34] Hypoplasia of the inferior caval vein has also been reported in the patient with the scimitar syndrome,[33,35] and we and others have seen persistence of the hepatic venous plexus with this syndrome as well.[35–37] A number of reports have documented a "scimitar-like" appearance on the chest radiograph, although further investigation demonstrates normal connection of the right pulmonary veins to the left atrium.[10,10A,11,38] Although connecting to the left atrium, the right pulmonary veins seem more tortuous in reaching the left atrium. Rarely the sword may be held in the left hand: i.e. a left-sided scimitar syndrome.[39,40] Others have described an incomplete scimitar syndrome.[40A]

The so-called horseshoe lung anomaly of the right pulmonary artery, or crossover lung anomaly is another malformation that may involve the right pulmonary artery in patients with the scimitar complex.[41–60] The horseshoe lung or crossover lung segment, an uncommon congenital anomaly, first described by Spencer in 1962,[41] is frequently associated with the scimitar syndrome in which the bases of the right and left lungs are joined by a parenchymal isthmus posterior to the heart.[41–60] This condition is readily diagnosed by the presence of a crossing pulmonary artery branch at angiography, or by demonstration at CT of fused lung tissue behind the heart.[44–60] Since the horseshoe lung often coexists with the scimitar syndrome, one should anticipate a similar constellation of cardiac anomalies. Occasionally the horseshoe lung anomaly will have anomalous pulmonary venous connections, but not pulmonary hypoplasia. One such patient in our series of patients with the hypogenetic right lung complex and horseshoe lung also had severe left pulmonary vein stenosis.[10,10A,47] The so-called crossover lung or horseshoe lung does not invariably coexist with the scimitar syndrome. There is another rare variant of the horseshoe lung, the so-called "inverted" horseshoe lung that has only been described once and this case was not associated with the scimitar syndrome.[48]

Anomalies of the right pulmonary veins are an essential component of the scimitar syndrome, and obstruction to pulmonary venous flow so well documented in this syndrome may contribute to the ipsilateral lung and pulmonary artery hypoplasia (Fig. 24B-2).[7–19,21–24,26–34,39,42–59] Thus patients with scimitar syndrome with or without a horseshoe lung may have extensive vascular anomalies involving their pulmonary arteries, pulmonary veins, and anomalous systemic arterial supply from the descending thoracic aorta or other systemic artery, as well as anomalies of bronchial supply.[7–19,21–24,26–34,39,42–59] Pulmonary



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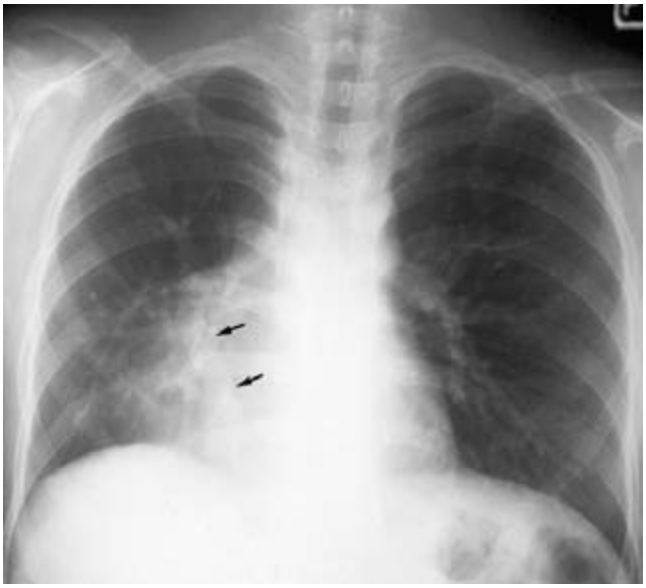

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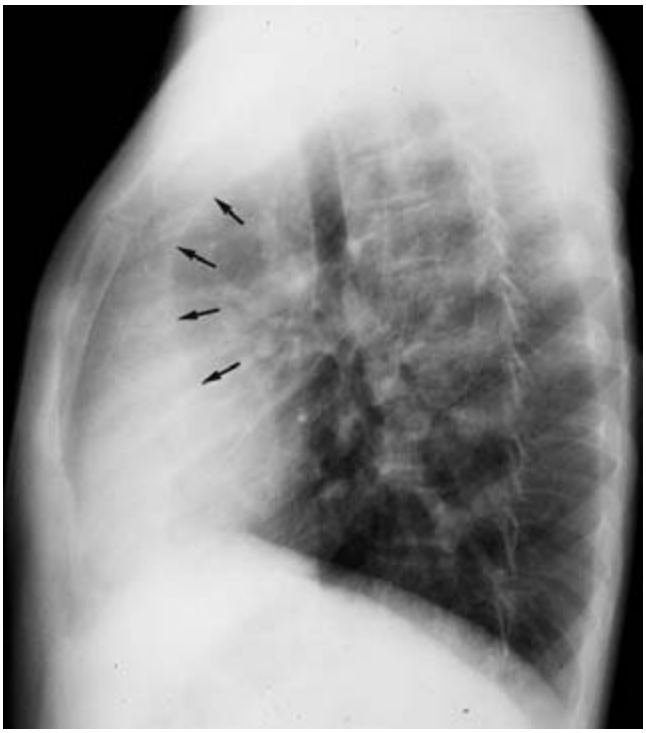

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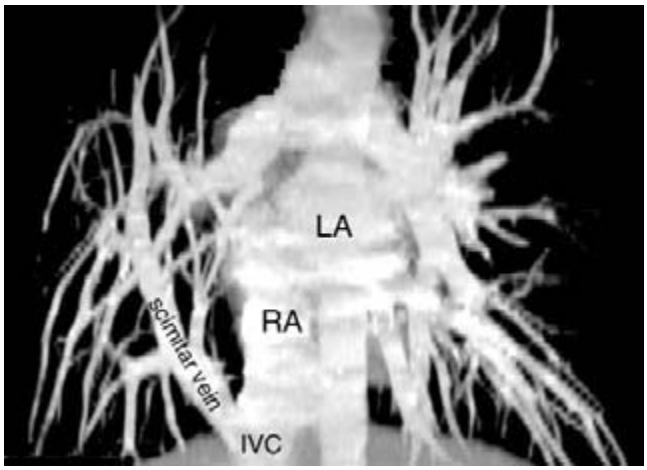

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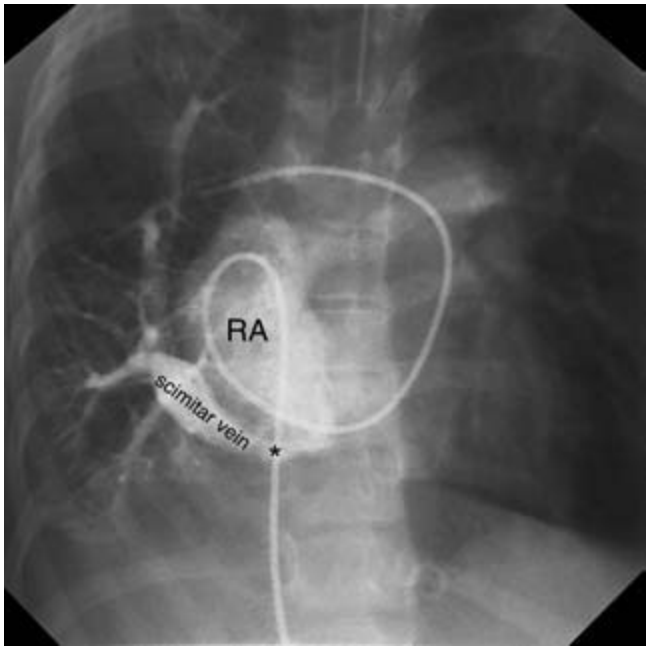
Fig. 24B-1 Scimitar vein. **A**. The scimitar, a short Turkish sword. **B**.Three-dimensional CT angiogram shows the scimitar-configuration of the confluent right pulmonary vein (S's). It has an anomalous connection to the right atrium (RA) at its junction with the interior vena cava (IVC). The orifice is mildly stenotic. **C**. Frontal chest radiogram from another patient shows small right thorax, rightward displacement of the heart, blurred right heart border, and scimitar vein (arrows). **D**. Lateral chest radiogram shows retrosternal haziness (arrows). It is the interface between the displaced mediastinal tissue and the right lung. (Fig. 24B-1B provided by Dr Yang Min Kim, The Sejong Heart Institute, Korea.)

artery hypertension in these patients may reflect several etiologies, including anomalous systemic arterial supply, pulmonary venous obstruction, redistribution of flow to the unaffected lung, associated cardiac malformations, or combinations of these factors.[7–19,21–24,26–34,39,42–59,62–67] Dua *et al.* have described a patient with totally anomalous pulmonary venous connection through the right lung and via a "scimitar" vein to the inferior caval vein.[61]

An anomalous systemic artery originating from the descending thoracic aorta may course into the affected, hypogenetic



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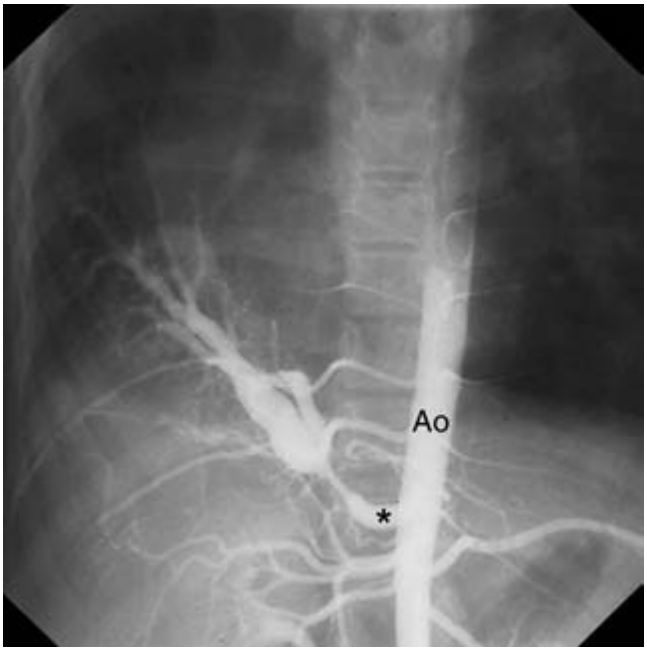

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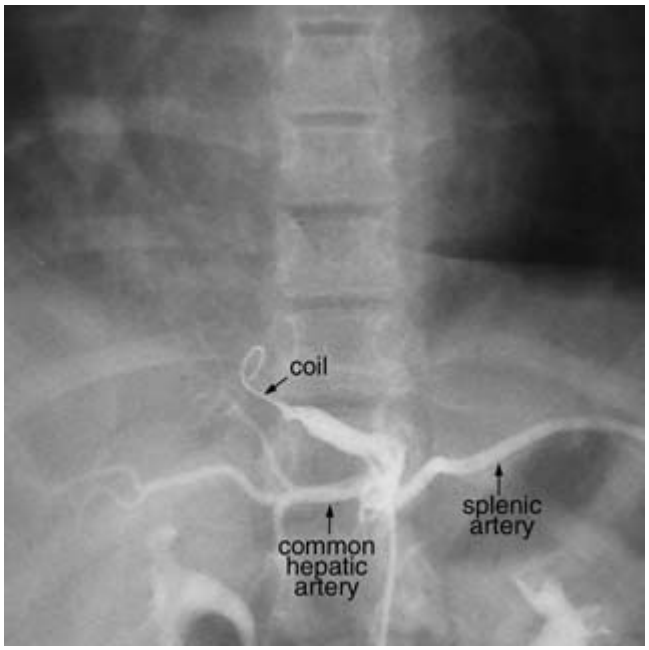

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Fig. 24B-2 Scimitar syndrome with anomalous systemic arterial supply to the right lower lung. **A**. Venous phase frame of the right pulmonary arteriography shows the scimitar vein draining the whole right lung. It shows mild stenosis (asterisk) of its connection to the right atrium (RA)–inferior vena caval junction. **B**. Abdominal aortogram shows an aberrant branch (asterisk) supplying the lower part of the right lung. **C**. The branch was embolized with a coil (arrow).

right lung.[7–24,26–34,39,42–59,62–67] This systemic artery when large causes a large left-to-right shunt, congestive heart failure, and pulmonary artery hypertension. In some patients, this anomalous systemic artery is the sole source of pulmonary blood flow, while in others it is part of dual supply (reflecting distribution of the ipsilateral pulmonary artery to the same segment of lung supplied by the anomalous systemic artery). However, true pulmonary sequestration from both bronchial and pulmonary arterial connections is not common.[7,9B,20,68–73] The unique patient with severe pulmonary artery hypertension reported by Goldstein and colleagues demonstrated severe hypoplasia of the right and left branch pulmonary arteries with a normal-sized main pulmonary trunk, bilateral infradiaphragmatic systemic arteries to the lungs, and abnormal systemic and pulmonary venous connections.[74] One can then tabulate the potential anatomical issues in the scimitar syndrome (see Table 24B-1).

Associated cardiovascular anomalies

Atrial septal defect of the secundum type is perhaps the most common associated cardiac anomaly. Other anomalies include patent arterial duct, coarctation of the aorta, tetralogy of Fallot, "single" ventricle malformation, anomalous left coronary artery from the pulmonary trunk, anomalous origin of the left circumflex coronary artery from the pulmonary trunk, double-outlet right ventricle, hypoplastic left heart syndrome, pulmonary vein stenosis of the unaffected lung, pulmonary

Table 24B-1 Variables in scimitar syndrome

Hypoplasia or absence, or abnormal branching of the right pulmonary artery
Abnormal branching and stenosis or the left pulmonary artery
Systemic arterial supply
Dual systemic and pulmonary arterial supply
Pulmonary sequestration from the bronchial supply
Pulmonary hypoplasia and/or dysplasia
Abnormal lung lobation including horseshoe lung
Diaphragmatic anomaly; defect and accessory diaphragm
Communication with gastrointestinal tract

arteriovenous fistulae, pulmonary arterial stenoses, persistence of the hepatic venous plexus, hypoplasia of the inferior vena cava, etc.[10,75–77]

Outcome analysis

There is little information on the fetal recognition of this syndrome or the outcome of pregnancies with this malformation. Abdullah and colleagues have shown that fetal cardiac dextroposition and right pulmonary artery hypoplasia in the absence of an intrathoracic mass are important signs of right lung hypoplasia, which can be associated with significant pathologic cardiac and extracardiac conditions.[78] Using this approach, they identified 10 cases by fetal echocardiography to have a normal cardiac axis, but the heart was shifted into the right chest and the amount of right lung tissue was reduced. At birth seven of the infants had confirmed structural heart disease (70%), including three with scimitar syndrome. Michailidis and colleagues reported the case of a fetus that presented with cardiac asymmetry and malposition of the fetal heart.[79] Postnatally, the scimitar syndrome was confirmed at cardiac catheterization. Retrospective reconstruction of three-dimensional power Doppler volumes, obtained during fetal life, allowed direct visualization of the abnormal aortopulmonary collateral vessel. This had not been seen on conventional scans. This case demonstrated the strength of three-dimensional sonographic techniques for the delineation of complex vascular anatomy confirming that a prospective diagnosis of scimitar syndrome should be possible during fetal life.[79] This syndrome has been identified in siblings and there is female predominance of about 1.4/1.[79A] Shibuya and his colleagues from the Toronto Hospital for Sick Children have assessed the accuracy of echocardiography in establishing and sorting out the many facets of this diagnosis.[80] The scimitar syndrome was diagnosed in 27 patients seen between July 1974 and May 1993. All available echocardiograms taken before surgery or death were reviewed. Age at presentation ranged from 1 day to 14 years. Dextrocardia or mesocardia was noted in 70%, atrial septal defect in 70%, and increased right ventricular dimension in 70% of the patients. The ratio of the proximal and distal diameters of the right/left pulmonary arteries was reduced 0.68 ± 0.17 and 0.66 ± 0.17, respectively. "Blunting" of the right side of the left atrium was seen in all patients with total anomalous right pulmonary venous drainage and none with partial drainage. Anomalous right pulmonary venous drainage was characterized in 91% of echocardiograms with color flow mapping vs. 14% without color flow mapping ($P < 0.0002$). Aortopulmonary collateral arteries were detected in all four cases in which color flow mapping was performed, but not detected otherwise. For those patients requiring surgical intervention, cardiac catheterization and angiographic investigations are still required.

The clinical expression of this syndrome is diverse.[10,10A,13,14,81] Some infants present in severe congestive heart failure and pulmonary artery hypertension, but this complex can also be diagnosed in an otherwise asymptomatic adult who has had a routine chest x-ray. A not infrequent mode of presentation is the recognition of this syndrome in the child being evaluated for recurrent chest infections. Because the chest ipsilateral to the hypogenetic right lung may be smaller than the contralateral chest, patients may present for evaluation of this asymmetry, or for scoliosis. Neonates or young infants with the scimitar syndrome may on occasion be very ill. Factors contributing to early presentation include severely obstructed pulmonary venous connections, usually right-sided, but occasionally bilateral; association with other complex cardiac malformations; and/or the presence of a very large systemic artery originating from the descending thoracic aorta and connecting to the sequestered lobe.[10,10A,12,13,16,20,21,23,26,47,62–67] Indeed, a large systemic artery alone originating from the descending thoracic aorta and terminating in one lung may result in congestive heart failure. Finally in the baby with scimitar syndrome, the presence of stridor should serve to remind one of the association of laryngeal problems, including clefts, etc.[82]

Apparently not all patients with scimitar syndrome require surgical intervention. The asymptomatic child, adolescent, or adult with a small left-to-right shunt, normal pulmonary artery pressures, and a normal left ventricular end-diastolic volume can be followed conservatively. Some patients with primary respiratory symptomatology who are found to have a sequestered right lower lobe may benefit from lobectomy and interruption of the systemic artery originating from the descending thoracic aorta.[83] Other patients may benefit solely from interruption of the collateral supply, either by catheter-based occlusion or surgical ligation assuming that there is dual vascular supply to the involved lung segment.[10,10A,62–71] For those who are only mildly symptomatic from a large left-to-right shunt, it may be difficult to sort out how much of the shunt is from: (1) the anomalous systemic arterial supply; (2) the left-to-right shunt from the anomalously connected right pulmonary veins; (3) shunting at atrial level through the often present atrial septal defect. Sometimes it is worth while to see how much interruption of the systemic collateral artery alone reduces the magnitude of the left-to-right shunt. There are two approaches to deal with the anomalously connected right pulmonary veins: (1) reimplantation into the left atrium; or (2) tunneling the right pulmonary veins within the right atrium to the left atrium either through a naturally occurring or surgically-created atrial septal defect. Both procedures can lead to right pulmonary venous obstruction postoperatively, especially in the young, small, ill neonate or infant. In our experience, this tunnel all-too-frequently becomes narrowed or obstructed, producing severe impedance to the right pulmonary veins.[66] For those patients with a crossover lung segment, it may be difficult to perform a lobectomy, so this complex is fraught with a host of potential complications related to surgical intervention.

Dupuis and his colleagues reported on the outcome of surgical intervention for the scimitar syndrome in 37 patients from a consortium of French hospitals.[84] The results were disappointing irrespective of the surgical technique that was

used (reimplantation of the right pulmonary veins in the left atrium, lobectomy, pneumonectomy). Only 12 patients had a satisfactory postoperative outcome and good long-term results; 21 patients had long-term chronic respiratory failure with a reduced exercise capacity and 4 patients died after surgery. Of the 21 patients with long-term sequelae, 17 had a thrombosis of the anastomosis between the right pulmonary veins and the left atrium; this occurred immediately after surgery.

Huddleston and his colleagues from the St Louis Children's Hospital have reviewed their experience with the infantile presentation of the scimitar syndrome.[65,85] They identified 12 such patients. The average age at presentation was 6 weeks. The most common symptom at presentation was tachypnea. The chest roentgenogram demonstrated dextroposition of the heart and hypoplastic right lung. Only 1 patient had the classic "scimitar sign." Cardiac catheterization demonstrated pulmonary hypertension (pulmonary artery systolic pressure, 73.9 ± 21.8 mmHg). The Qp:Qs was 3.1 ± 1.5:1. Two patients with severe associated anomalies were treated medically and both died. Two patients underwent occlusion of the systemic collaterals; one died and the other ultimately underwent complete repair because of persistence of the symptoms of heart failure. Two patients had primary right pneumonectomy and both are alive and well. Seven patients underwent complete repair (one after coil occlusion of the systemic arterial collaterals) and 1 died; 3 subsequently developed occlusion of the baffle from the orifice of the anomalous pulmonary vein and required pneumonectomy. Two patients required lung transplantation due to persistent pulmonary hypertension in 1 and recurrent bilateral pulmonary venous stenosis in the other. They concluded that although repair of the anomalous venous return and ligation of collaterals is generally recommended, right pneumonectomy (either as primary therapy or if repair failed) had similar early and late results.

Gao and his colleagues from the Hospital for Sick Children in Toronto[62] reviewed those anatomic and physiologic factors most responsible for severe symptoms and poor prognosis of infants with the scimitar syndrome. Identifying 13 consecutive infants with this syndrome, it became apparent that anomalous systemic arterial supply, severely obstructed pulmonary venous connections, and complex congenital heart malformations not surprisingly contributed to the poor prognosis in young infants. While the outlook for the symptomatic baby or infant with the scimitar syndrome is poor, the prognosis for the patient with the so-called "adult" form of the scimitar syndrome is excellent. These patients characteristically have normal pulmonary pressure and a small left-to-right shunt, and most should live a normal life without surgical intervention.[62]

Several years ago we reviewed our surgical experience with the scimitar syndrome.[66] Thirty-two patients with scimitar syndrome were seen in the period between 1975 and 1995 at the Toronto Hospital for Sick Children. There were 11 male and 21 female patients. The median age at diagnosis was 7 months (mean, 7.7 years; range, 1 day to 70 years). Patients in whom the diagnosis was made during the first year of life (infantile group, $n = 19$) had more severe symptoms and had a higher incidence of heart failure (11/19 vs. 0/13) and of pulmonary hypertension (11/19 vs. 1/13) than did the patients in whom the diagnosis was made after age 1 year (adult group, $n = 13$). In 17 patients the anomalous pulmonary venous drainage was repaired by baffling the vein to the left atrium. The median age at this operation was 5.8 years (mean, 14.8 years; range, 6 months to 70 years). No deaths occurred in this surgical group during a mean follow-up period of 8.9 years (range, 1.6–17 years). Eight patients (47%), however, had evidence of pulmonary venous stenosis or obstruction after repair, and two required reoperation for pulmonary venous obstruction. All six children in the infantile group had postoperative pulmonary venous stenosis, compared with two of 11 older patients. Postoperative quantitative pulmonary perfusion scans performed in 15 patients demonstrated reduced flow to the right lung (24%; range, 0–59%). On the basis of this experience we concluded that age at detection of scimitar syndrome is important in predicting outcome. Furthermore surgical repair seldom results in normal blood flow to the right lung but may abolish the left-to-right shunt. Unfortunately, postoperative pulmonary venous obstruction is prevalent, especially in the infants. This experience has led us to be quite conservative in the surgical management of the anomalous pulmonary venous connections in this syndrome.

Brown and his colleagues have reported excellent results of direct anastomosis of the scimitar vein into the left atrium without the use of cardiopulmonary bypass.[66B] The series was small, only 9 patients, and the mean age was 11.5 ± 17.6 years. None of the nine patients had an associated atrial septal defect and none had pulmonary artery hypertension. At a modest follow-up, echocardiography demonstrated a patent anastomosis without restenosis. This approach seems applicable to this subset of patients.

Lobectomy has been advocated for those patients with bronchiectasis and severe refractory chronic infection. In some patients this has proven quite beneficial, but in others, lobectomy and/or pneumonectomy have resulted in chronic respiratory insufficiency.[83] Hemoptysis may on occasion be particularly severe, again a possible indication for lobectomy.[86] Thus surgical extirpation of lung tissue should be carried out with caution.

In those patients who are followed medically, the following issues are important to evaluate and consider in follow-up:

- recurrent chest infections – ?bronchiectasis
- evidence of pulmonary artery hypertension
- right ventricular volume overload
- left ventricular volume overload
- cardiopulmonary function with ventilation/perfusion mismatch
- skeletal deformities.

Some of the same issues are germane to the patient who has been operated upon with diversion of the right pulmonary veins to the left atrium:

- recurrent chest infections – ?bronchiectasis
- ?right pulmonary vein obstruction
- evidence of pulmonary artery hypertension
- right and/or left ventricle volume overloading
- cardiopulmonary function with ventilation/perfusion mismatch
- skeletal deformities.

From clinical experience, especially in the symptomatic neonate or young infant, one must be cognizant of the high frequency of postoperative difficulties related to re-implantation or diversion of the right pulmonary veins to the left atrium. One should remember that stenosis of the pulmonary veins in the contralateral lung may also be present, further complicating an already difficult situation.

All references can be found at the end of the book. See pp. 732–4 for Chapter 24B.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

24C

Anne I. Dipchand, Robert M. Freedom, and Shi-Joon Yoo

The Divided Left Atrium (Cor Triatriatum)

Cor triatriatum, the classic form of a divided left atrium, refers to a condition in which the left atrium is partitioned by a membrane into two chambers. The signal description was made by Church in 1868,[1] with successful operative intervention first described in 1956 by two different groups.[2,3] The number of reported cases, treated or untreated, since that time is small owing to its rarity.

Incidence

Cor triatriatum is a rare cardiac diagnosis, being found in 9 of 15 104 children (0.06%) at the Hospital for Sick Children over a 24-year period (1950–1973).[4] Similarly, Boston Children's Hospital Experience reported 25 cases in *c.* 14 000 cardiac patients.[5] In the New England Regional Infant Cardiac Program, cor triatriatum was found in 5 of 2251 infants with heart disease (0.22%).[6] Most recently, the prospective Bohemian Survival Study reported 5 cases in 5030 patients with congenital heart disease (0.01%) or a prevalence of 0.006 per 1000 live births.[7] The defect is not genetically transmitted and familial aggregation has not been described.

Morphology

Hearts with cor triatriatum are usually left sided with a normal atrial arrangement and concordant atrioventricular and ventriculoatrial connections. In cor triatriatum, a fibromuscular membrane separates the left atrium into an upper and a lower chamber[8–15] (Figs 24C-1, 24C-2). The upper chamber usually communicates with the pulmonary veins while the lower chamber communicates with the atrial appendage and the vestibule of the atrioventricular valve. The position of the membrane relative to the left atrial appendage is the feature that distinguishes cor triatriatum from the supravalvular stenosing mitral ring (see Chapter 12). The impact of the membrane is to impede the flow of pulmonary venous blood into the systemic circulation, thus promoting pulmonary hypertension. Most commonly, the membrane has one or more small perforations allowing blood to flow from the upper to the lower chamber. The perforation(s) between the upper and lower chambers varies in size which accounts for the variability in timing of presentation. The morphogenesis of cor triatriatum remains contentious.[10,16]

Associated cardiac lesions

An atrial septal defect is associated with cor triatriatum in 70% to 80% of cases.[9,11,12,17–19] The atrial septal defect has been reported to communicate with either the upper or the lower chamber, thereby influencing the symptoms and mode of presentation.[11,12,18] Other rare morphologic forms have been reported and several classification schemes have been reported, taking into consideration the location of the atrial septal defect and the drainage of the pulmonary veins.[8,9]

Associated cardiac lesions are common with cor triatriatum, occurring in over 75% of cases in reported series.[9,17–19] Most commonly, cases of cor triatriatum have been reported associated with both total and partial anomalous venous drainage,[8,9,11,12,17–23] left superior vena cavae,[8,9,11,12,17–19,22,23] atrioventricular septal defect,[5,8,9,12,17,19,23] patent ductus arteriosus,[8,9,12,19,23] and ventricular septal defect.[5,9,11,12,17] Also described, though rare, include tetralogy of Fallot,[9,12,17] mitral stenosis or atresia,[9,12] double outlet right ventricle,[9] coarctation of the aorta,[5,9,12,18] Ebstein's anomaly of the tricuspid valve,[12] aortic atresia,[12,23] complete and corrected transposition of the great arteries.[5,12,19,23] A divided left atrium has been occasionally observed in the patient with juxtaposition of the atrial appendages.[15]

Associated non-cardiac lesions

There are very few reported non-cardiac anomalies associated with cor triatriatum. Geggel and Fulton, reported an infant with Dandy-Walker malformation and multiple facial and intrathoracic hemangiomas.[22] Marin-Garcia *et al*. reported the anatomy of a heart from an infant with Hurler's syndrome and cor triatriatum.[12] Van Son reported a 7-month-old infant with unspecified chromosomal abnormalities and severe associated cardiac defects.[17]

Outcomes

The timing and mode of presentation in patients with cor triatriatum varies significantly depending on the degree of obstruction to pulmonary venous return and associated lesions. The condition rarely presents in isolation in the neonate, but young infants, symptomatic from pulmonary venous obstruction, have been recognized by echocardiography or angiocardiography to have cor triatriatum. When there is no or just mild obstruction, there may be no symptoms and no reason to suspect disease, with reports of incidental diagnoses in adulthood as late as in the eighth decade.[5,24–26] In terms of imaging algorithms, invasive imaging for this condition has been completely replaced by cross-sectional echocardiography, MR imaging and computed tomography.[15,25,27–36]

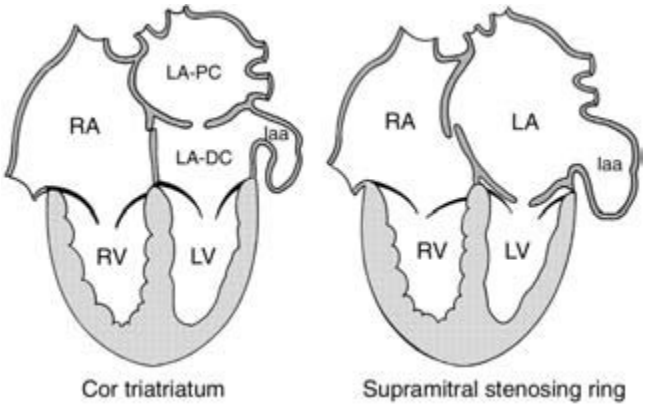
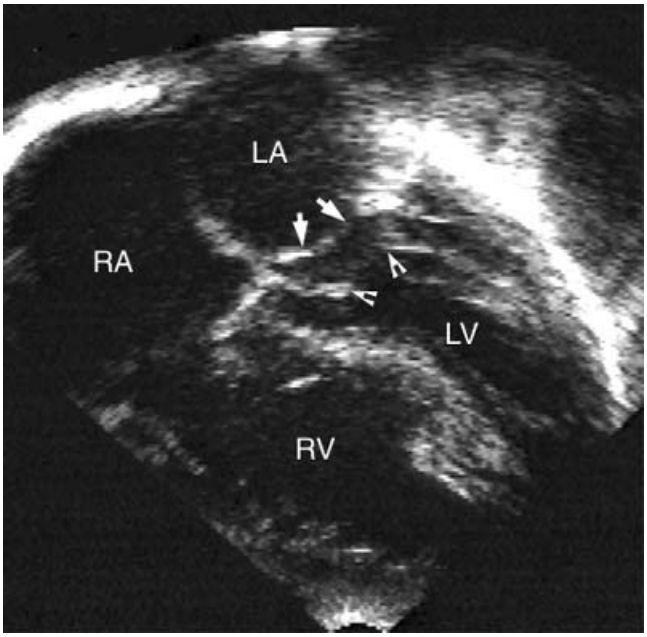


Fig. 24C-1 Obstruction within the left atrium, cor triatriatum vs. supramitral stenosing ring. In cor triatriatum, the obstructing membrane is above the orifice of the left atrial appendage (laa). In contrast, the membrane of the supramitral stenosing ring is below the left atrial appendageal orifice. Notice that the left atrial appendage is dilated in supramitral stenosing ring because it is above the obstruction, while it is not dilated in cor triatriatum. LA, left atrium; LA-DC, left atrium, distal chamber; LA-PC, left atrium, proximal chamber; LV, left ventricle; RA, right atrium; RV, right ventricle.



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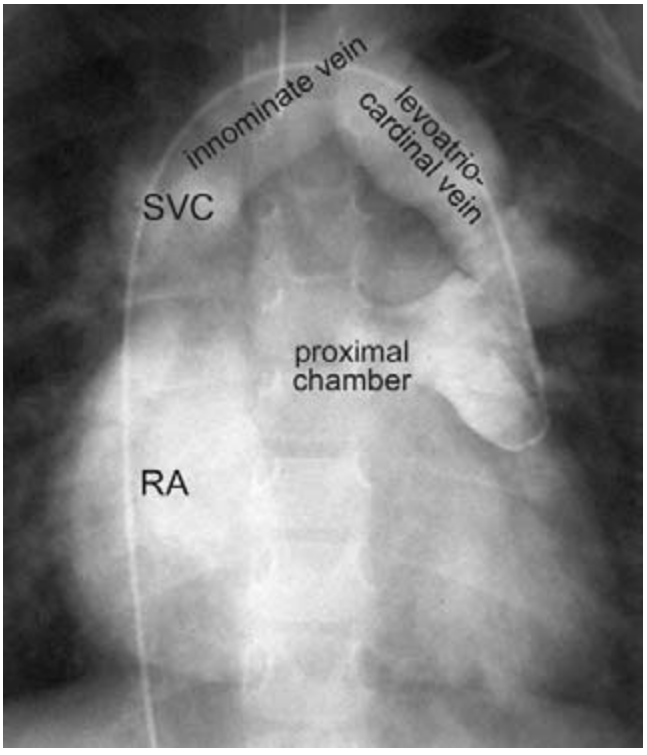

B

Fig. 24C-2 Cor triatriatum. **A**. Echocardiogram in four-chamber view shows a membrane (arrows) in the left atrium (LA) above the mitral valve (arrowheads). The membrane arises from the lower part of the atrial septum. The atrial appendage opened to the distal chamber in other plane. **B**. Injection into the proximal chamber shows drainage of the pulmonary venous return into the innominate vein through the levoatriocardinal vein. LV, left ventricle; RA, right atrium; RV, right ventricle; SVC, superior vena cava.

The mortality for untreated cases that present in the first year of life is as high as 70%.[12,18] Operative resection of the obstructing membrane is the treatment of choice.[8,11,18,19,23] Cor triatriatum is a relatively simple defect to correct with a low operative mortality[18] and excellent long-term results in the absence of severe cardiac anomalies or severe clinical instability at the time of surgery.[8,11,17,19,23] Most deaths reported in the literature were in earlier series,[12,17,19,23] critically ill infants,[8,11,12,19] or patients with severe associated cardiac defects.[8,12,17,19,23]

Richardson *et al.* reported outcomes of 21 patients from 1955 to 1978.[23] Age at time of diagnosis ranged from 1 day to 13 years. Fourteen patients (67%) underwent operative repair (13 with isolated cor triatriatum). Eight survived operative repair (62%), with 7 (88%) experiencing excellent long-term survival (all with isolated cor triatriatum). The major challenges in this series related to actual diagnosis, with only 9 of 18 patients catheterized having a correct diagnosis made before operation or death.

Oglietti *et al.* reported outcomes of 25 patients from 1959 to 1980.[19] Patients ranged from 4 months to 38 years. Again, preoperative diagnosis was made in only 56% of patients. Four patients died early, all of whom were infants with severe associated cardiac anomalies. Results were excellent in 20 of the surviving 21 patients. Similarly, Gheissari *et al.* reported outcomes of 12 patients from 1960 to 1988.[18] Age ranged from 1 month to 7.5 years. Five patients died before diagnosis or treatment. All patients treated since 1979 were correctly diagnosed by echocardiography. Six of the 7 patients who underwent operative repair survived.

Van Son *et al.* reported 13 patients who underwent surgical repair from 1960 to 1992.[17] Age ranged from 7 months to 57 years. Eleven were correctly diagnosed preoperatively (the other 2 were in 1963 and 1966). Of the 2 deaths in the series, 1 was a critically ill infant in 1963 and the other had major associated cardiac defects and a chromosomal abnormality. There

were 11 long-term survivors with 9 being in New York Heart Association functional class I. The other 2 were class II and had major associated cardiac anomalies.

Looking at the more recent surgical era, Salomone *et al.*, reported 15 patients who underwent operative repair between 1973 and 1988.[11] Age range was 15 days to 48 years. The diagnosis was correctly made in 10. There were 3 (20%) early deaths, all of whom were < 3 months old and in critical condition. There were no late events amongst the 12 survivors who were all NYHA functional class I. Rodefeld *et al.* described 12 patients seen between 1979 and 1989.[8] All patients were diagnosed before death or operation. One patient died before repair, following cardiac catheterization. Two patients died in the postoperative period, both with severe associated cardiac defect, giving a surgical mortality rate of 17% and overall mortality rate of 25%. All 9 survivors were clinically well with no late events.

HSC experience

From 1982 to 2002, there have been 34 cases of cor triatriatum diagnosed at the Hospital for Sick Children in Toronto. The median age at diagnosis was 10 months (0 days to 16 years). Modes of presentation are outlined in Table 24C-1. Associated cardiac lesions occurred in 65% of cases and are outlined in Table 24C-2. The 3 patients with complex single ventricle diagnoses included 1 with right atrial isomerism and total anomalous pulmonary venous drainage, 1 with left atrial isomerism, atrioventricular septal defect, and pulmonary atresia, and 1 with a double inlet left ventricle. Only 1 patient had associated syndromic characteristics including mild dysmorphic features and developmental delay.

Thirty-two of 34 patients were diagnosed by echocardiography. One patient in 1985 was diagnosed by cardiac catheterization and 1 of the single ventricle patients was diagnosed at the time of stage surgical palliation (previously felt to be a deviated atrial septum). Characteristics of the cor triatriatum are outlined in Table 24C-3. Patients with severe restriction to flow through the membrane or an intact membrane were diagnosed earlier as a group, at a median of 6 months.

Surgical repair specifically for cor triatriatum was undertaken in 29 patients (85%). The median time from diagnosis to surgery was 22 days (0 days to 5.7 years). Patients with severe restriction to flow through the membrane or an intact membrane had a median time from diagnosis to surgery of 1 day (0–8 days). Of these 29 patients, there have been no mortalities in up to 19 years of follow-up. Of the remaining 5 patients, 3 underwent staged surgical palliation for complex single ventricle anatomy and the cor triatriatum was not an independent factor, the 1 syndromic patient died of aspiration pneumonia before repair, and 1 patient with an unrestrictive membrane has never undergone surgical repair.

Reported rarely in the literature, restenosis of a completely excised left atrial membrane is uncommon.[8,17–19,23,37] Reoperation for incomplete resection of the membrane has rarely been reported, underlining the need for complete resection at the time of the first surgical procedure.[12,19] There are isolated reports of both blade septectomy[38] and balloon dilatation[37] for enlarging the communication between the upper and lower chambers of cor triatriatum, though operative intervention remains the procedure of choice.

The conundrum occurs when an asymptomatic child or adult is found to have a non-obstructing membrane.[20,24,26,39,40] What is the indication to remove such a membrane if a child or adult is unequivocally asymptomatic? There are a number of reports of adults surviving into their sixth, seventh, and eighth decades of life before the diagnosis of cor triatriatum is made.[20,24,26,39,40] Amongst 4000 transesophageal echocardiograms performed in one institution in adult patients, obstructive and non-obstructive forms of a divided left atrium were identi-

Table 24C-1 Mode of presentation

Asymptomatic	11 (32%)
CHF related to cor triatriatum (SOB, sweatiness, tachypnea, lethargy, grunting, cough, hepatomegaly)	10 (29%)
Failure to thrive	3 (9%)
Nonspecific respiratory complaints/URTI	3 (9%)
Low cardiac output	2 (6%)
CHF related to associated lesions	2 (6%)
SOB with exertion	1 (3%)
Chest pain	1 (3%)
Incidental finding	1 (3%)

CHF, congestive heart failure; SOB, shortness of breath; URTI, upper respiratory tract infection.

Table 24C-2 Associated cardiac lesions

None	12 (35%)
Isolated ASD	10 (29%)
PAPVD	4 (12%)
Complex single ventricle	3 (9%)
AVSD, PDA	2 (6%)
TAPVD	1 (3%)
Primum AVSD	1 (3%)
Multiple VSDs and PAPVD	1 (3%)
CoA, ASD, VSD	1 (3%)
PS, supravalve AS	1 (3%)

AS, aortic stenosis; ASD, atrial septal defect; AVSD, atrioventricular septal defect; PAPVD, partial anomalous pulmonary venous drainage; PDA, patent ductus arteriosus; PS, pulmonary stenosis; TAVPD, total anomalous pulmonary venous drainage; VSD, ventricular septal defect.

Table 24C-3 Echo characteristics of cor triatriatum

Unrestrictive hole in membrane	13 (38%)
Partial cor triatriatum – RPVs	2
Partial cor triatriatum – LPVs	1
Severely restrictive hole in membrane with systemic or suprasystemic pulmonary hypertension	13 (38%)
Mild restriction to flow through membrane	6 (18%)
Intact membrane	2 (6%)
With TAPVD	1
With decompressing vein from LA to SVC	1

RPV, right pulmonary vein; LA, left atrium; LPV, left pulmonary vein; SVC, superior vena cava; TAPVD, total anomalous pulmonary venous drainage.

fied in 7 patients.[41] Yet in other adults with previously asymptomatic cor triatriatum, the first sign leading to this diagnosis may be acute onset atrial fibrillation,[42] or in other patients important systemic thromboembolic events may be the precipitating event.[43] LeClair and colleagues reported a patient with previously undiagnosed cor triatriatum presenting with postcesarean section pulmonary edema.[44] We have attempted to clinically "unmask" or precipitate a Doppler gradient in the patient with asymptomatic cor triatriatum by giving the patient an inotrope with or without volume expansion. Although there is probably no consensus as to whether to intervene in the asymptomatic adolescent or adult, we tend towards intervention, especially in those who participate in vigorous athletic activities, or in those women considering pregnancy.

All references can be found at the end of the book. See pp. 734–5 for Chapter 24C.

The Natural and Modified History of Congenital Heart Disease
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24D

Robert M. Freedom and Shi-Joon Yoo

Partial Anomalous Pulmonary Venous Connections

One or more pulmonary veins from the right lung may connect to the superior caval vein, azygous vein, right atrium, coronary sinus, or inferior caval vein (Fig. 24D-1).[1–10] In some patients all the right-sided pulmonary veins or just one or two from one lung may connect to one of these sites. Similarly, one or more left-sided pulmonary veins may connect anomalously to the brachiocephalic vein; to the coronary sinus; to the right atrium; or to the inferior caval vein; or to the ductus venosus or portal system. A syndrome of particular interest is the scimitar syndrome, designated as such because of the radiographic appearance of the anomalously draining right pulmonary veins on the chest radiograph (See Chapter 24B). Usually, partial anomalous pulmonary venous connection is from one lung. Less commonly, both lungs may have a solitary pulmonary vein connecting anomalously either to a systemic vein or to the right atrium or coronary sinus, usually with and rarely without a coexisting interatrial communication.[4,5,9,11,12] The most common associated cardiac anomalies include the sinus venosus atrial septal defect, followed by a true secundum atrial septal defect and then the patent foramen ovale.[4,9,12] One or more pulmonary veins may connect anomalously in association with many forms of congenital heart disease. Among the more common associations include the scimitar complex ± crossover lung segment; left isomerism; complex forms of divided left atrium, etc. The diagnosis of partial anomalous pulmonary venous connection has evolved from angiographic imaging to echocardiographic imaging, and today, especially in the pediatric patient, angiographic imaging is rarely required.[12–15] Wong and her colleagues from the Toronto Hospital for Sick Children studied with echocardiography 50 patients between January 1983 and December 1993, with partial anomalous pulmonary venous drainage (with or without an associated atrial septal defect as the only other significant intracardiac defect).[13] Routine echocardiographic reports were reviewed, and the results were compared with surgical or catheterization findings. Confirmation of the diagnosis was available in 45 patients whose data were subsequently used for risk factor analysis. The median age at echocardiography was 4.1 years (range 1 month to 18 years). Right-sided drainage was present in 43 patients (86%), with left-sided drainage in 7 (14%). Thirteen patients had an intact atrial septum, 7 a patent foramen ovale and 30 a secundum atrial septal defect. Right ventricular dilation was observed in 46 patients. Two had normal dimensions (two not assessed). The diagnosis was missed by echocardiography in 15 (33%) of the 45 patients with a confirmed (surgical or angiographic) diagnosis. The year of study and use of color flow mapping were the only significant variables related to detection rate (7% missed diagnosis with vs. 62% without the use of color flow, $P < 0.0005$). The median year of missed diagnosis was 1985 versus 1990 ($P < 0.002$).[13] Transesophageal echocardiography accurately defined the site of drainage in all three patients in whom it was utilized. Hemodynamic evaluation may be required for determination of operability in the adult with pulmonary vascular disease.[16,17]

Outcome analysis

The presence of one or two anomalously draining pulmonary veins in isolation does not impact on fetal cardiac form and function. As stated elsewhere, the clinical findings may be similar to that of an uncomplicated atrial septal defect, or even more subtle if there is only one anomalously connected pulmonary vein. Thus usually these patients come to attention beyond early infancy, similar in timing of presentation like the child with a secundum atrial septal defect. The indications to repair partial anomalous pulmonary venous connections include clinical and echocardiographic evidence of right ventricular volume overload.[4,9] We have used nuclear medicine to quantitate the magnitude of the left-to-right shunt. Kirklin and Barratt-Boyes and others have reviewed the various types of surgical procedures used for correction of this anomaly.[18–28] Suffice it to say, surgical mortality approaches zero for repair of partial anomalous pulmonary venous connections in isolation.[18] Van Meter and colleagues identified 13 patients with anomalous pulmonary venous return from the left lung, all of whom underwent surgical correction.[20] The patients ranged in age from 15 months to 40 years. Seven were asymptomatic, and six had symptoms ranging from recurrent pulmonary infection to moderate congestive heart failure. Six had anomalous venous return from the entire left lung, and seven had anomalous return from the upper lobe only. Eight of the patients had associated cardiovascular anomalies. Four of the patients underwent surgical correction via a sternotomy approach with cardiopulmonary bypass to allow correction of coexisting intracardiac anomalies. The remaining patients underwent surgical repair through a left thoracotomy. The technique included high ligation and division of a persistent left vertical vein with anastomosis to the left atrium at the site of partial excision of the atrial appendage. There were no deaths in this series.[20] There is less information concerning residual patency of the reconnected pulmonary vein, especially when a left-sided pulmonary vein is reattached to the left atrial appendage.[18, 27–29]

Essene and Moller have reported the outcomes of surgery for partial anomalous pulmonary venous connections for the

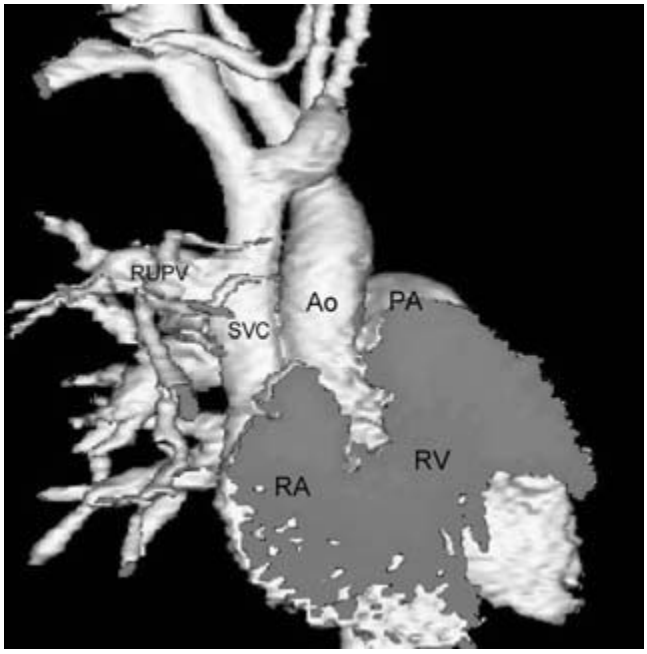
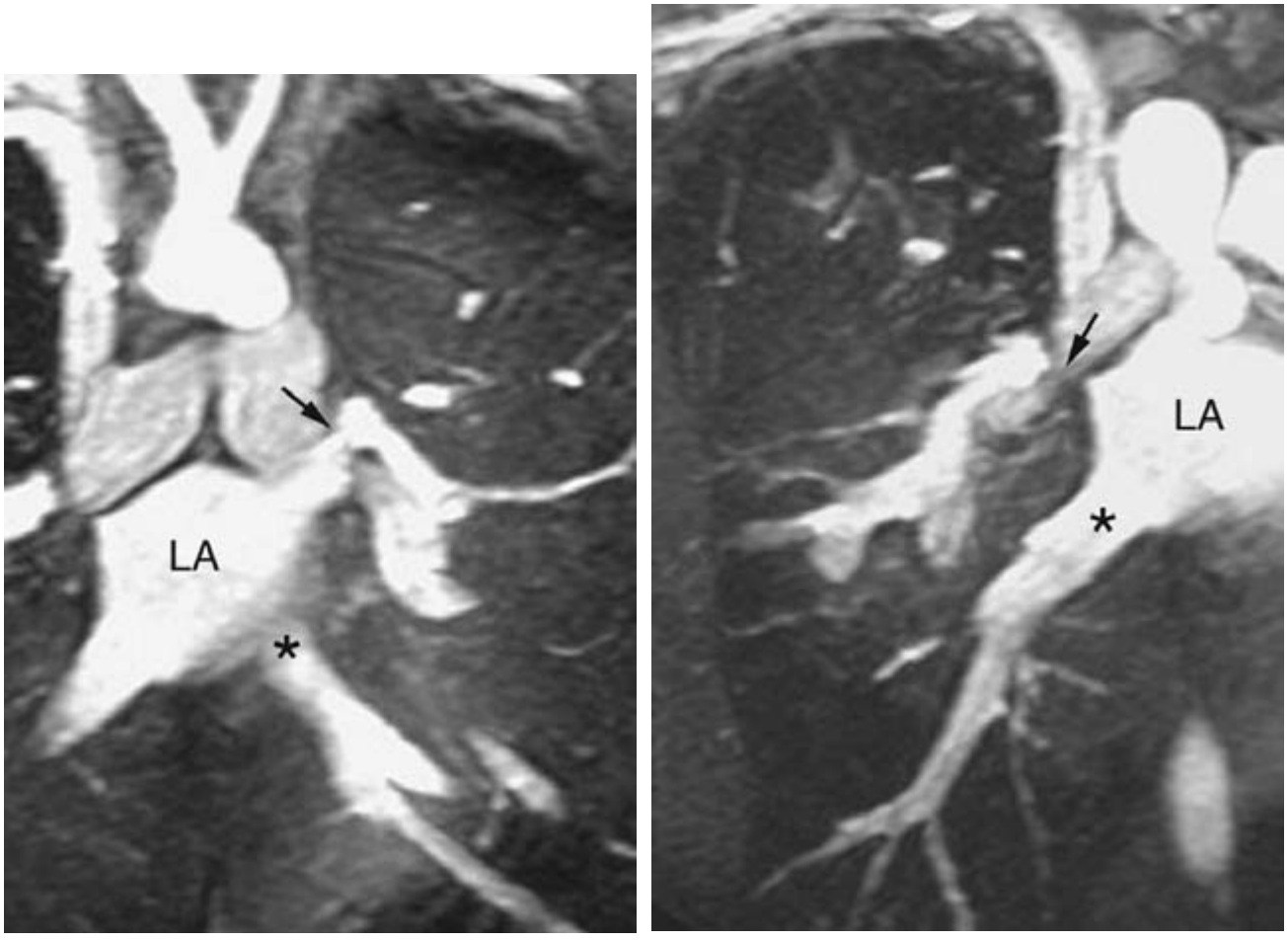


Fig. 24D-1 Three-dimensional image of contrast-enhanced MR angiography shows partial anomalous pulmonary venous connection of the right upper pulmonary vein (RUPV) to the superior vena cava (SVC). Ao, aorta; PA, pulmonary artery; RA, right atrium; RV, right ventricle.



A B

Fig. 24D-2 Postoperative obstruction of the pulmonary veins after surgical repair of partial anomalous pulmonary venous connection of the right upper and left upper pulmonary veins. Contrast-enhanced MR angiogram shows complete occlusion of the right upper pulmonary vein (arrow in **A**) and severe stenosis of the left upper pulmonary vein (arrow in **B**). Both sides lower pulmonary veins (asterisks) are not stenotic. LA, left atrium.

Pediatric Cardiac Care Consortium.[30] Excluding the patients with the scimitar syndrome, 42 patients underwent operation for partial anomalous pulmonary venous connections.[30] The connection was to the superior vena cava in 37%, to the right atrium in 18%, and to the left innominate vein in 17%. There were no deaths in this series, but again no information about residual patency was provided, etc.[30] Gustafson and his colleagues reported their experience between 1964 and 1987, with 39 patients with partial anomalous pulmonary venous connection to the right side of the heart, ranging from 2 to 52 years old.[23] At least one anomalous pulmonary vein arose from the right upper lobe in 38 patients and right middle lobe in 30 patients and connected to the superior vena cava in 28 patients and the right atrium only in 11 patients. An atrial septal defect was present in 32 patients (82%). Patients who had partial anomalous pulmonary venous connection to the superior vena cava–right atrium junction, the right atrium or both were treated by septal translocation (two patients) or patch redirection of the anomalous pulmonary venous flow to the left atrium through a native atrial septal defect (eight patients) or a surgically created atrial septal defect in two patients with intact atrial septum. For partial anomalous pulmonary venous connection to the high superior vena cava (27 patients), the superior vena cava was transected and oversewn above the anomalous veins. The anomalous pulmonary venous flow was redirected through the proximal superior vena cava into the left atrium across a sinus venous atrial septum defect (22 patients) or a surgically created atrial septal defect in five patients with intact atrial septum. The atrial septal defect was coapted to the intracardiac orifice of the superior vena cava, and the distal superior vena cava was anastomosed to the right atrial appendage. One 31-year-old woman with severe pulmonary hypertension died early and was the only death in the series. A technical error early in the series resulted in one symptomatic superior vena cava obstruction. Only one patient remains in sick sinus syndrome late. All patients remain well over long follow-up (1 to 24 years). Postoperative catheterization or echocardiography has revealed no intracardiac defects, pulmonary venous obstruction, or superior vena cava obstruction (except the one technical error). Correction of partial anomalous pulmonary venous connection should be individualized according to the site of connection of the anomalous pulmonary veins and the location of the atrial defect to minimize undesirable postoperative sequelae often associated with other methods of repair.

Stewart and his colleagues reviewed the early and late surgical results in 15 consecutive patients with partial anomalous pulmonary venous connection operated between 1973 and 1983, and all survived.[25] They have been followed for a mean of 6 years and a minimum of 2 years. Nodal rhythm and atrial dysrhythmias were present in 6 patients (40%) early after operation. However, every patient resumed normal sinus rhythm prior to hospital discharge except 1 adult who remained in the preoperative rhythm of atrial flutter-fibrillation. No patient has clinical evidence of a residual atrial level shunt or superior vena cava obstruction. All have received an excellent clinical result, and none, except the patient in chronic atrial fibrillation, require cardiac medication.

Among the cataloged, albeit uncommon complications of surgery for partial anomalous pulmonary venous connections is included residual pulmonary venous obstruction (Fig. 24D-2), pulmonary venous collaterals secondary to superior vena cava stenosis resulting in right-to-left shunting following repair of a sinus venosus atrial septal defect; superior vena caval obstruction, and a residul right-to-left shunt.[4,9,17,18,20,23,24,31–33] In this last situation, some have used a Rashkind double-umbrella occlusion device to close the defect.[33] We have been tempted not to intervene on the pediatric patient with a solitary anomalously connected right pulmonary vein to the superior vena cava, especially when there is no or minimal evidence of right ventricular volume loading. Yet some of these patients many years later in adulthood demonstrate clinically important findings of a volume-loaded right ventricle, requiring surgical intervention. Furthermore, some of the adult patients with partial anomalous pulmonary venous connections had developed severe pulmonary hypertension or congestive heart failure, again similar to the adverse outcomes for some adults with secundum atrial septal defects. As with the experience with the surgical repair of the sinus venosus atrial septal defects, postoperative sinus node dysfunction has not been a problem following repair of partial anomalous pulmonary venous connections.[34]

All references can be found at the end of the book. See pp. 735–6 for Chapter 24D.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

24E

Robert M. Freedom, Ian Adatia, John G. Coles, and Igor Konstantinov

Congenital Stenosis of the Individual Pulmonary Veins

Individual stenosis of one or more pulmonary veins is a rare and very serious malformation (Figs 24E-1, 24E-2). First described by Reye in 1951,[1] it is perhaps the least common of those anomalies obstructing inflow to the left heart, certainly less common than divided left atrium, supravalvular stenosing mitral ring or congenital mitral stenosis.[2–16] When this condition involves importantly all four pulmonary veins, the condition produces severe pulmonary hypertension, then right ventricular failure and is usually refractory to routine surgical and catheter-based therapy, concluding in death of the patient. In some aspects this disorder resembles pulmonary veno-occlusive disease or syndrome (see Chapter 43). Postoperative pulmonary venous obstruction is considered in Chapter 24A.

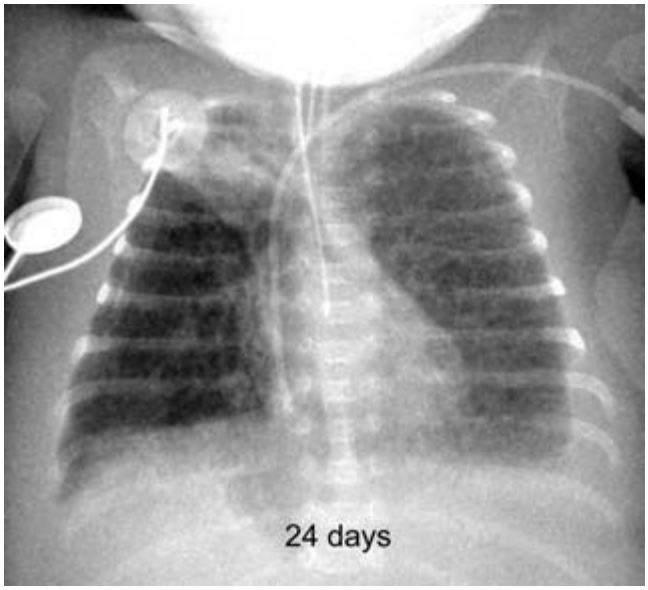
Prevalence

This condition is rare and is not listed in the New England Regional Infant Cardiac Program, the Baltimore–Washington Infant study, nor in the Prospective Bohemia Survival Study.[17–19] Pulmonary vein stenosis accounted for only 0.4% to 0.6% of specimens published from large registries of cardiovascular abnormalities.[2,7] The Cardiac Registry of the Children's Hospital in Boston has about 3216 specimens, 30 of which demonstrate congenital pulmonary vein stenosis (0.093%). An additional 3 specimens were diagnosed with pulmonary veno-occlusive disease (personal communication, Richard Van Praagh, March 8, 2002). There is no known genetic nor gender predilection, although familial cases have been reported.[2] Mortensson and Lundstrom in March 1974 reported a patient with congenital obstruction of the pulmonary veins and commented that only 12 patients had been described with this rare condition at that time.[8] Also in 1974, Park and his colleagues reported 2 patients with this condition, and their review of the literature to the time of their publication yielded 22 additional cases including the signal case of Reye.[7] Bini and her colleagues in 1984 reviewing the literature found 38 reported cases, and they stated that in most the diagnosis was made at surgery or at post-mortem.[9] By 1986, Belcourt and his colleagues state that about 49 cases had been reported in the English and French literature.[20] The Mayo Clinic with its large practice of congenital heart surgery reported in 1995 its experience with congenital and acquired pulmonary vein stenosis.[21] This group identified 8 patients (age range, 3 months to 43 years; median age, 1.5 years) who underwent surgical relief of pulmonary vein stenosis. Only 2 of these 8 had congenital pulmonary vein stenosis, while 5 had pulmonary vein stenosis that was acquired after surgical treatment of total anomalous pulmonary venous connection. One patient had pulmonary vein stenosis associated with idiopathic mediastinal fibrosis and calcification.[22–27] More recently, the Texas Children's Hospital reported catheter-based intervention in 33 patients with pulmonary vein stenosis, 20 of whom had congenital stenosis of one or more pulmonary veins.[28]

Pathology

Congenital pulmonary vein stenosis is a complex condition characterized by anatomic and functional narrowing of the junctional area between one or more pulmonary veins and the left atrium.[1–15] Individual stenosis of one, two, three or all the pulmonary veins may occur either in isolation or with a wide range of congenital heart malformations.[1–15] The incidence of associated cardiac defects has been reported to range from 30% to 80%, occasionally higher.[9,29–31] Among the associated cardiac anomalies include ventricular septal defect, atrial septal defect, patent arterial duct, complete transposition of the great arteries, divided left atrium, total anomalous pulmonary venous connections, direct entry of the superior caval vein into both atria, Ebstein's anomaly of the tricuspid valve; dominant right form of atrioventricular septal defect, valvar aortic stenosis, tetralogy of Fallot; pulmonary atresia and intact ventricular septum; scimitar syndrome with crossover lung segment, etc.[2–15,28–39]

Congenital pulmonary vein stenosis is usually considerably more complex than merely stenosis of the pulmonary vein–left atrial junction.[2–14,30,40–42] The obstruction may seemingly be diaphragmatic, and this type seems the most likely to respond to surgical intervention.[8] However, both the extraparenchymal and intraparenchymal pulmonary veins may be hypoplastic, with marked alteration of the normal morphology of the pulmonary veins.[2,40–42] With conspicuous involvement of all four pulmonary veins, the prognosis is even worse. Conceivably in some patients the disease is less complex in the neonatal period, but with the passage of time, the increased velocity of pulmonary venous blood and the effects of pulmonary venous hypertension together promote progressive distortion of the integrity of the pulmonary venous pathways. Some patients have been identified with unilateral pulmonary vein atresia, presumably, but not invariably, reflecting progression of the stenotic process. It is clear that in some patients pulmonary vein atresia is a true congenital condition probably reflecting incomplete incorporation of a pulmonary vein into the left atrium.[42–52] The condition of isolated pulmonary vein atresia is only rarely established in the neonate.[45] More commonly pulmonary vein atresia is defined as the etiology of both hypoplasia of the pulmonary artery ipsilateral to the pulmonary vein atresia as well as



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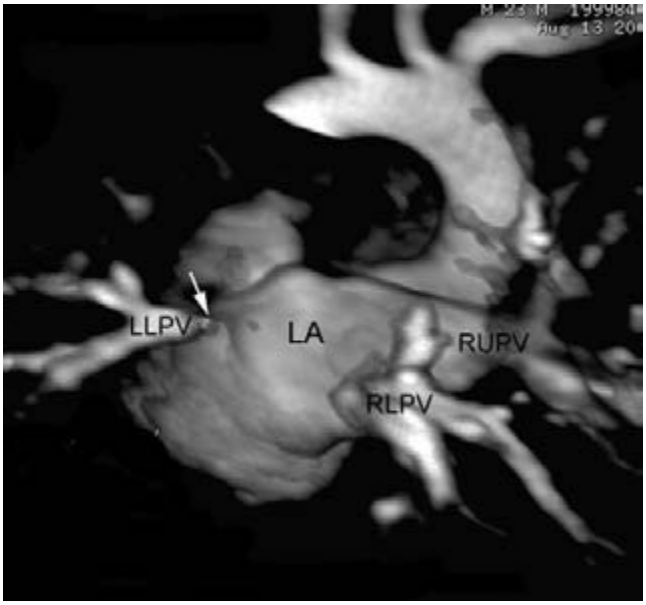

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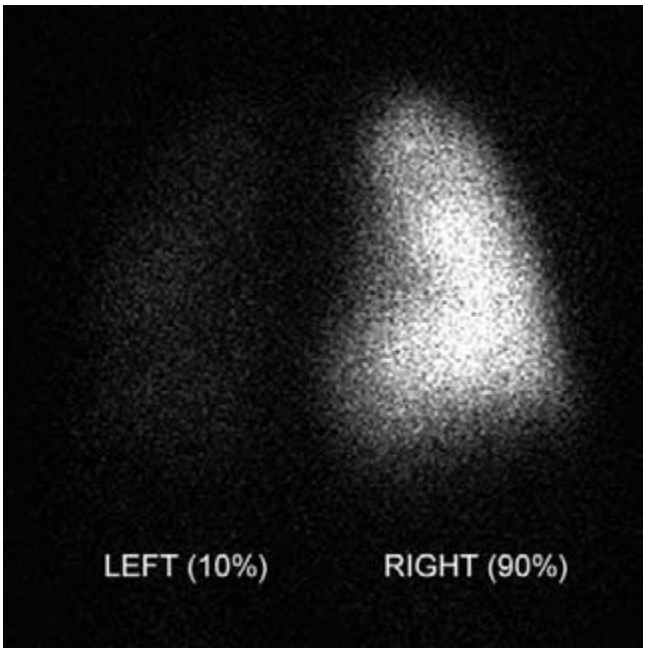


C

Fig. 24E-1 Unilateral pulmonary vein stenosis and atresia. **A**. Chest radiogram showing severe edema of the left lung. **B**. Posterior view of 3-D MR angiogram showing severe stenosis (arrow) of the left lower pulmonary vein (LLPV). Left upper pulmonary vein is completely atretic. **C**. Radioisotope perfusion scan showing markedly diminished left lung perfusion. LA, left atrium; RLPV, right lower pulmonary vein; RUPV, right upper pulmonary vein.

abnormally slow arterial and venous flow on the involved side. Congenital unilateral pulmonary venous atresia has been identified in a child with pulmonary veno-occlusive disease in the contralateral lung.[44] Thapar and colleagues described a 3-year-old boy with agenesis of the intrapulmonary and extrapulmonary veins of the right lung who presented with a history of recurrent lung infections since birth. Once the diagnosis was made, a right pneumonectomy was performed.[40] Other processes seemingly contributing to obstruction of the pulmonary veins include pulmonary interstitial fibrosis and *in situ* thrombosis.[14,53,54] LaBourene and his colleagues created a pig model of progressive pulmonary venous obstruction.[55] This group demonstrated alterations in elastin and collagen in this pig model, with extensive fibrosis of the pulmonary veins.[55] In the absence of complicating congenital heart malformations, stenosis of the four pulmonary veins results in the development of progressive pulmonary venous hypertension, and then pulmonary artery and right ventricular hypertension.[7,9,11,15,16,30,31]

The clinical findings in patients with unilateral stenosis of the pulmonary veins may be confusing as we pointed out some years ago.[56,57] The radiographic appearances of patients with pulmonary vein stenosis or atresia have been reviewed.[7,9,20,27,30,31,40–42,45,47,48,50–52A,58] The lung ipsilateral to the pulmonary venous obstruction may appear normal on

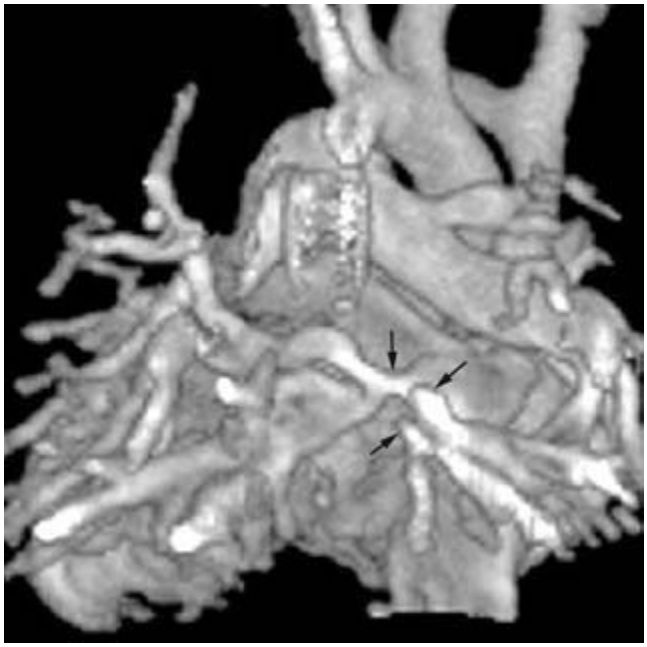


Fig. 24E-2 Posterior view of 3-D MR angiogram showing severe stenosis (arrows) of all pulmonary veins.

frontal chest radiography as in the patient reported by Johnson and his colleagues.[49] In some patients with unilateral stenosis of the pulmonary veins, it is the contralateral lung on the frontal chest radiograph that appears edematous, not invariably the involved lung. This reflects the maldistribution of pulmonary blood flow away from the side of pulmonary venous obstruction. The pulmonary perfusion scan may be very helpful in sorting out which lung has more important pulmonary vein obstruction. In other patients the findings of unilateral pulmonary edema, Kerley lines, and peribronchial thickening may be more pronounced on the side of the narrowed and stenotic pulmonary veins.[52]

In advanced instances of stenosis of all the four pulmonary veins, hemodynamic investigation documents pulmonary artery hypertension at systemic levels or above. A raised capillary wedge pressure is usually but not invariably present.[7,9,30,31,59] The left atrium and then the pulmonary vein(s) can often be probed through a defect of the foramen ovale, or using a transseptal technique. A pressure difference, often very substantial, between the involved pulmonary vein or veins and the left atrium confirms pulmonary vein stenosis. Selective injection of contrast into each of the four pulmonary veins will provide visual definition as to the relative discreteness of the obstruction, and the degree of pulmonary vein hypoplasia.[7,9,28] If the left atrium cannot be entered (i.e. azygos continuation of the inferior caval vein), selective pulmonary artery wedge injections will also demonstrate to advantage the pulmonary venous obstructions.[9,60,61] There is considerable experience with the use of cross-sectional echocardiography and color-flow mapping in the diagnosis of pulmonary vein stenosis, both congenital and acquired,[56,57,57A,62,63] and there is increasing experience with magnetic resonance flow studies as well in the diagnosis of pulmonary vein stenosis.[64,65]

Outcome analysis

There is virtually no information on fetal recognition of stenosis of the individual pulmonary veins. At least 1 fetal death has been attributed to "occlusion of pulmonary veins," but this case was reported before the era of fetal cardiac diagnosis.[66] Stenosis of a single pulmonary vein may produce little if any symptomatology, and patients with mild obstruction of all pulmonary veins may present late, even as adults.[9,15,28,30,31,67] Unilateral severe pulmonary vein stenosis may lead to significant hypoperfusion of the involved lung, eventuating in unilateral pulmonary hypoplasia. The involved lung may demonstrate lymphangiectasia and dilated bronchial veins may develop in response to pulmonary venous obstruction, contributing to the potential to vascular rupture and hemoptysis.[2–6,14] Patients with severe congenital stenosis of all four pulmonary veins often have a chronic history of tachypnea and are seemingly prone to recurrent pneumonia. Failure to thrive is common in this group of patients, usually infants and most are cyanotic.

The numerous reports in the literature indicate that for the majority of patients with severe stenosis of all four pulmonary veins, the prognosis is poor, with death in the first year of life.[2–7,9,12,14–16,28,30,31] Kawashima and his colleagues are considered the first group to report successful repair of pulmonary vein stenosis in a 15-year-old boy with an associated large atrial septal defect.[68] Subsequently, a variety of surgical procedures to relieve the junctional obstruction and catheter-based therapies have been used with marginal success.[7–9,12,16,21,28,30,31,68–76] The patient with membranous obstruction is seemingly the best candidate for surgical excision and relief of the obstruction.[8] Pneumonectomy has also been used for unilateral pulmonary venous obstruction. More recently, a number of so-called sutureless techniques have been used with some success, [72–74] and there is increasing experience with heart or lung transplantation.[77,78] The pathology of congenital pulmonary vein stenosis has continued to frustrate standard surgical and catheter-based therapies. Pacifico and his colleagues some years ago advocated repair of congenital pulmonary venous obstruction with living autologous atrial tissue.[70] This was applied to 2 patients, and while the early results seemed promising, the late results have not been published. Our own experience with this technique has been disappointing.

Nearly two decades ago in 1984, Bini and her colleagues reported on 10 patients with congenital pulmonary vein stenosis.[9] In 2, the condition was recognized only at autopsy. Eight patients underwent cardiac operation, with three early operative deaths. In the 5 survivors, all developed rapid and progressive restenosis over the next several months. Three of these 5 underwent reoperation and all eventually died of this condition. Both before this report and after, there have been other publications of small numbers of patients or single case reports, the majority of these reports documenting the dismal outcomes for these patients using conventional surgical techniques. Mendelhoff and his colleagues reported in 1995 their results with lung transplantation for congenital pulmonary vein stenosis.[77] Six patients were listed, but 3 patients died before donor lungs became available. Three patients underwent successful bilateral sequential lung transplantation and were alive and well 6–24 months after transplantation.[77]

Spray and Bridges reported in 1999 the outcomes of 11 patients with congenital pulmonary vein stenosis.[78] Two of the patients had large pulmonary veins with discrete obstruction

at atrial level. Both of these patients underwent repair and were reported to be alive and well 1 year after repair, acknowledging that 1 patient had flow to only one lung. Nine of the 11 patients were considered to have small pulmonary veins with severely elevated pulmonary vascular resistance.[78] Seven were listed for lung transplant and died on the waiting list. Two were transplanted and were alive and well 1 and 3 years following transplant.[78] Breinholt and his colleagues have reported the outcomes of 13 children with congenital pulmonary vein stenosis.[31] In this series, all the patients had associated cardiac anomalies. All four pulmonary veins were stenosed in 5 patients, three pulmonary veins in 1 patient, two pulmonary veins in 5 patients, and one pulmonary vein in 2 patients. Significantly more patients with three or four stenosed pulmonary veins died (83%) compared with patients with one or two stenotic pulmonary veins (0%). Seven patients (54%) underwent attempted repair of pulmonary vein stenosis, 2 of whom did well. Two patients with associated inoperable cardiac defects underwent heart transplantation and both survived, albeit with mildly elevated pulmonary artery pressures. In this series, 8 of 13 patients (62%) were alive 42 ± 30 months after surgery, likely reflecting a spectrum of disease weighted towards the less severe.[31]

The experience with balloon dilatation of congenital pulmonary vein stenosis has generally been poor.[28,30,76] Similarly the use of catheter-introduced endovascular stents or stents implanted at the time of surgery has afforded only temporary relief, and in most patients, endothelial proliferation through the interstices of the stent in concert with the egregious nature of the underlying disease has thwarted this approach as well.[71] This has certainly been our experience. Alomrani and colleagues reported in abstract form in 2002 the results of transcatheter therapy of pulmonary vein stenosis in 33 patients treated at the Texas Children's Hospital from January 1980 to July 2001.[28] It is unclear from their abstract how many patients had congenital pulmonary vein stenosis and how many had pulmonary vein stenosis following repair of total anomalous pulmonary venous connections. Two transcatheter strategies were employed: balloon dilatation and stent implantation.[28] At follow-up, 15 patients had died, and 9 of these 15 were < 1 year of age. Twelve of the 15 had bilateral pulmonary vein stenosis.[28] Although some patients seemingly demonstrated acute improvement, this group concluded that recurrent stenosis or progression of the disease occurs following either procedure.[28] We have used the *in situ* pericardial repair in 6 patients with congenital pulmonary vein stenosis. Pulmonary vein stenosis was isolated in 2 patients and associated with other congenital heart disease in 4 patients (ASD, 1; VSD, 1; hypoplastic left heart syndrome, 2). Mortality was 50%. At autopsy one patient had recurrent, as opposed to residual pulmonary vein stenosis and one patient died late from overwhelming respiratory syncytial virus infection. In the latter patient there was no evidence of recurrent or residual pulmonary vein occlusion. One of the 3 survivors is 5 years out from operation.[72–74] Sadr and colleagues have taken a novel approach to the treatment of the infantile form of congenital pulmonary vein stenosis.[79] In their study of the pathologic material they identified myofibroblastic proliferation as a cause for recurrent pulmonary venous obstruction in this setting.[79] They raised the possibility of treating these patients with this uniformly fatal process with one of a variety of proliferation inhibitors, including radiation, chemotherapy or gamma interferon.[79] Whether this approach will afford any long-term palliation is yet to be determined.

In summary, congenital pulmonary venous obstruction, especially when all four pulmonary veins are importantly stenosed, is a particularly egregious condition and unfortunately is usually fatal. Some patients seemingly improve after surgical reconstruction, especially when the sutureless technique is used. Whether treatment of myelofibroblastic proliferation inhibitors alters the relentless course of this disorder is yet to be defined. It is likely that the nature and extent of the pulmonary venous pathology with involvement of the intraparenchymal pulmonary veins determines in large part the response to intervention. For those who survive surgical or catheter-based intervention, long-term surveillance of the pulmonary veins and pulmonary artery pressures will be necessary. This surveillance will necessitate sequential Doppler assessments of pulmonary venous flow patterns, magnetic resonance flow assessments in those patients not treated with endovascular stents, and pulmonary perfusion scans.

All references can be found at the end of the book. See pp. 736–8 for Chapter 24E.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

25A

Robert M. Freedom, Shi-Joon Yoo, and William G. Williams

Complete Transposition of the Great Arteries: History of Palliation and Atrial Repair

Complete transposition of the great arteries is the most classical form of cyanotic congenital heart disease in which there is an atrioventricular concordant connection and a ventriculoarterial discordant connection (Fig. 25A-1). There is a long history of the many early recorded observations of the heart exhibiting complete transposition of the great arteries. Keith *et al.* attribute the earliest observations to Steno in 1672, Morgagni in 1761 and Baillie in 1797.[1] How the fortune of these cyanotic patients with transposition of the great arteries has changed in the past 40 years. The evolution from the first successful atrial repair (Fig. 25A-2) in 1959 to the initial successful arterial repair in 1975 took place in about 25 years, and today a favorable outcome for most babies with complete transposition of the great arteries is taken for granted. But as we will see, this wasn't always so, indeed, far from it. Congenital heart disease is a global disorder, with some particular ethnic biases, and so it is fitting that the first successful atrial switch procedure was performed by Ake Senning (1915–2000) of Stockholm, Sweden,[1A] and the first successful arterial switch repair with coronary relocation by Adib Jatene of Sao Paulo, Brazil.[2,3] William Thornton Mustard (1914–87) of Toronto, Ontario, Canada, first an orthopedic surgeon,[4] then later a congenital heart surgeon, with his colleagues at the Toronto Hospital for Sick Children attempted various approaches to the arterial switch procedure in the early to mid 1950s, but all of their patients died.[5] Although the Senning procedure (Fig. 25A-3) had the potential to redefine the outcome of patients with complete transposition of the great arteries, other surgeons found this procedure difficult to perform. Several years after the seminal Senning publication, the inventive surgeon, Bill Mustard, devised a baffling procedure to physiologically correct the parallel circulations of complete transposition (Fig. 25A-4).[6] In his operation, the atrial septum was completely excised. A trouser-shaped baffle made from pericardium was then sewn into the atria in such a way that systemic venous return was baffled through the mitral valve to the left ventricle and pulmonary artery, and the pulmonary venous return to the tricuspid valve, right ventricle and aorta. Maria Surnoski, his first patient, was operated on May 16, 1963.[7] A small ventricular septal defect was also closed in this patient by direct suture. She was introduced to the attendees of the Third World Congress of Pediatric Cardiology and Cardiovascular Surgery held in Toronto at its opening ceremony, May 27, 2001. Indeed, the Mustard operation was reproducible by other surgeons and in a short time the Mustard operation was assimilated into the surgical algorithm for patients with complete transposition of the great arteries. There are pictures of Bill Mustard with his plastic, see-through traveling atrium that he took on his many lecture trips, demonstrating in a most entertaining way how the baffle was to be constructed.[7] I can still remember the occasion, although not the specific day in late 1974 or early 1975, when I (RMF) had heard/read of Jatene's accomplishment. I ran into Bill Mustard as I was making rounds on the cardiac ward of the Hospital for Sick Children and mentioned that a Brazilian surgeon had just performed a successful arterial switch procedure. Bill, never long on words, stated eloquently "it's about time" (see Chapter 25B).

Incidence

Transposition of the great arteries is a relatively common congenital heart malformation and is the most common of the cyanotic lesions. The New England Regional Infant Cardiac Program provided a diagnostic frequency for transposition of the great arteries of 0.215/1000 live births.[8,9] A very similar prevalence at live birth of 0.211/1000 was obtained from the Baltimore–Washington Infant Study.[10] In the New England Regional Infant Cardiac Program, about two-thirds of the patients with transposition were boys, a very consistent finding in studies of patients with complete transposition.[8] Very few major extracardiac anomalies were associated with transposition, and low birth weight was also uncommon.[8,9] Data from the Alberta Heritage study of the prevalence of congenital heart disease found 0.280/1000 live born infants had transposition of the great arteries.[11] The Prospective Bohemia Survival Study identified 271 children with transposition of the great arteries from the 815 569 children born between 1980 and 1990 in that region.[12] This gave a prevalence of 0.33 per 1000 live births, and patients with transposition accounted for 5.39% of all heart malformations encountered in this study.[12]

Transposition of the great arteries is thought only rarely to be associated with genetic syndromes and to have a low risk of precurrence among relatives of affected patients.[8,9] In an interesting series of reports,[13–15] Digilio and her colleagues evaluated from January 1997 to December 2000, 370 patients with nonsyndromic transposition of the great arteries.[13] Relatives with congenital heart disease were identified in 37 of the 370 families (10%), including 5 of the 37 families with > 1 affected relative (13.5%). Transposition of the great arteries was the most common precurrent malformation, occurring in 6 familes. Interestingly, double discordance was found in 5 families. Precurrence risks for congenital heart disease were calculated at 1.8% (8 of 436) for siblings, 0.85% (4 of 470) for parents, 0.5% (16 of 3261) for first cousins, 0.2% (4 of 2101) for uncles/aunts, and 0.06% (1 of 1480) for grandparents.[13] These data demonstrated

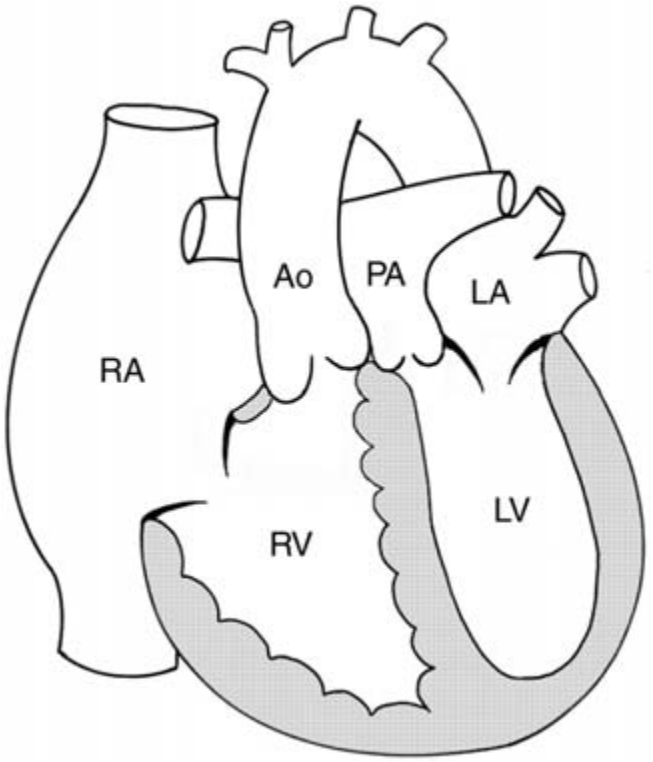


Fig. 25A-1 Complete transposition of the great arteries; a discordant ventriculoarterial connection with concordant atrioventricular connection. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

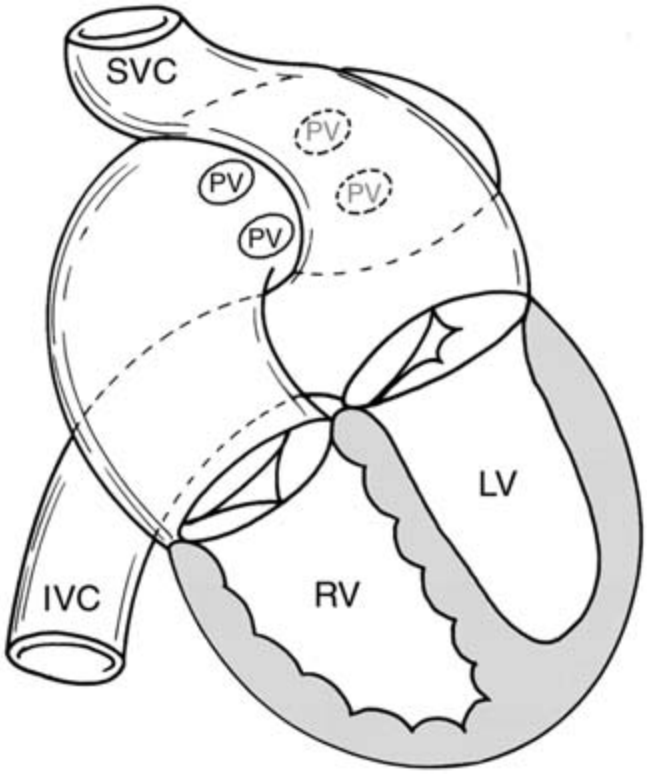


Fig. 25A-2 Circuits in Senning and Mustard atrial switch operations. The superior (SVC) and inferior (IVC) venae cavae are diverted to the left into the mitral valve and left ventricle (LV). The pulmonary venous (PV) return flows behind the baffle into the right ventricle (RV).

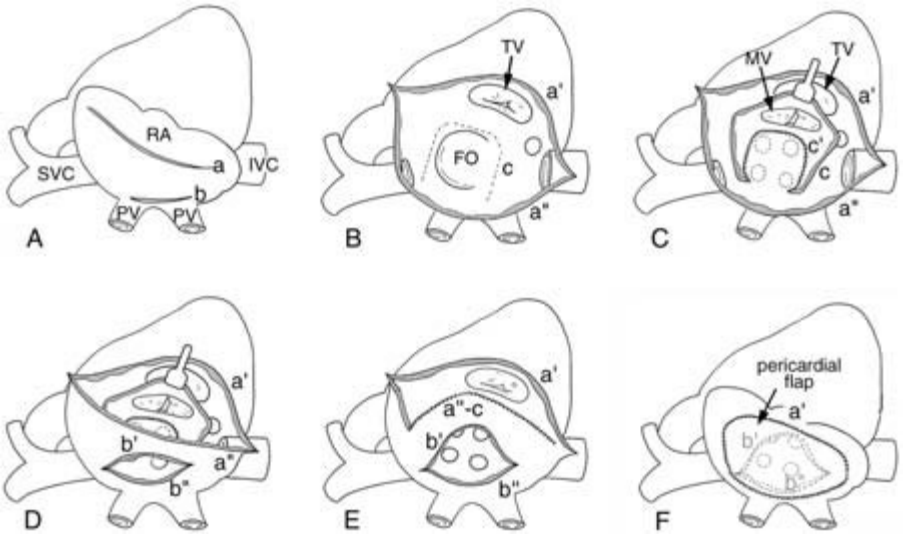


Fig. 25A-3 Senning procedure. **A**. The right (a) and left (b) atrial incisions are made. **B**. The inside of the right atrium (RA) is exposed, and the atrial septum is detached from the base of the septum (interrupted line c). **C**. The detached septum is sutured to the posterior wall of the left atrium anterior to the two left pulmonary veins, adjacent to the left atrial appendage. **D**. The left atrial incision is extended (b′ and b″). **E**. The medial free margin (a″) of the right atrial incision is sutured to the base of the atrial septum (c), thereby creating a baffle that diverts the venae cavae and coronary sinus to the mitral valve. **F**. The pulmonary venous pathway is constructed by using a pericardial flap patch. IVC, inferior vena cava; MV, mitral valve; PV, pulmonary vein; RA, right atrium; SVC, superior vena cava; TV, tricuspid valve.

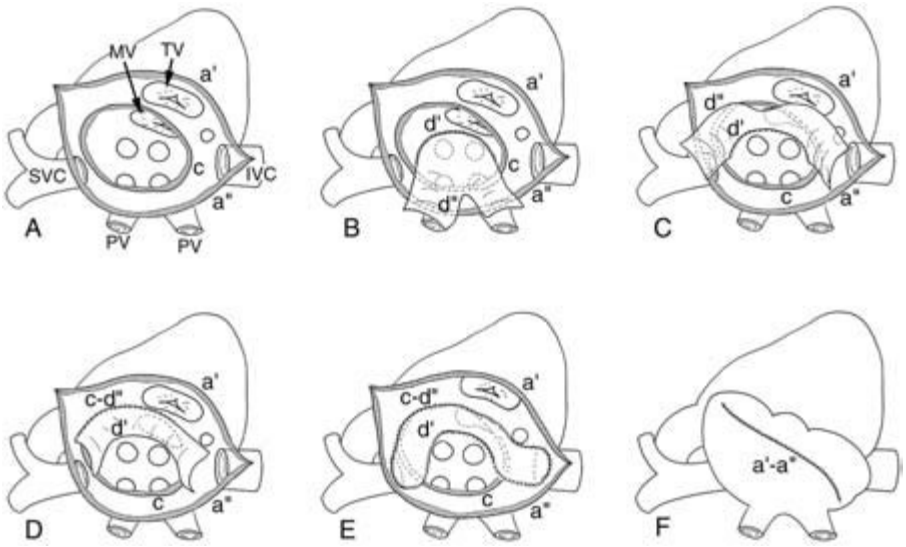


Fig. 25A-4 Mustard procedure. **A**. A right atrial incision (a and a′) is made just anterior and parallel to the pectinate line. The atrial septum is resected. **B**. A large pericardial patch (usually 5 × 7 cm with a narrow waist) is sutured to the posterior wall of the left atrium anterior to the two left pulmonary veins (d′). **C**. The pericardial patch is inverted and its free margin is aligned with the free margin of the resected atrial septum (d″). **D**. The pericardial patch is sutured to the anterior free margin of the resected atrial septum (c-d″). **E**. The extremities of the pericardial patch are sutured around the superior (SVC) and inferior (IVC) venae cavae to complete the systemic venous pathway. **F**. The right atriotomy is closed to complete the pulmonary venous pathway (a-a′). MV, mitral valve; PV, pulmonary vein; RA, right atrium; TV, tricuspid valve.

that transposition of the great arteries is not always sporadic in families. Precurrence of concordant cardiac defects within affected family members supports a monogenic or oligogenic inheritance in certain kindreds. These authors also suggest that the occurrence of complete transposition and double discordance among first-degree relatives in several different families suggests an underlying pathogenetic link between these two malformations not previously recognized.[13]

Morphology

The fascinating history of "transposition of the great arteries" has been thoughtfully and thoroughly provided by Richard Van Praagh.[16] Baillie in 1797 was the first to describe a heart in which the "aorta arose out of the right ventricle and the pulmonary artery out of the left."[17] He further characterized this malformation as "a very singular malformation of the heart," but did not use the terminology of "transposition of the great arteries." The second case of the malformation that would eventually be known as transposition of the great arteries was described by MR Langstaff in 1811, again using the description as "a very singular malformation of the heart."[18] The designation "transposition of the aorta and pulmonary artery" was introduced by John Richard Farre in 1814.[19] Others who contributed to our early knowledge of complete transposition of the great arteries include Carl von Rokitansky of Vienna, Herman Vierodt of Tubingen, Germany, Maude Abbott of Canada in 1915, Alexander Spitzer of Vienna, Lev and Saphir in 1937, and Harris and Farber in 1939.[16,20] Indeed, the most striking external feature of the heart with complete transposition of the great arteries is the abnormal spatial relationship between the great arteries: the rightward, anteriorly placed aorta and the leftward, posteriorly positioned pulmonary artery in the usual form of transposition of the great arteries. Discussion has continued for years as how best to define transposition of the great arteries, and at times, the discussion and debate became quite heated.[21–38] Transposition of the great arteries is more than a statement of infundibular anatomy.[28] It is not simply an abnormal spatial relationship between the great arteries. It is unequivocally an abnormal connection or alignment between the ventricles and great arteries. Most will now agree that transposition of the great arteries is characterized by origin of the aorta from the morphologically right ventricle and pulmonary trunk from the morphologically left ventricle.[16,39–41] It is an abnormal ventriculoarterial connection with both great arteries placed across the ventricular septum to originate above the morphologically inappropriate ventricles.[16,39–41] In the patient with solitus or normally related atria and a concordant atrioventricular connection, complete, simple or regular transposition of the great arteries is characterized by a discordant ventriculoarterial connection (Fig. 25A-1).[40] In the most common form of complete transposition, there is a subaortic infundibulum, but no subpulmonary infundibulum. The next most frequent pattern of infundibular anatomy amongst hearts with transposition is that with bilateral muscular infundibulum. Hearts with transposition and bilaterally deficient infundibulum or those with only a subpulmonary infundibulum are uncommon.[16] Pasquini and his colleagues assessed echocardiographically the infundibular anatomy of 119 patients with complete and in the terminology of Van Praagh d-loop transposition of the great arteries and large ventricular septal defect.[42] One hundred and five patients (88.2%) had only a subaortic infundibulum with no subpulmonary infundibulum; bilateral infundibular musculature was identified in 8 patients (6.7%); a subpulmonary infundibulum in 4 patients (3.4%); and bilaterally absent or deficient infundibulum in 2 patients (1.7%).

The spatial relationships between the great arteries are also quite variable, but the most common pattern is a right-sided and anterior aorta, followed by side-by-side great arteries with the aorta to the right. An aorta directly anterior to the pulmonary trunk is also relatively common. A leftward and anterior or side-by-side aorta is less frequent and posterior transposition is the least common.[16,23,43–49]

Associated malformations

The most common associated anomalies include a ventricular septal defect, left ventricular outflow tract obstruction, a patent foramen ovale, and an arterial duct.[49] The ventricular septal defect is usually perimembranous, but often involves the infundibular septum.[50–60] The ventricular septal defect can involve any portion of the interventricular septum, may be multiple, or so-called "Swiss cheese." Left ventricular outflow tract obstruction has been thoroughly documented in the patient with transposition of the great arteries, occurring in patients with an intact ventricular septum as well as in those with a ventricular septal defect(see Chapter 25C, Figs 25C-4, 25C-5). Data published by the Congenital Heart Surgeons Study which enrolled from the 20 participating institutions from 1985 to March 1, 1989, 889 patients with transposition showed that 74% have "simple" transposition; transposition with large ventricular septal defect, 21%; transposition, ventricular septal defect, and important pulmonary stenosis, 5%; and transposition, an essentially intact ventricular septum, and important pulmonary stenosis, 0.7%.[61] The mechanisms of left ventricular outflow tract obstruction are fully discussed in Chapter 25C.[60–95] In those patients with an intact ventricular septum, dynamic left ventricular outflow tract obstruction may result in acquired, fixed secondary fibromuscular changes. Less commonly, the pulmonary valve will be bicuspid or frankly stenotic in the patient with transposition of the great arteries and an intact ventricular septum. The left ventricular outflow tract may be crowded by attachment of the chordal apparatus from the anterior leaflet of the mitral valve. As will be discussed fully in Chapter 25C, those patients with associated caudal malalignment ventricular septal defect often have a tunnel-form of left ventricular outflow tract obstruction with a well-defined subpulmonary infundibulum preventing fibrous continuity between mitral and pulmonary valves.[60–95]

The aortic arch is usually left-sided, but a right-sided arch is not uncommon, especially in those patients with associated ventricular septal defect and left ventricular outflow tract obstruction (see Chapter 25C).[49,57,96] A double aortic arch has been rarely noted in the patient with complete transposition.[97–99] Other associated malformations include juxtaposition of the atrial appendages, the entire spectrum of anomalies of systemic and pulmonary venous connections, abnormalities of the atrioventricular junction including those preventing a biventricular repair, an atrioventricular septal defect, variable degrees of right or left ventricular hypoplasia, aortic atresia or pulmonary atresia, isolation of a subclavian artery; origin of a coronary artery from the pulmonary trunk, an aortopulmonary window, and obstructive anomalies of the aortic arch (literature pertaining to associated anomalies summarized in ref. 49). There are many variations in coronary artery anatomy, including origin and epicardial distribution. The coronary artery anatomy will be discussed in detail in Chapter 25B.

Perhaps not germane to an analysis of outcomes, but still of great importance to those caring for the patient with congenital heart disease is the interesting dialogue about cardiac nomenclature, and ite evolution. We all acknowledge the important contributions of Richard Van Praagh (a native Torontonian) to the segmental approach to congenital heart disease, beginning in Toronto at the Hospital for Sick Children in the early 1960s, then continuing in Chicago, and then for the next 35 years in Boston as director of the Cardiac Registry of the Children's Hospital. With his wife Stella and their colleagues, they developed the initial "Esperanta" for congenital heart disease, and fully described a wide variety of congenitally malformed hearts, using their segmental approach to describe congenitally malformed hearts.[21–29,100–106] They were the first to fully define the various cardiac segments (atria, ventricles, and great arteries) and then to catalogue hearts by nature of their segmental anatomy, with an important emphasis on infundibular anatomy.[28] At least initially, the particular connections between the various segments were deduced from the spatial relationships between the great arteries, using the so-called "loop rule" concept. Robert H. Anderson of the United Kingdom and his colleagues extended these concepts focusing not just on the segments, but on the sequential connections between the segments.[30–36] In this particular nosology there was less emphasis on ventricular loops and the spatial relationships between the arterial trunks. Transposition of the great arteries in its classical form using the nomenclature of Van Praagh would be (SDD) complete transposition, while Anderson would define this entity by virtue of its connections: atrioventricular concordance and ventriculoarterial discordance. The inference in this latter system was that with solitus atria and a concordant atrioventricular connection the internal organization of the morphologically right ventricle conformed to a right-hand pattern. While this is usually true, there are enough exceptions in other complex cardiac malformations, especially those with twisted atrioventricular connections to necessitate an accurate statement of the pattern of ventricular organization (i.e. right or left-hand pattern, d-loop or l-loop ventricle).[107–114] The sequential system advocated by Anderson and his colleagues did not emphasize infundibular anatomy. Over the years, however, these two systems and their various advocates were quite polarized, but the passage of time has blunted some of the polemic, and despite some unresolved differences, both systems are complementary and indeed some now use an amalgam of these systems.[49,115]

Outcome analysis

There is considerable experience with fetal recognition of transposition of the great arteries as well as other conotruncal abnormalities (see Chapters 16–18).[116–121] Fermont summarized a decade ago his extensive experience with the prenatal recognition of transposition of the great arteries.[116] Of 108 fetuses recognized to have some "malposition" of the great arteries, 37 had transposition of the great arteries. There were only four terminations of pregnancy amongst this group. Allan reported the outcome of 53 fetuses with transposition of the great arteries.[117] These included 31 cases of simple transposition and 22 cases of more complex forms. Of the entire cohort, 73% were diagnosed before 24 weeks' gestation. The complex cases included 13 with a ventricular septal defect, 4 with a coarctation and ventricular septal defect, 4 with pulmonary stenosis and a ventricular septal defect, and 1 with a ventricular septal defect and left atrial isomerism. Amongst the group with simple transposition, 3

families chose termination of pregnancy. There were 2 neonatal deaths and 25 survivors of the arterial switch repair who are doing well. Of the 22 cases of complex transposition, there were 10 pregnancy interruptions, 1 neonatal and 2 infant deaths, with 9 survivors. The outcome was unknown in one patient.[117] Maeno and his colleagues have addressed the effects of ductal constriction and a restrictive foramen ovale in the fetus diagnosed with complete transposition.[122] They reviewed the prenatal and postnatal echocardiograms and outcomes of 16 fetuses with transposition with intact ventricular septum or small ventricular septal defect. Of the 16 fetuses, 6 prenatally had an abnormal foramen ovale (fixed position, flat, and/or redundant septum primum). Five of the 6 had restrictive foramen ovale at birth. Five fetuses had ductus arteriosus narrowing at the pulmonary artery end *in utero*, and 6 had a small arterial duct (diameter *Z* score of < –2.0). Of 4 fetuses with the most diminutive arterial duct, 2 also had an abnormal appearance of the foramen ovale, and both died immediately after birth. One other fetus had persistent pulmonary hypertension. Eight fetuses had abnormal Doppler flow pattern in the arterial duct (continuous high velocity flow, $n = 1$; retrograde diastolic flow, $n = 7$). Abnormal features of the foramen ovale or arterial duct or both are present in fetuses with transposition at high risk for severe postnatal hypoxemia. They concluded that a combination of restrictive foramen ovale and ductal constriction in transposition may be associated with early neonatal death from profound hypoxemia.[122] Kumar and colleagues have shown that prenatal diagnosis of transposition of the great arteries improves the preoperative condition of the patient, but may not significantly improve preoperative mortality or early postoperative outcome among neonates managed at a tertiary care center.[123] These observations differed from those of Bonnet and his colleagues who found that prenatal diagnosis of transposition of the great arteries conferred an advantage to those recognized *in utero* when compared to those diagnosed postnatally.[124] Preoperative mortality was 15 of 250 (6%; 95% CI, 3% to 9%) in the neonatal group and 0 of 68 in the prenatal group ($P < 0.05$). Postoperative morbidity was not different (25 of 235 vs. 6 of 68), but hospital stay was longer in the neonatal group (30 ± 17 vs. 24 ± 11 days, $P < 0.01$). In addition, postoperative mortality was significantly higher in the neonatal group (20 of 235 vs. 0 of 68, $P < 0.01$); however, the known risk factors for operative mortality were identical in the two groups. This group concluded that prenatal detection of this specific cardiac defect must be increased to improve early neonatal management. *In utero* transfer of fetuses with prenatal diagnosis of transposition of the great arteries in an appropriate unit is mandatory.

There are many studies of the natural and modified history of the patient with complete transposition of the great arteries.[125–134] With the advances over the past five decades in the medical and surgical management of these patients, most such studies conducted in the 1950s and 1960s are now of historical interest only. Perhaps some of the most compelling data on the natural history of transposition come from the publication of Liebman *et al*. based on the outcomes of 742 cases of transposition of the great arteries seen between 1957 and 1964 in California.[125] For the entire group, by 1 week of age 28.7% had died; by 1 month, 51.6%; and by 1 year, 89.3% had died. Associated lesions had a marked effect on prognosis. As one would anticipate the outcome was worse for those with only a patent foramen ovale with 24% dying in the first 6 days, by 1 month 66.1% had died, and by 1 year 98.4% had died. Of the cohort of 127 patients with transposition and a patent foramen ovale, by 1 year of age, only 2 patients were still alive.[125] The outlook was somewhat better for those with a true atrial septal defect, or in those with ventricular septal defect > 3.0 mm, but still rather bleak. The patient with transposition of the great arteries and a large patent arterial duct did very poorly.[125] How unusual it is therefore to find patients with transposition of the great arteries surviving into the sixth decade of life without intervention.[135]

Like *Old Books, Rare Friends*,[136] the wonderful history of our great specialty is quickly being lost and forgotten, and like so many other aspects of modern society, the accomplishments of today are taken for granted. This is certainly true for the patient with transposition of the great arteries. The outlook for patients with complete transposition of the great arteries began to change just over half a century ago with the closed atrial septectomy of Blalock and Hanlon[137] published in 1950 and various forms of partial venous switches suggested by Lillehei and Varco in 1953,[138] Albert in 1954,[139] Baffes in 1956,[140] and W Sterling Edwards in 1964.[141] The Blalock–Hanlon atrial septectomy was the initial palliative maneuver introduced for the patient with complete transposition of the great arteries, but because of the usually critically-ill and precarious nature of these patients, this procedure had a very substantial mortality. The history leading Blalock, Hanlon and Thomas to develop this technique makes fascinating reading.[137A] According to Thomas when Blalock saw the atrial septal defects made in the dog by the closed technique, Blalock said the defect looked "like something the Lord made."[137B] Lillehei and Varco published in 1953 a treatment of complete transposition based on transposing the venous return.[138] Two patients were improved by anastomosing the right pulmonary veins to the right atrium. In an additional 4 patients, the inferior vena cava was anastomosed to the left atrium at the site of the cardiac end of the transected right pulmonary veins without success.[138] Albert in 1954 published a paper entitled "Surgical correction of transposition of the great vessels."[139] Despite the tantalizing title of this paper, Albert's suggested procedure was carried out in 20 dogs (but no humans in the initial report). Basically his procedure consisted of making an incision into the atrial septum, producing flaps and then by shifting and re-suturing of these flaps into new positions, he accomplished transposition of the venous return. Two years later Baffes published his paper entitled "A new method for surgical correction of transposition of the aorta and pulmonary artery."[140] His procedure diverted the right pulmonary veins to the right atrium and the inferior vena cava was diverted using an aortic graft into the left atrium. This operation now known as the Baffes' procedure was first performed successfully on May 6, 1955.[140] It is of interest that the first reference in Baffes' paper was to Albert's publication.[140] Also in 1955 Kay and Cross reported an attempt at a complex way to switch the great arteries, albeit unsuccessfully in 3 patients[142] (see Chapter 25B). Merendino and his colleagues used an Ivalon prosthesis to accomplish an interatrial venous transposition.[143] This group operated on 2 patients, a 6-year-old and a 6.5-year-old, but both died despite this innovative approach. It is interesting to compare the shape of this prosthesis (fig. 5 in ref. 143) with the trouser-shaped baffle used by Mustard (fig. 2 in ref. 6). The final paper on a partial venous switch was published by W. Sterling Edwards and his colleagues on May 11, 1964 which illustrated his technique for his venous palliation of transposition of the

great vessels,[141] some 5 years after Senning's benchmark paper.[1] W. Sterling Edwards describes his "closed heart" technique to reposition the right pulmonary veins so they drain directly into the right atrium.[141] The first such operation of the three reported by Sterling Edwards was performed on December 14, 1963, now 6 months after Mustard's successful atrial repair for transposition of the great arteries.[6] The Toronto group had considerable experience with the Edwards septal shift procedure.[141A] Ake Senning published his open heart approach to atrial repair of transposition of the great arteries in 1959.[1] The Senning technique is similar in some respects to the experimental procedure carried out by Albert, and indeed Senning's initial reference is to Albert.[139] A series of flaps are made into the atrial septum and atria and these are then repositioned and sutured in such a way to completely redirect the systemic and pulmonary venous flow. Many found the concept difficult to apply, and there was little interest in the Senning procedure until 1977 when there was a revival of interest in this technique, hoping that this procedure might avoid some of the complications attributed to the Mustard procedure.[144–152] The drawings of the Senning operation as carried out by Quaegebeur and his colleagues illustrated with clarity the nature of the Senning procedure (Fig. 25A-3).[144]

Trusler some years ago published a paper addressing the historical aspects of the Mustard procedure (Fig. 25A-4).[153] Dr George Trusler, a friend and long-term colleague of Bill Mustard's at the Hospital for Sick Children, succeeded Bill as head of the division of cardiovascular surgery. George scrubbed with Bill Mustard on the first Mustard atrial repair, Maria. According to Trusler, Mustard was aware of Senning's operation, but found it too complicated and difficult to perform. He was also likely aware of the partial venous switch procedures referred to earlier. One of Mustard's surgical residents at that time, according to Trusler, Whit Firor attributes the stimulus for the Mustard procedure to the inadvertent diversion of the inferior vena cava to the left atrium during the repair of the atrial septal defect.[153] Whatever the stimulus, the baffling operation of Mustard[6] was found to be reproducible, and this heralded a new era and outlook for the patient with complete transposition of the great arteries. Mustard also commented just before his retirement on some of the technical issues of his operation.[153A]

Two other innovations also dramatically contributed to a more favorable prognosis for the patient with complete transposition of the great arteries: (1) the balloon atrial septostomy pioneered by William J. Rashkind (1922–1986) of the Children's Hospital of Philadelphia and published in 1966 (Fig. 25A-5);[154–158] (2) the application of an E-type prostaglandin to maintain patency of the arterial duct.[159–162] According to Dr Milton Paul,[157] Rashkind astounded his colleagues with a signal 10-min presentation on October 23, 1965 at the Cardiology Section meetings of the American Academy of Pediatrics where he described his technique of using an inflated balloon at the end of a catheter to create an atrial septal defect in 3 infants with transposition of the great arteries. The first clinical application of this technique was on May 10, 1965. In Paul's contribution published in 1992 in the symposium dedicated to transposition of the great arteries 25 years after Rashkind balloon septostomy, the woman who benefited from the first Rashkind balloon septostomy was alive 26 years later, although she had suffered a cerebrovascular accident in the interval between the balloon septostomy and the Mustard operation performed at 3 years of age.[157] The second very important contribution to the baby with complete transposition of the great arteries was the application of an E-type prostaglandin. From the first publication emanating from Toronto by Olley and his colleagues on the clinical application of an E-type prostaglandin to maintain ductal patency in certain cyanotic conditions,[159] this was then extended to neonates with transposition of the great arteries, again with gratifying results.[160–162] Prostin therapy was usually well tolerated in the short term, but prolonged administration could have some important consequences.[163–169] This is not the appropriate forum to discuss all those other innovations in the care of the critically ill neonate that also contributed substantially to their well-being and survival. The Mustard operation was only rarely performed in the neonate and uncommonly in the younger infant.[170,171] Most surgeons preferred to defer this surgery until the patient was 1 year of age or older. Thus, especially, but not exclusively in the era before the neonatal arterial switch, morbidity and mortality in babies with transposition of the great arteries is related to hypoxemia, congestive heart failure, adverse neurological events and intercurrent infection. In this regard, it seemed that neonates with transposition were prone to develop necrotizing enterocolitis. This complication may reflect decreased mesenteric blood flow, a finding supported by the mesenteric blood flow velocities found by Campbell and Robertson in infants with transposition.[171A] With the renaissance of the Senning procedure in the 1970s, there was a tendency to earlier repair than in the Mustard population.[144–152,172,173] In the interval from birth to the Mustard or Senning repair, there was, sadly enough, attrition in any cohort of patients with transposition which could be attributed to hypoxemia, congestive heart failure, infection, adverse neurological events, etc. This attrition was substantial with some institutions reporting > 20% of babies with transposition of the great arteries, dying before atrial repair. Data published from Toronto in 1971[130] showed that in the era before 1963, babies with transposition of the great arteries had a 95% 2-year mortality, similar to the findings of Campbell who described a 1-year mortality approaching 90%.[134] In 1971 Tynan reported on the survival of infants with transposition of the great arteries after balloon septostomy.[174] His data suggested that survival to $2^1/_2$ years of age was only *c.* 50%, and the probability of survival to 9 months was 65%. Parsons and his colleagues published a paper also in 1971 studying 65 infants with transposition of the great arteries followed for 1 to 4 years after balloon atrial septostomy.[131] Thirty-two infants died, and 25 deaths occurred in the months or years after septostomy but before Mustard's operation.[131] Leanage and his colleagues published a similar paper also addressing survival after balloon atrial septostomy a decade later, demonstrating a progressive improvement in survival for each 3-year period from 1966.[175] The most pronounced difference between these eras was in survival to 6 months, which was 54.6 ± 7.5% in 1970–72; 72.4 ± 8.5% in 1972–75; and 86 ± 5.8% thereafter. Rashkind reported his observations on the fate of the patient with transposition of the great arteries in the years from May 1965 to May 1975, but before a Mustard operation was performed.[156] May 1965 is the date at which Rashkind carried out the first balloon septostomy. The 30-month survival for his cohort of 135 patients with transposition was *c.* 70%, with the exception of the patient with a "malignant" patent arterial duct where 16 of 17 patients died. Kidd at the Toronto Hospital for Sick Children reported in 1976 that of 245 patients seen before 1966, the survival rate was 50% at 1 month, 33% at 3 months and under 10% at 1 year. In the years 1969 and 1970,

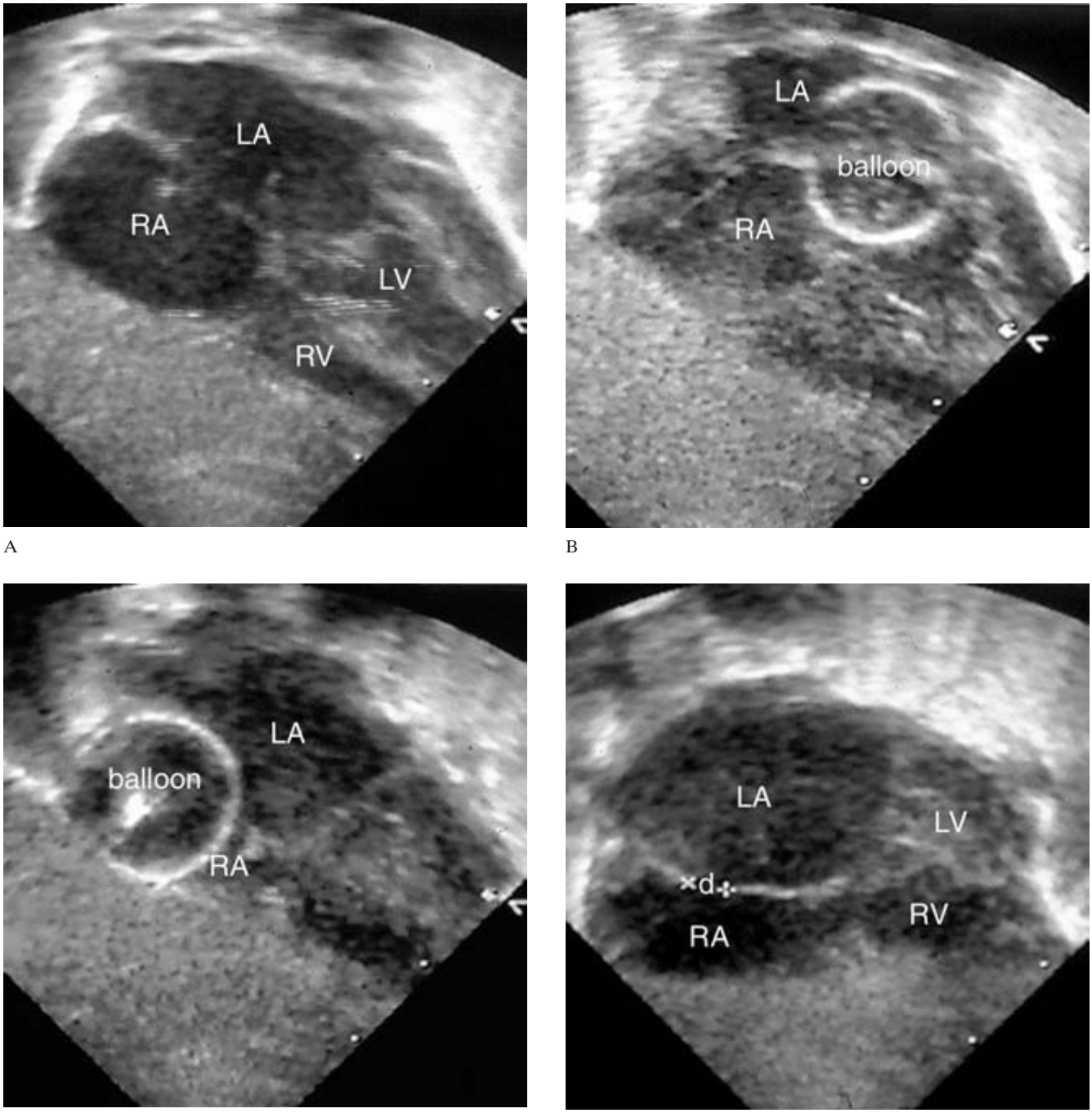


Fig. 25A-5 Echocardiograms showing Rashkind septostomy. **A**. Subcostal four-chamber view shows that atrial septum is intact. **B**. The venous catheter is introduced into the left atrium (LA) and the balloon is inflated. **C**. The balloon is pulled back into the right atrium (RA). **D**. After septostomy, a defect (d) is created. LV, left ventricle; RV, right ventricle.

the 1-year survival was 78%.[175A] He goes on to show that in the years from 1970 to 1976, the total mortality from birth to Mustard operation was 17%. Gilljam reviewed the incidence of transposition of the great arteries in western Sweden from 1964 to 1983, addressing as well survival, complications and modes of death.[176] Seventy-three children with simple transposition and 35 with complex transposition were born in this period, for an incidence of 0.24 per 1000 live births. For the entire experience in this admittedly early Scandinavian experience, the cumulative 20-year survival was 32% in simple transposition and 17% in those with complex transposition. Samanek and Voriskova reported the outcome of 271 children born with transposition of the great arteries from the Prospective Bohemia Survival Study.[12] A total of 82.7% survived the first month; an additional 13.9% died in the first 6 months, and at this time 69.7% of the children born with transposition of the great arteries survived.

By 1 year of age, 61.6% were still alive and at age 10 years 53.9% were still alive.[12] Nieminen and colleagues have recently published the late results of pediatric cardiac surgery in Finland.[177] This is a population-based study with 96% follow-up and traces the late results of pediatric cardiac surgery in Finland from 1953 to 1989, with actuarial survival for the 45 years ending on October 28, 1998. The survival rates were compared with those of an age- and sex-matched general population. The actuarial survival for the entire patient group was 78% vs. 93% for the general population, 15% lower than the general population.[177] Two hundred and ninety-eight patients with transposition of the great arteries were identified in this study. Patients with both simple and complex transposition are included in this compilation, and the operative mortality in the present study was 13%. The calculated 15- and 30-year survival rates in this study were 65% and 49%, respectively.[177] Many patients had been only palliated. The results of the Senning operation in Finland were published in 1999, and this data showed a 15-year survival of 90% including operative mortality.[178]

Gutgesell and McNamara published in 1975 their experience from the Texas Children's Hospital with a treatment plan of early palliation and late intracardiac repair in 62 patients with complete transposition.[129] The patients were managed with balloon atrial septostomy, palliative surgery if any surgery was required in the first year of life and Mustard's operation thereafter. Of the 47 patients with transposition and intact ventricular septum treated on this protocol, 41 (87%) were alive at 3 months of age, 36 (77%) at 1 year, and 31 (66%) at 2 years of age. Survival was even poorer at each age for those with associated lesions. At 2 years only 50% of patients with transposition of the great arteries and ventricular septal defect were alive.[129] In relation to therapeutic interventions in the 62 patients, there were 6 medical deaths within 1 week of balloon atrial septostomy, 3 deaths during palliative operations, and 8 deaths associated with the 31 Mustard operations.[129] Three patients with transposition and intact ventricular septum and 5 with associated ventricular septal defect developed pulmonary vascular obstructive disease, while 2 patients had strokes.[129] At the end of the study only 39 of the 62 original patients were alive, and this does not define the later outcome of those with pulmonary artery hypertension, etc. They extended these observations in 1979 defining the clinical course and outcome of 112 consecutive neonates with complete transposition.[127] The first month of life, not unexpectedly, was the period of greatest risk with 8% mortality. Between balloon septostomy and Mustard repair (median age at repair 21 months), 14% either died or had a cerebral vascular accident. A further 14% died at the time of the Mustard operation and there were 3 late deaths. Their data showed an actuarial survival to 5 years of *c.* 50%.[127] In all of these surveys, death from the complications of hypoxemia contributed substantially to this attrition and in Toronto we were quite aggressive in treating important hypoxemia following balloon atrial septostomy with a Blalock–Hanlon atrial septectomy.[153] Despite this aggressive two-stage approach to the management of babies with complete transposition (Blalock–Hanlon followed by the Mustard operation), Trusler and his colleagues still documented about an 11% attrition from birth to Mustard's operation.[179] During much of the first decade of the Mustard experience at the Toronto Hospital for Sick Children 49% of the children had undergone a Blalock–Hanlon atrial septectomy.[127] The Blalock–Hanlon procedure also had substantial mortality, and in our early experience published by Trusler and his colleagues in 1968 the mortality was high, approaching 50%.[180] Over the next few years the mortality for palliation substantially declined, to < 10% after the era of balloon atrial septostomy.[180A] The Toronto group utilized both the Blalock–Hanlon as well as the Sterling Edwards septal shift[141] to enhance mixing in the patient with transposition, the latter more frequently with pulmonary artery banding in the patient with associated large ventricular septal defect.[141A] Our mortality for banding of the pulmonary trunk with the Edwards septal shift was 14.3%.[180A] Unfortunately for several reasons, banding sometimes did not adequately protect the pulmonary vascular bed and some patients went on to develop pulmonary vascular disease.[180A] Conceivably in some of these patients, the banding itself was inadequate while in others pulmonary vascular disease was already evident, but not clinically recognized. This latter situation may reflect the inherent difficulties in calculating a meaningful pulmonary vascular resistance in the patient with parallel circulations. Our group had little experience with the Baffes procedure,[140] a procedure that would complicate the performance of the Mustard operation.[180B-D] Because of the hypoxemia of the patient with transposition and ventricular septal defect, banding of the pulmonary artery could acutely worsen the severity of the hypoxemia. Thus these patients had to have an adequate atrial septal defect and banding would have to be performed judiously.[180E] Thus it is evident that while palliation in the forms of balloon atrial septostomy, the Blalock–Hanlon atrial septectomy and the Edwards septal shift enhanced the outcomes for patients with transposition of the great arteries, there was still considerable attrition before the physiological atrial repairs.

Subsequent to Mustard's seminal publication in 1964, there was ever increasing experience with the Mustard baffle operation.[153,181–191] Then in the mid-to-late 1970s there was a renewed interest in the Senning operation, hoping that the latter would obviate some of the complications of the Mustard operation.[144–152] Modifications of the Mustard operation and Senning procedure were made to accommodate juxtaposition of the atrial appendages.[192–196] Trusler and his colleagues reported in 1987 the results with the Mustard operation in 329 patients with "simple" transposition of the great arteries, an experience encompassing May 1963 to December 1985, at the Toronto Hospital for Sick Children.[191] These patients included those with a small ventricular septal defect or mild left ventricular outflow tract obstruction, neither of which required surgical attention. To assess improvements with time, those who had repair during the first decade (May 1963 to December 1973; group I, $n = 106$) were compared to those having repair in the next 12 years from January 1974 to December 1985 (group II, $n = 223$). The mean age at operation of those in group I was 37.5 months, ranging from 27 days to 161 months. For those in group II, the mean age at Mustard repair was 14.25 months, ranging from 2 to 131 months. During the last 5 years of the experience most of the Mustard repairs were carried out between 6 and 12 months of age. The frequency of Blalock–Hanlon atrial septectomy, early and late deaths in the two groups is shown in Table 25A-1.

As one can see from Table 25A-1, nearly half of all patients underwent an atrial septectomy, and there was dramatic improval in early and late mortality between the two groups. In the more recent experience which is encompassed by group II, there were no deaths in the last 176 cases.[191] Actuarial survival of the 329 children showed an 85% 10-year survival rate and an 81.5% 15 year survival rate.[191] When the two groups are com-

	Group I (1963–73)	Group II (1974–85)
No. of patients	106	223
Age at operation (mean)	27 days to 161 months (37.5 months)	2–131 months (14.25 months)
Previous atrial septectomy	52 (49.1%)	110 (49.3%)
Early deaths	11 (10.4%)	2 (0.9%)
Late deaths	21 (22.1%)	10 (4.5%)

Table 25A-1 Mustard repair of simple transposition of the great arteries: the Toronto Hospital for Sick Children experience (1963–85)

pared, group II patients had a 5- and 10-year survival of 93.7% and 93.7% respectively, while the respective rates in group I patients was 75.4% and 73.4% respectively. Most of the difference is reflected in the greatly reduced operative mortality from 10.4% to 0.9% between the two groups, and as well the difference in late mortality rate from 22.1% in group I patients and 4.5% in group II between 1 month and 4 years.[191] The overall Mustard experience at the Toronto Hospital for Sick Children for patients with transposition of the great arteries is shown in Fig. 25A-6. The outcome for those with associated ventricular septal defect was considerably worse than for those with an intact ventricular septum (Fig. 25A-7). The arterial switch protocol is considered in the subsequent chapter (Chapter 25B), but the outcomes of the Mustard and arterial switch protocols for both groups of patients are depicted in Fig. 25A-8 (see also Figs 25B-5 and 25B-11 to 25B-14). Other centers also had excellent surgical results with the Mustard procedure, for simple transposition, acknowledging the attrition before the Mustard, both in terms of mortality and morbidity.[181–187] Several years later in 1988, Castaneda and his colleagues reported the early results of the Congenital Heart Surgeons Study with 187 neonates with simple transposition.[197] These patients were entered into this study between January 1, 1985 and June 1, 1986. Three surgical protocols were used by the 20 participating institutions: Mustard atrial repair, Senning repair and arterial switch repair[197] (see also Chapter 25B). Overall survival of the entire cohort was 87% at 1 year. Twenty-one Mustard operations were carried out with no surgical mortality; 35 Senning operations were performed with 4 deaths (11% mortality); and 71 arterial switch procedures with 13 deaths (18% mortality) (see Chapter 25B). No deaths were encountered before the arterial switch operation for those entered into this protocol, while 5 deaths occurred in those patients entered into the atrial switch protocols.[197] Sarkar and his colleagues reported the long-term outcomes of atrial repair in 358 patients with simple transposition, comparing the late Mustard survivors (n = 226, 1965–80) with those late survivors of the Senning operation (n = 132, 1978–92).[198] Of the 141 Senning operations performed, there were 9 early deaths (6.4%) and 12 late deaths (9%) to the conclusion of the study. Of 249 Mustard operations, there were 23 early deaths (9.2%), and 50 late deaths (22%) during the follow-up. For the > 30 day survivors of the Senning operation, the actuarial survival rate at 5, 10, and 15 years was 95%, 94% and 94%, respectively. For the > 30 day survivors of the Mustard operation, the actuarial survival rate at 5, 10, and 15 years was 86%, 82%, and 77%. Re-intervention in this experience was considerably more common in the Mustard group when compared to the Senning group.[198] The Pediatric Cardiac Care Consortium reported its experience with 252 baffle procedures, primarily Sennings with about 30% Mustard procedures.[199] Twenty-two infants died, for a mortality of 8.7%. The Mustard mortality was 5.3% and the Senning mortality 9.1%. The average age at baffle operation was 5.2 months. Eight of 28 (28.6%) operations in neonates resulted in death, while 93.7% of 224 infants over 1 month survived.[199] Others had somewhat better success in early Mustard and Senning procedures.[171–173,200] One of the variations in Mustard's procedures that caused an increased number of baffle complications was the use of Dacron, not pericardium.[201–209] With the number of reports of baffle-related complications attributed to Dacron, this material was soon abandoned.

The outcomes for patients undergoing atrial repair of transposition and ventricular septal defect closure were certainly less

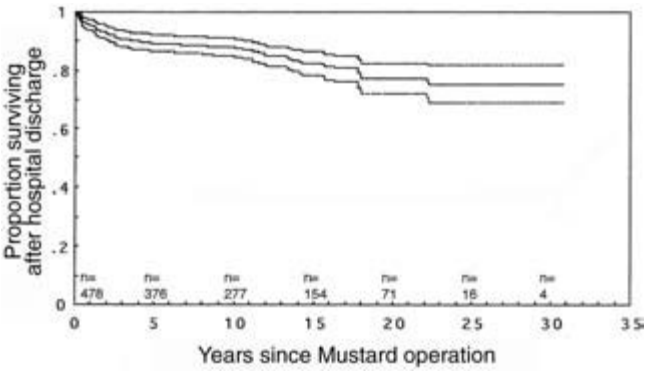


Fig. 25A-6 Kaplan–Meier estimates of late survival after hospital discharge of entire cohort of patients with transposition of the great arteries after the Mustard procedure. Top and bottom lines indicate 95% CL. (From Gelatt *et al.*[265] with permission.)

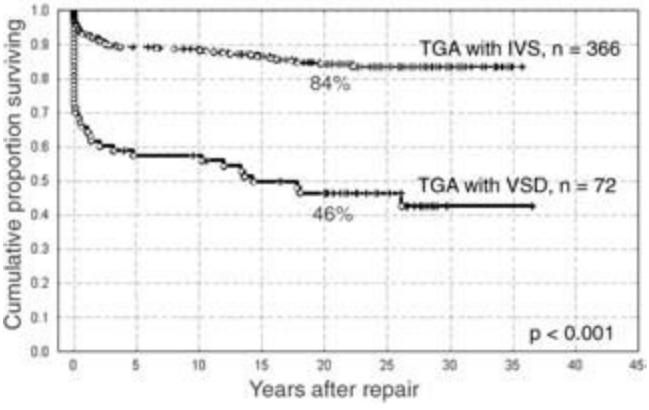


Fig. 25A-7 Data from the Toronto Hospital for Sick Children show very much poorer survival in patients with associated VSD compared to those patients with transposition and intact ventricular septum; both groups undergoing the Mustard protocol.

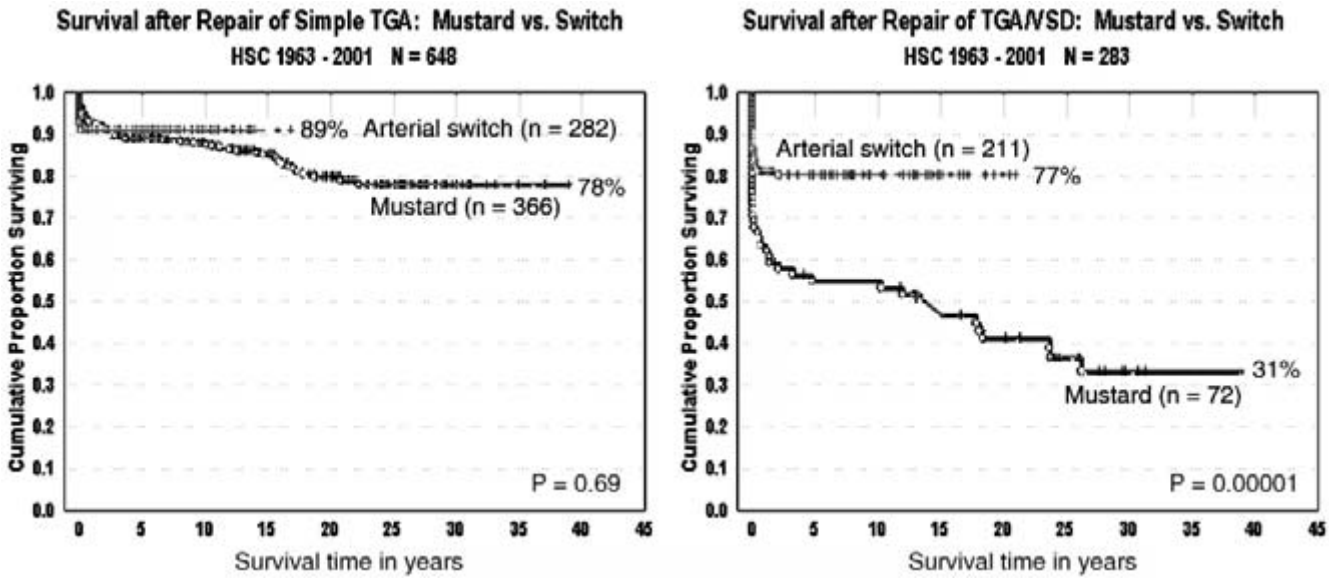


Fig. 25A-8 Data from the Toronto Hospital for Sick Children compare Mustard and arterial switch protocols for transposition (TGA) with intact ventricular septum (left panel) vs. Mustard and switch protocols for transposition and ventricular septal defect (right panel). Most of the difference in outcomes of the TGA and VSD reflects the outcome of the Mustard protocol during the earlier part of the experience. See also Chapter 25B, Fig. 25B-5A–C.

satisfying[60,210–220] (Figs 25A-7, 25A-8). Many of these patients had been palliated with pulmonary artery banding,[180] but still many developed pulmonary vascular obstructive disease. Some with pulmonary vascular obstruction were palliated with a Mustard operation with the ventricular septal defect left open, while the others eventually died. For those who underwent a Mustard operation and closure of the ventricular septal defect, the early and late results were certainly poorer than in the simple group, indeed concerning. The outcome of this particular group of patients was one of the reasons that compelled our group to abandon atrial repair for the arterial switch (see Chapter 25B).[190,191] Results with either the Mustard or Senning repair with closure of the ventricular septal defect have been associated with substantial mortality, varying from 10% to 60%.[49,181,184–187,210–213,215–220] Penkoske and her colleagues from the Boston Children's Hospital published their results in 1983 with the Senning operation and ventricular septal defect closure in 46 infants between 1978 and 1982.[214] A wide spectrum of ventricular septal defect morphologies were encountered, with nearly 76% of either the perimembranous or malalignment type.[214] The hospital mortality was 15.2% and the late mortality was 5.1%. There was considerable morbidity in these patients with mild tricuspid regurgitation in 3 patients and severe regurgitation in 3 requiring tricuspid valve replacement; residual ventricular septal defect in 3 patients, pulmonary venous obstruction in 3 patients, and permanent complete heart block in 4. George and her colleagues reported the outcome of 10 infants with transposition and ventricular septal defect who underwent a Senning and VSD closure.[172] While in this small series there was no hospital mortality, 3 died late (30%). Several years later Trusler and his colleagues for the Congenital Heart Surgeons Study reported the then current results of management in transposition of the great arteries, with emphasis on those patients with ventricular septal defect.[213] Two hundred and forty-five patients with transposition of the great arteries with or without a ventricular septal defect were entered into this study between January 1, 1985 and June 1, 1986. The 12-month overall survival among the 245 patients was 80%, and neither treatment protocol, Mustard, Senning, nor arterial switch was a risk factor for death. Fourteen patients among the 245 died before undergoing repair. The early results by either arterial switch or atrial repair of transposition of the great arteries with ventricular septal defect were similar. Of 187 patients with simple transposition, 29 or 16% died while 9 of 36 patients or 25% of patients with transposition and ventricular septal defect died.[213] Of the 245 patients in this study, 60 underwent either a Mustard or Senning repair.

Wells and Blackstone have recently reported for the Congenital Heart Surgeons Study the intermediate outcome of the Mustard and Senning procedures.[221] The results are considerably different than those reported by Sarkar and colleagues.[198] Between 1985 and 1989 20 participating centers of the Congenital Heart Surgeons Study registered 281 patients < 15 days of age who eventually underwent an atrial switch operation.[221] There were 108 Mustard procedures and 173 Senning procedures. Unlike Sarkar and his colleagues' findings,[198] results were better with the Mustard operation than for the Senning with survival at 1 month, 5 years, and 10 years being 96% vs. 86%, 95% vs. 80%, and 93% vs. 78% ($P < 0.01$) for Mustard vs. Senning. While most of the mortality was in the first postoperative month, the late rate of death from 1 to 10 years after operation was 0.78%/year for the Senning vs. 0.23%/year for the Mustard group. Overall survival at 10 years was 84%. Wells and Blackstone found a number of incremental risk factors for death after an atrial switch procedure. The association of transposition with ventricular septal defect most strongly correlated with mortality particularly when combined with young age. Other factors correlating with mortality included younger age and lower weight at repair, cardiac positional anomalies, and a need for a procedure for left ventricular outflow tract obstruc-

tion.[221] Perhaps the most important difference in this study compared to others is the unusually high overall mortality with the Senning operation compared to the Mustard (22% vs. 7% at 10 years). Interestingly as well, the incidence of right ventricular failure was only 1% in this study, considerably lower than other estimates of 10% from an earlier era.[215]

Another group of patients that has proven particularly difficult to treat are those with transposition of the great arteries, intact ventricular septum, or nearly so, and severe left ventricular outflow tract obstruction.[65–67,81,87,88] These patients have been treated with a number of operations including the Mustard with resection of the left ventricular outflow tract obstruction, Mustard and a left ventricle-to-pulmonary artery conduit, and in those with dynamic left ventricular outflow tract obstruction an arterial switch operation (see Chapter 25B). Other miscellaneous operations including the arterial switch procedure with the Ross–Konno and other variations have also been used (see Chapter 25B). We reported our institutional experience with this group of patients in 1989.[67] From 1963 to 1987, we identified 46 children with transposition of the great arteries, intact ventricular septum, or nearly so, and left ventricular outflow tract obstruction who underwent Mustard's operation and surgical relief of the left ventricular outflow tract obstruction. These patients had a combination of dynamic and fixed forms of obstruction, and certainly in the present era those with dynamic and important obstruction would best be treated with the arterial switch option (see Chapter 25B). The early mortality was 17.8% and the late mortality 10.5%. The overall survival at 2.5 years was 71.3%. The majority of patients in this experience had direct surgical relief of the left ventricular outflow tract obstruction, but several required a left ventricle to pulmonary artery conduit. Those requiring the conduit immediately after a Mustard procedure did poorly. In 1985, Crupi and his colleagues reported a smaller experience of 16 patients with transposition of the great arteries and fixed subpulmonary obstruction who underwent repair by means of a combined Mustard procedure and placement of a conduit between the left ventricle and main pulmonary artery between January 1976, and June 1983.[65] Their mean age and weight were 5.3 years and 19 kg. Ten patients had an intact ventricular septum and 6 had a ventricular septal defect, which because of its size or location precluded a Rastelli repair (see Chapter 25C). A fibromuscular tunnel was the most common type of subpulmonary obstruction (10/16, 62%). There were 3 early deaths and 1 late death. These patients will certainly require conduit replacement. A group of patients may develop important left ventricular outflow tract obstruction after Mustard's or Senning's operation. In some patients the obstruction may be resectable, but in others the obstruction may be related to anomalous attachment of the mitral valve or to a long tunnel form of obstruction, both forms not amenable to resection.[67] Schmid and his colleagues reported in 1995 10 such patients who developed important left ventricular outflow tract obstruction 4–13 years after the atrial repair of transposition.[222] All patients survived placement of a left ventricle to pulmonary artery conduit, but 1 patient died suddenly 2.5 years after conduit placement. Within the 8-year follow-up, 2 patients have already required conduit replacement. The intervention and outcome of those patients with transposition of the great arteries, ventricular septal defect, and pulmonary outflow tract obstruction are dealt with in Chapter 25C.

The Mustard and Senning operation both confer a physiological repair on the patient with transposition and both before and after the atrial switch operations, the morphologically right ventricle retains its function as the systemic right ventricle. One should not be surprised, therefore, that the modified history of the patient with transposition of the great arteries after these physiological "corrections" can be complicated by right ventricular dysfunction[223–249] and tricuspid regurgitation.[250–256] Other concerning issues are related to important rhythm disturbances, reflecting damage to the sinoatrial node and its artery (Fig. 25A-9).[60,144–151,205,257–271] There are data to suggest that this damage does not usually result from balloon septostomy, but both the Blalock–Hanlon atrial septectomy as well as the atrial switch operation are well known to promote sick sinus syndrome, again reflecting damage to the sinoatrial node and its artery.[257–270] Other mechanisms implicated in the genesis of the atrial rhythm disturbances include the extensive suture lines used in both the Mustard and Senning procedures, and as well atrial distension related to right ventricular failure and tricuspid regurgitation.[257–270] Finally, both the Mustard operation and the Senning operation have the potential to narrow the caval channels or the pulmonary venous channel (Fig. 25A-10). Furthermore with dehiscence of the suture line there is always the potential for leaks in the baffle which may result in bidirectional shunts.[49,60,95,149,150,152,153,183,184,186,197,189–191,205–209,216,240,271–289]

We reported some years ago from postoperative cardiac catheterization data the specific baffle complications encoun-

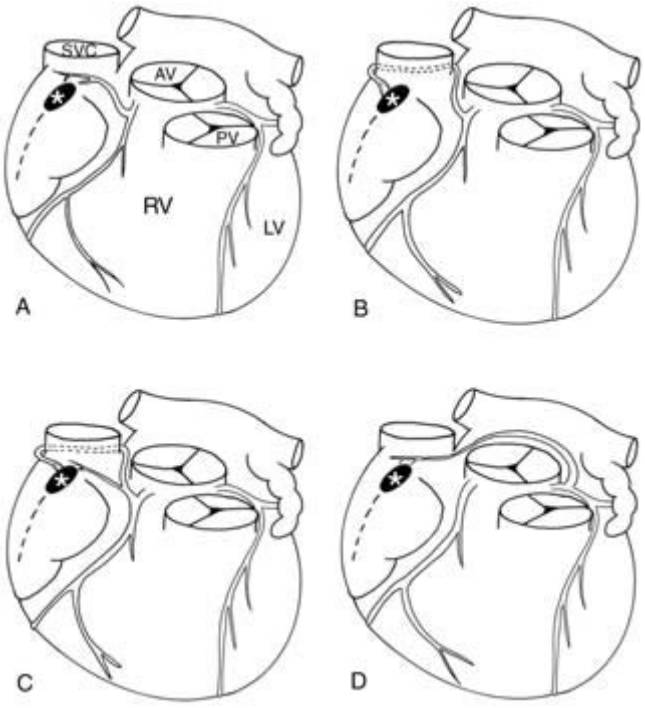
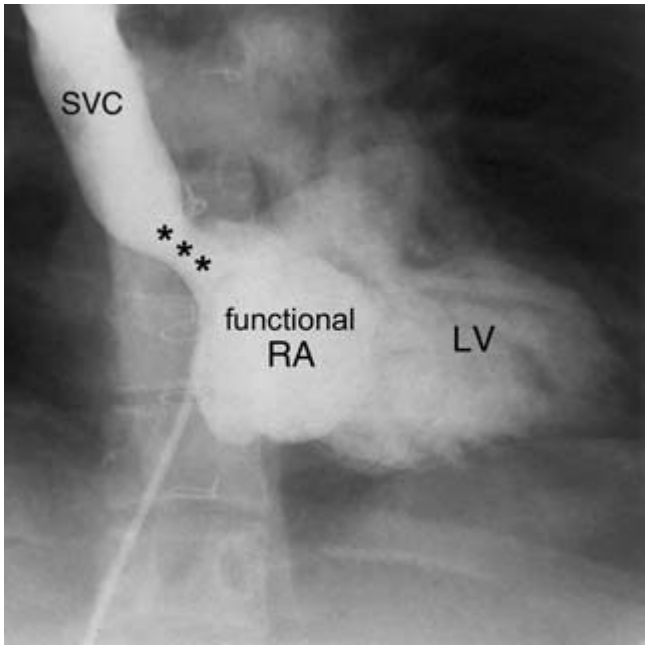
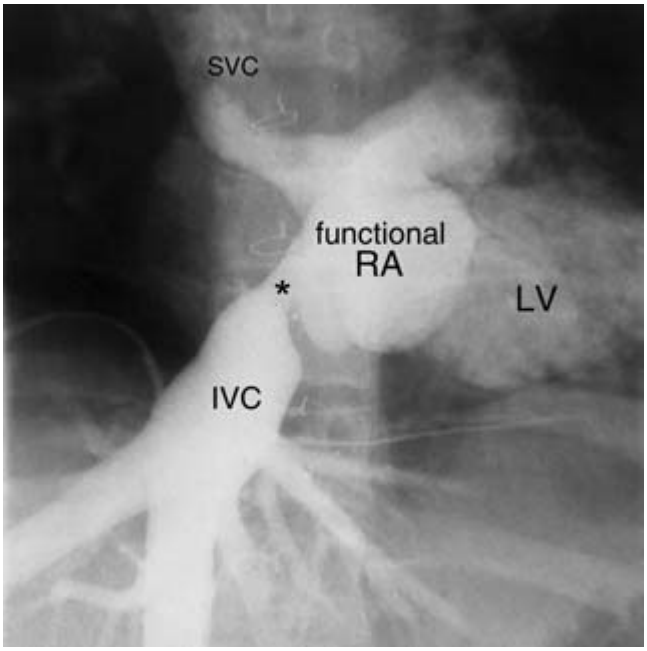


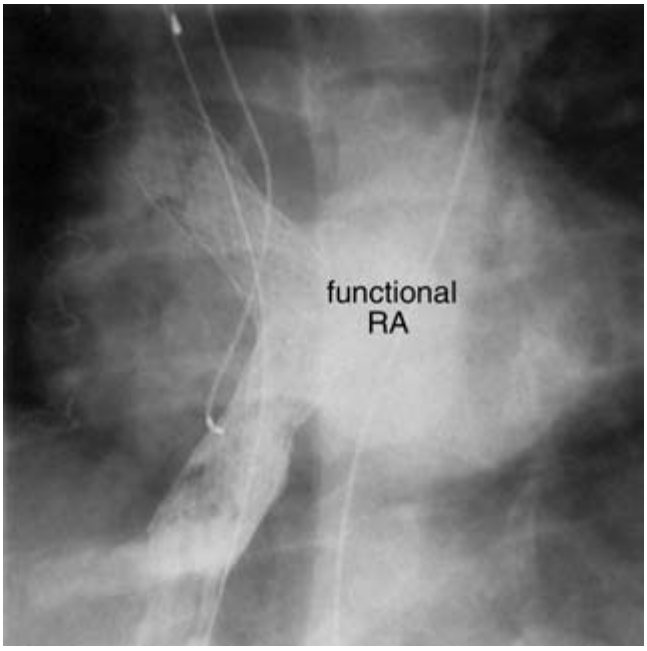
Fig. 25A-9 Anatomy of the sinoatrial node (asterisk) and its artery in normal heart. The sinoatrial nodal artery arises from the right coronary artery and approaches the node anterior (**A**) or posterior (**B**), or both anterior and posterior (**C**) to the superior vena cava (SVC). It may also arise from the left coronary artery (**D**). Both structures can easily be damaged by the incisions made at Blalock–Hanlon atrial sepetectomy or Mustard or Senning procedure. AV, aortic valve; LV, left ventricle; PV, pulmonary valve; RV, right ventricle.



A



B



C

Fig. 25A-10 Narrowing of both superior and inferior vena caval baffles. **A**. Injection into the superior vena cava (SVC) shows narrowing (asterisks) of the superior limb of the baffle. **B**. Injection into the inferior vena cava (IVC) shows more severe narrowing (asterisk) of the inferior baffle limb. **C**. Both limbs were dilated with placement of stents. RA, right atrium; LV, left ventricle.

tered in our patients with simple transposition who had undergone Mustard's operation(Table 25A-2).

As one can define from Table 25A-2, baffle leaks were relatively common, but frequently were not detected clinically, and were only defined and imaged at a postoperative cardiac catheterization (Fig. 25A-11). Most of the shunts were small, but 5 children required re-intervention with one surgical death. Some narrowing of the superior vena caval channel was quite common, and the majority of such patients were asymptomatic. Only two children required in this era surgical revision of the superior caval pathway. From our own experience and that in the literature, even complete obstruction of the superior caval limb by the baffle was often well tolerated and some patients with this complication were virtually asymptomatic. Interestingly in these patients, the azygos vein dilates and there is retrograde venous flow down the azygos vein into the paravertebral plexus and then back to the heart via the inferior vena caval vein.[290,291] The paravertebral veins may considerably dilate, simulating in some patients paravertebral masses.[291] In some patients raised superior caval vein pressure promotes communicating hydrocephalus.[282,283] Some years ago, Coulson and colleagues treated severe symptomatic obstruction of the

	Group I	Group II	Total	% of survivors	% of catheters
Early survivors	95	221	316		
No. of catheterizations	45	81	126	39.9	
Baffle leaks	22	18	40	12.7	31.7
SVC stenosis	7	19	26	8.2	20.6
IVC stenosis	2	1	3	0.9	
Pulmonary vein stenosis	4	2	6	1.9	
Isolated LPV stenosis	2	4	6	1.9	

Table 25A-2 Baffle complications in patients with simple transposition after Mustard's operation: the Toronto Hospital for Sick Children experience

SVC, superior vena cava; IVC, inferior vena cava; LPV, left pulmonary vein.

superior vena caval pathway with hydrocephalus by anastomosing the innominate vein to the left atrial appendage.[283] This provided prompt relief. We have not used this approach in our patients with symptomatic superior vena caval obstruction. Chylothorax, protein-losing enteropathy, and pulmonary edema may reflect elevated superior caval pressure. As we have stated, mild degrees of superior limb narrowing may be well tolerated. However, in some patients should they require transvenous pacing, the superior baffle narrowing may become more pronounced and symptomatic. Significant stenosis of the inferior caval channel is poorly tolerated because of the impact on the liver (Fig. 25A-10). Three patients were found to have inferior caval narrowing, and two of these required surgical intervention. In the past decade, there has been increasing experience with balloon dilatation of the stenotic pathways, especially the superior limb of the baffle and in some patients stents have been implanted to achieve an adequate caliber (Fig. 25A-10).[271–275] Just as the technology has evolved from the surgical theatre to the catheter laboratory with balloons and stents to treat post-atrial repair pathway obstruction,[271–277] the imaging modalities have also evolved from a catheter-based investigation to magnetic resonance imaging.[249,278,288,289] Historically, symptomatic obstruction of the superior vena caval pathway was initially treated surgically, then with balloon dilatation and in the past decade or so with stent placement, occasionally in tandem.

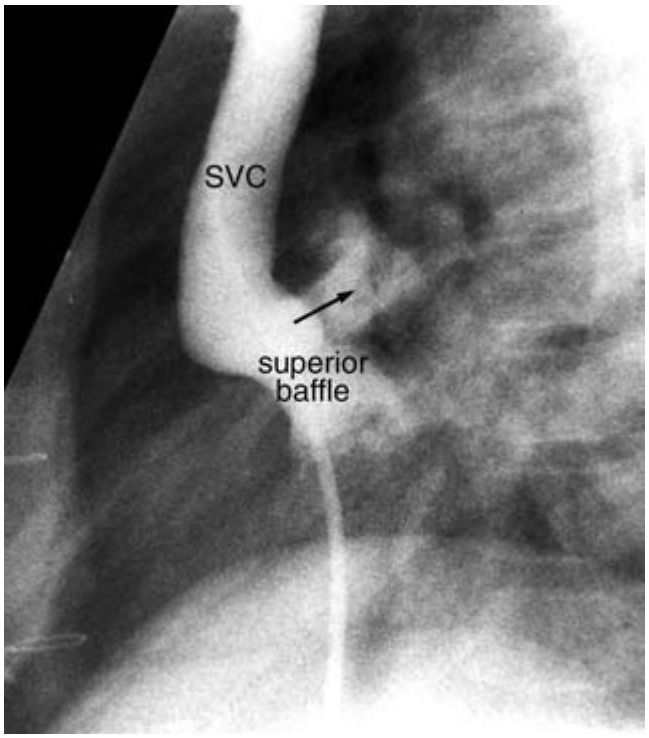


Fig. 25A-11 Injection into the superior vena cava (SVC) shows small baffle leak (arrow).

Pulmonary venous stenosis was and remains a serious complication of the Mustard and Senning operation.[153,190,191,276,280,285] Partial obstruction of the pulmonary venous channel was encountered in 12 (3.8%) of the 316 early survivors in our experience.[190,191] In 6 children (4 in group I and 2 in group II) all of whom died, stenosis occurred at the plane of the original atrial septum, the baffle apparently adhering to the area of septal excision, then contracting to obstruct all four pulmonary veins. In the other 6 children (4 in group I and 2 in group II), the stenosis was more posterior in the left atrium, between the entrance of the right and left pulmonary veins, obstructing only the left pulmonary veins. Five of these children survived operative re-intervention, but 1 died later. Ostial stenosis of the pulmonary veins was found at reoperation in 6 children with pulmonary venous obstruction and was refractory to surgical therapy. Vogel when in Toronto and his colleagues reported congenital left-sided unilateral pulmonary vein stenosis complicating transposition of the great arteries.[292] This was attributed to the maldistribution of flow to the right lung, reflecting the orientation of the left ventricular outflow tract.[292] Pappas has reported similar findings.[293] Some have advocated balloon dilatation or even stent placement to palliate important pulmonary venous obstruction after Mustard's operation.[276,280,285] The resulting pulmonary hypertension may be so severe as to "prepare" the left ventricle for an arterial switch procedure. In some such affected patients the Mustard or Senning has been taken down and an arterial switch procedure carried out, sometimes many years after the original atrial switch surgery.[294–296] Wells and his colleagues showed that the actuarial freedom from systemic or pulmonary venous pathway obstruction 9 years after atrial switch was 95%.[221] Of the 19 reoperations required after the initial atrial switch, 12 were in the Senning group and 7 in the Mustard group.[221] Campbell and colleagues have reported the development and recognition of symptomatic pulmonary venous obstruction in an adolescent when the Mustard repair had been performed in infancy.[190A]

As stated earlier, two other major issues further clouded the future of patients surviving the Mustard or the Senning opera-

tion: important rhythm disturbances and right ventricular dysfunction and failure. There is a very substantial literature addressing those issues promoting atrial rhythm disturbances and their incidence in patients with transposition of the great arteries. Important atrial rhythm disturbances persisting after balloon atrial septostomy are uncommon.[60,144–151,205,257–271] However such atrial rhythm disturbances are a well-documented consequence of the Blalock–Hanlon atrial septectomy and likely result from damage to the sinoatrial node and its artery, the same mechanisms implicated in such rhythm disturbances following the Mustard or Senning operation. In 1997 we reviewed the records of all 534 children who had undergone Mustard's operation at the Toronto Hospital for Sick Children from 1963 to 1993.[265] There were 52 early deaths. Survival analysis was undertaken for 478 early survivors with a mean follow-up interval of 11.6 ± 7.2 years. There were 77 late deaths (16.1%) with sudden death (n = 31) the most frequent cause. Survival estimates were 89% at 5 years and 76% at 20 years of age (Figs 25A-6 to 25A-8). Risk factors were an earlier date at operation, operative period arrhythmia, and an associated ventricular septal defect. The risk (hazard) for late death declined in the first decade, with further peaks in the second decade. Sinus rhythm was present in 77% at 5 years, but only 40% at 20 years. Loss of sinus rhythm was associated with previous atrial septectomy, postoperative bradycardia and late atrial flutter (Fig. 25A-12). Freedom from atrial flutter was 92% at 5 years and 73% at 20 years of age. Risk factors for atrial flutter were the occurrence of perioperative bradyarrhythmias, reoperation and loss of sinus rhythm during follow-up. Fifty-three patients (11%) required pacemaker implantation, 10 of which were placed during the operative period before hospital discharge. Sinus node dysfunction was the primary indication for pacing in 33 patients, and complete heart block in 14 patients during the follow-up period.[265] Atrial flutter was not an independent risk factor for death in our analysis, and this departs from the findings of Flinn, Gewillig, Vetter and their respective colleagues and others.[218,261,262,262A] Turning again to the paper from Sarkar and his colleagues who reviewed the atrial switch experience of the Great Ormond Street Hospital for Sick Children, loss of sinus rhythm occurred progressively and to a similar extent after both Mustard and Senning procedures.[198] At 10 years, nodal rhythm had been documented in 26% of the Mustard group and 35% of the Senning group. Atrial flutter developed in 16% of the Mustard group and 6.1% of the Senning group. For the Mustard patients, freedom from atrial flutter at 5, 10, and 15 years was 89%, 75%, and 69%, respectively. The comparative data for the Senning group were 98%, 91%, and 88%, but in the Senning patients 3 late cases of atrial flutter developed in the oldest patients. After era correction, the incidence of atrial flutter was similar and strongly associated with late deaths in both groups.[198] In both groups ventricular failure was uncommon, and at last follow-up 92% of the Senning group and 89% of the Mustard group were in New York Heart Association class I.[198] Data provided by Wells and Blackstone for the Congenital Heart Surgeons Study showed no difference in arrhythmias between those undergoing the Mustard or Senning procedure.[221] The Congenital Heart Surgeons Study showed that the actuarial freedom from permanent pacemaker therapy 9 years after atrial switch was 91%. Sudden death is tragically a well-known phenomenon in patients who have undergone a Mustard or Senning atrial repair for simple or complex transposition.[262A] The mechanisms responsible for sudden death include sinus node dysfunction with either a profound bradycardia or atrial flutter with a very rapid ventricular response.[257–270]

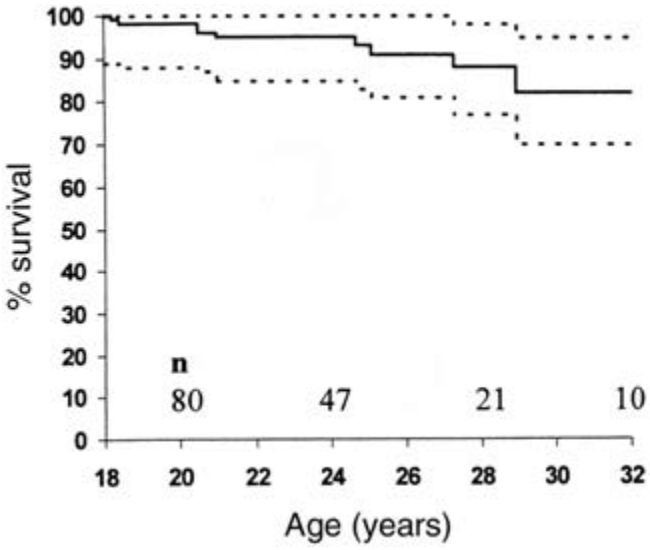


Fig. 25A-13 Kaplan–Meier survival curve (solid line) depicting all cause mortality beyond the age of 18 years. n, number of patients remaining in follow-up at the corresponding age in years (n = 86 at age 18 years). (Reprinted from Puley *et al.*,[270] Copyright (1999), with permission from Exerpta Medica, Inc.)

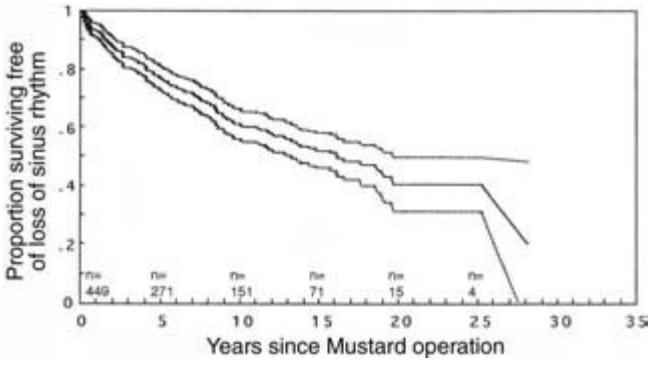


Fig. 25A-12 Kaplan–Meier estimates of late survival free of loss of sinus rhythm after the Mustard procedure. Top and bottom lines indicate 95% CL. (From Gelatt *et al.*[265] with permission.)

Several years ago, Puley and his colleagues addressed survival and arrhythmia in patients > 18 years of age after the Mustard operation for complete transposition of the great arteries.[270] This study conducted at the Toronto Congenital Cardiac Center for Adults reviewed the outcome of 86 consecutive adults who had undergone the Mustard operation at the Hospital for Sick Children between May 1963 and June 1981 at a median age of 2 years[270] (Figs 25A-13, 25A-14). The median time since Mustard's operation was 23 years, ranging from 14 to 34 years and the median length of follow-up beyond the age of 18 was 8 years (range, 0.1–27 years). The median age of these patients at their last follow-up was 25 years (range, 18–45). The Kaplan–Meier survival curve continued to demonstrate attrition from sudden death, congestive heart failure and pulmonary

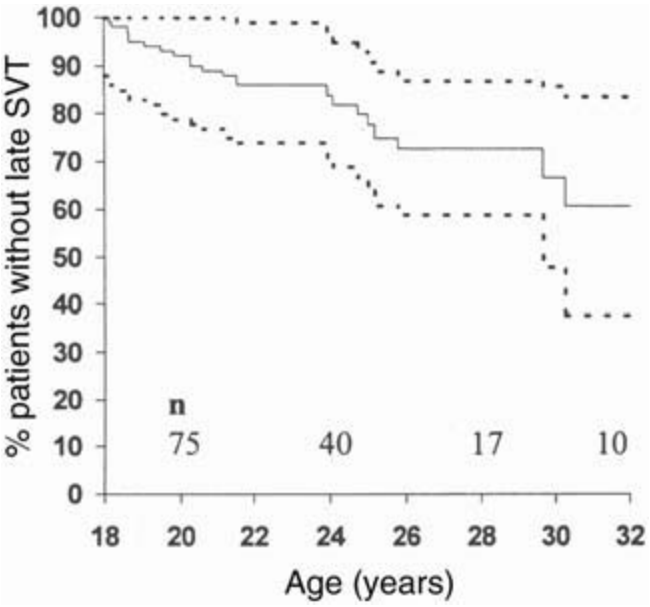


Fig. 25A-14 Kaplan–Meier survival curve (solid line) depicting freedom from supraventricular tachycardia (SVT) after the age of 18 years. *n*, number of patients remaining in follow-up at the corresponding age in years ($n = 86$ at age 18 years). (Reprinted from Puley *et al.*,[270] Copyright (1999), with permission from Exerpta Medica, Inc.)

artery hypertension, with 8 deaths after the age of 18 years. Sinus rhythm was present in 63 patients (73%) at presentation, but only 54 (63%) were still in sinus rhythm at last follow-up. Only 29 patients (34%) remained arrhythmia-free between the time of the Mustard operation and the last adult follow-up. Of the other 57 patients, 31 (54%) had their first documented arrhythmia before, and 26 (46%) after age 18 years. Supraventricular tachycardia was documented in 41 patients, atrioventricular block in 3, and ventricular tachycardia in 2. Junctional rhythm or sinus bradycardia requiring pacing accounted for the loss of freedom from arrhythmia in the remaining 11 patients. Nineteen patients required permanent pacemakers, 6 before 18 years and 13 after age 18. Eight other patients had pacemakers implanted to permit treatment of tachyarrhythmias. Thirty-two per cent of the adult patients had moderate or severe reduction in the systemic ventricular function on echocardiography, and multivariate analysis identified systemic ventricular dysfunction as an independent risk factor for death. Data from several large pediatric series addressing Mustard follow-up suggest a bimodally distributed hazard of death with early postoperative mortality and then late mortality as these patients approach aduthood. The study of Puley *et al.*[270] extends these observations, showing that the hazard of death persists in this cohort of patients > 18 years of age.

One of the more important inferences from many of the follow-up studies of Mustard and Senning survivors is that of dysfunction of the systemic right ventricle, congestive heart failure and death. The etiologies of the right ventricular dysfunction are likely multifactorial including: longstanding hypoxemia, the increased afterload of the transposition circulation with a systemic morphologically right ventricle, chronic volume loading, inadequate myocardial protection in the earlier eras of atrial switch surgery, episodes of atrial flutter/fibrillation, and the data provided by Millane and colleagues also suggest ischemia and infarction as contributory to late right ventricular dysfunction.[244]

Hornung and his colleagues have provided interesting data showing that in adults with transposition of the great arteries late after the Mustard procedure there is frequently an excessive right ventricular hypertrophic response, possibly contributing to right ventricular dysfunction though demand ischemia.[239A] Furthermore this excessive hypertrophy could promote myocardial perfusion abnormalities as shown by Lorenz and Lubiszewska and their respective colleagues, also contributing to myocardial dysfunction.[236,239,239B] The methodologies for assessing systemic right ventricular function have evolved with the era in which this was studied, and for many years the assessment was qualitative, based on the angiographic appearance of the right ventricle. Then ventricular function was assessed from radionuclide imaging and echocardiographic analysis and even more recently from magnetic resonance imaging. Our own observations indicate that systemic right ventricular dysfunction has been particularly common, both early and late, after Mustard's operation for patients with complex transposition (i.e. those with associated large ventricular septal defect). While there are also data addressing the assessment of right ventricular dysfunction in those patients with simple transposition who survived either the Mustard or Senning operation, it is unclear how common is important dysfunction of the systemic right ventricle. Williams and our colleagues in Toronto suggested that important right ventricular dysfunction late after a Mustard repair appears to be present in at least 10% of the patients.[215] Sarkar and his colleagues[198] found that clinical systemic ventricular failure was uncommon in this group of patients, with 92% of the Senning patients and 89% of the Mustard group in late follow-up in New York Heart Association class I. Helbing and his colleagues in 1994 reported the long-term results of atrial correction for transposition of the great arteries, comparing the Mustard and Senning operations.[219] Firstly except for the difference in loss of sinus rhythm, no important differences were identified in the long-term clinical results of the two types of operation. Approximately 45% of patients in both the Mustard group and Senning group showed evidence of depressed right ventricular function. Indeed, Graham and his colleagues found that in many patients with post-atrial switch functional abnormalities, preoperative abnormalities had already been identified.[223] It has been suggested that inadequate atrial filling contributes to poor right ventricular function, and that this is exaggerated in Mustard's operation when compared to the Senning as in the latter operation more atrial function is preserved.[241,242] There is no doubt that abnormalities of right ventricular function are present both before and after atrial repair of simple and complex transposition of the great arteries, and in some patients progressive deterioration of function may occur. In this regard, Oechslin and colleagues found that the three major causes of death in the growing population of adults with congenital heart disease are sudden, perioperative, and progressive heart failure.[242A] However, despite such abnormalities of function using a variety of methodologies, many of the post-Mustard or Senning patients are in New York Heart Association class I or II. In this regard, lack of symptoms many years after the Mustard operation does not exclude hemodynamic and electrophysiologic abnormalities which may be severe as shown in the study of Bink-Boelkens

and her colleagues.[297] Similar findings have been published by Carvalho and her colleagues.[298] Recently Piran and colleagues documented that adult patients with a systemic right ventricle are at significant risk for heart failure and ventricular dysfunction, and that such patients have a high mortality.[298A]

Tricuspid regurgitation is a well-known phenomenon in patients with transposition of the great arteries and may reflect congenital abnormalities of the tricuspid valve, disruption of the chordal apparatus by balloon atrial septostomy, distorsion of the septal leaflet of the tricuspid valve at the time of ventricular septal defect repair, or some combination of these factors.[250–256] Tricuspid incompetence is also often associated with failure of the systemic, morphologically right ventricle, and is perhaps more common in those who have undergone an atrial switch repair and closure of an associated ventricular septal defect repair than in those with an intact ventricular septum.[252,254] In these patients it is not clear whether the tricuspid regurgitation causes or is caused by the right ventricular failure. Suffice it to say, tricuspid valve replacement in the patient with a failing right ventricle and severe tricuspid regurgitation is often disappointing. Several therapies have been employed to improve the difficult situation of these patients:

- a trial of angiotensin-converting enzyme (ACE) inhibitors[299]
- tricuspid valve replacement
- pulmonary artery banding to prepare the left ventricle for an arterial switch operation, with subsequent arterial switch[252]
- cardiac transplantation.

While some patients may experience some clinical improvement with ACE inhibitors[299] and other anticongestive therapy, such benefits are usually short-lived. Similarly an occasional patient will benefit from tricuspid valve repair, annuloplasty, or replacement, but all-too-frequently, this maneuver will worsen the already failing right ventricle by increasing ventricular afterload, thereby hastening clinical deterioration and death. Van Son and his colleagues have shown regression or improvement in the severity of tricuspid regurgitation after preparatory banding of the pulmonary trunk as a prelude to an arterial switch operation after an earlier atrial switch operation.[252] The intraoperative observations made by transesophageal echocardiography after pulmonary artery banding showed a shift of the ventricular septum from leftward to a midline or nearly midline position, a decrease in right ventricular end-diastolic and end-systolic volumes, improved tricuspid valve coaptation, and a decrease in the severity of tricuspid regurgitation. After the arterial switch procedure, there may be further improvement in the severity of the tricuspid regurgitation. There is now considerable experience with "re-training" of the left ventricle in the patient with a failing right ventricle after the atrial switch operation, with subsequent conversion to an arterial switch.[300–308] The upper age limit for this operation is unclear,[305] but there is some suggestion that this maneuver should not be considered any later than the mid-to-late second decade of life. Clinical experience has demonstrated that some of these patients may require re-banding to obtain an adequate left ventricular myocardial mass before an arterial switch operation can be carried out. Retraining the left ventricle in the face of a failing right ventricle certainly has risk associated with it, and some patients will succumb before the arterial switch operation can be performed, and in some patients an adequate left ventricular mass will not be achieved.[300–308] Amin and colleagues have found that in some symptomatic patients after atrial repair of transposition the absolute and indexed diameter of the left coronary artery was smaller than the right, and the the absolute and indexed diameters of the right coronary artery were greater in symptomatic patients than in asymptomatic patients or control patients.[308A] This may have an impact on the ability to retrain the left ventricle in the post-atrial repair of transposition patient with a failing right ventricle. Sadly, late functional deterioration of the systemic right ventricle after atrial repair is a reality, especially after atrial repair of complex transposition.[309]

There has been considerable interest in the pulmonary vascular bed in patients with simple and complex transposition, and attention has been focused on the development of pulmonary vascular obstruction before and following surgical intervention.[310–328] The presence of bronchopulmonary collateral arteries has been amply documented in the patient with transposition,[324,326–328] and the presence of these collateral arteries makes calculation of pulmonary vascular resistance difficult in the patient with complete transposition.[325] The patient with transposition of the great arteries, large ventricular septal defect, and pulmonary vascular obstructive disease also poses a therapeutic challenge. Some of these patients may benefit from a palliative Mustard or Senning procedure, with the ventricular septal defect left open.[329–335] Some have also advocated a palliative arterial switch, although the pulmonary artery will have a considerably larger caliber than the aortic root.[336,337] The palliative Mustard strategy has also been used in patients with other complex forms of congenitally malformed hearts who have "transposition physiology" with unfavorable intraventricular streaming.[333] From the available clinical reports and from our own experience, the palliative Mustard in the patient with transposition of the great arteries, large ventricular septal defect, and pulmonary vascular obstructive disease has a low operative mortality and results in excellent long-term palliation until the patient is in the fourth decade of life.[331,332,334] There is also limited experience with the creation of a ventricular septal defect and a palliative Mustard operation in the patient with transposition of the great arteries, an intact ventricular septum, and pulmonary vascular obstruction,[335] although we have not had experience with this procedure. Fortunately, pulmonary vascular disease in the young patient with transposition of the great arteries and an intact ventricular septum is uncommon.[320]

Today, the Mustard operation is only rarely used to treat the patient with simple transposition of the great arteries. Some centers will still treat the older patient presenting late with transposition with an atrial switch operation rather than retraining the left ventricle. This approach may still be indicated in the uncommon patient with transposition of the great arteries and fixed left ventricular outflow tract obstruction where an arterial switch operation may be contraindicated. Several years ago, a 17-year-old man was referred to our institution for treatment of complete transposition of the great arteries and a small atrial septal defect. He was profoundly hypoxemic, but had a low pulmonary vascular resistance. Because we were concerned about the ability to retrain the left ventricle in a patient this age, we elected to perform a Mustard operation, and he was discharged home 5 days after this successful surgery. More commonly, the Mustard or Senning operation is combined with either an arterial switch or ventricular switch operation to achieve an anatomic repair in the patient with double discordance (see Chapter 26A). In a rare patient with complete transposition of the great arteries, the morphologically left ventricle will be hypoplastic.[49] In this situation we have combined the Mustard

operation with a bidirectional cavopulmonary connection to unload the ventricle.[338]

Finally, there are a number of reports of successful pregnancy in long-term survivors of the Mustard operation. It is not surprising that some women might experience deterioration in systemic ventricular dysfunction and clearly all such pregnancies must be carefully monitored.[339–342]

What, then are the issues about the atrial forms of palliation (Mustard and Senning procedures) for complete transposition of the great arteries?

- These procedures along with balloon atrial septostomy revolutionized the treatment of patients with transposition of the great arteries.
- The Mustard and Senning repairs conferred a physiological repair because the morphologically right ventricle retained its function as the systemic ventricle.
- Baffle complications of either the systemic venous limb or pulmonary venous limb were not uncommon.
- Severe bilateral pulmonary venous obstruction was unforgiving.
- Because of the frequent damage to the sinus node and its artery, sick sinus syndrome was common, and with time many patients lost normal sinus rhythm.
- Because of the orientation of the left ventricular outflow tract, pulmonary perfusion favors the right lung. This will promote a ventilation/perfusion mismatch.
- Atrial flutter/fibrillation as a consequence of sick sinus syndrome could seriously compromise these patients.
- Sudden cardiac death is a reality for some late survivors of atrial repair.
- Late systemic right ventricular dyfunction may jeopardize the long-term well-being of Mustard–Senning survivors, but this complication seems more severe in the transposition and VSD group.
- Late tricuspid regurgitation could reflect right ventricular failure and annular dilatation; it also could be related to congenital or acquired problems with the tricuspid valve especially in the transposition and VSD group.
- Some patients with progressive and refractory right ventricular failure could undergo left ventricular retraining, followed by Mustard or Senning takedown and arterial switch operation.
- The maximum age to consider left ventricular retraining is unclear, but likely in early-to-mid adolescence.
- Severe baffle-related pulmonary venous obstruction may prepare the left ventricle of an occasional patient for an arterial switch operation.
- The Mustard or Senning survivor requires careful lifelong cardiac surveillance.
- The Mustard or Senning operation may still be an option for the patient whose anatomy is not favorable for an arterial switch or Rastelli-type repair.
- The rare patient with complete transposition of the great arteries and an intact ventricular septum presenting in late adolescence or adulthood may be candidates for an atrial repair.
- The patient with transposition, VSD, and pulmonary vascular disease may be a candidate for either a palliative Mustard or arterial switch repair, leaving the VSD open.
- The Mustard or Senning operation is still performed as part of the double-switch option for patients with congenitally corrected transposition of the great arteries (see Chapter 26A).

All references can be found at the end of the book. See pp. 738–47 for Chapter 25A.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

25B

Robert M. Freedom, Shi-Joon Yoo, and William G. Williams

Transposition of the Great Arteries: Arterial Repair

Despite some subtle and not so subtle anatomical differences between the normal heart and the heart with simple or complete transposition of the great arteries and no other associated cardiac anomalies,[1–3] the logical approach to correction would be to switch the aorta and its coronary arteries with the pulmonary trunk. This would then position the aorta with the coronary circulation above the appropriate morphologically left ventricle and the pulmonary trunk above the morphologically right ventricle. As we discussed in the previous chapter (Chapter 25A), this logic had not escaped the early surgical pioneers of our specialty, but the technical challenges thwarted the attempts of anatomical repair performed in the early 1950s.[4–9] It is now over a quarter of a century ago when Adib Jatene of Sao Paulo, Brazil, performed the first successful arterial switch operation with coronary artery relocation in a patient with transposition of the great arteries and ventricular septal defect. The left ventricle had been prepared for the arterial switch operation by virtue of the large ventricular septal defect (Fig. 25B-1).[10,11] This achievement was accomplished some 16 years after Senning's method of atrial repair for transposition[12] and 12 years after Mustard's "baffling" operation.[13] This chapter will review the results and follow-up issues for patients undergoing arterial switch surgery for transposition of the great arteries.

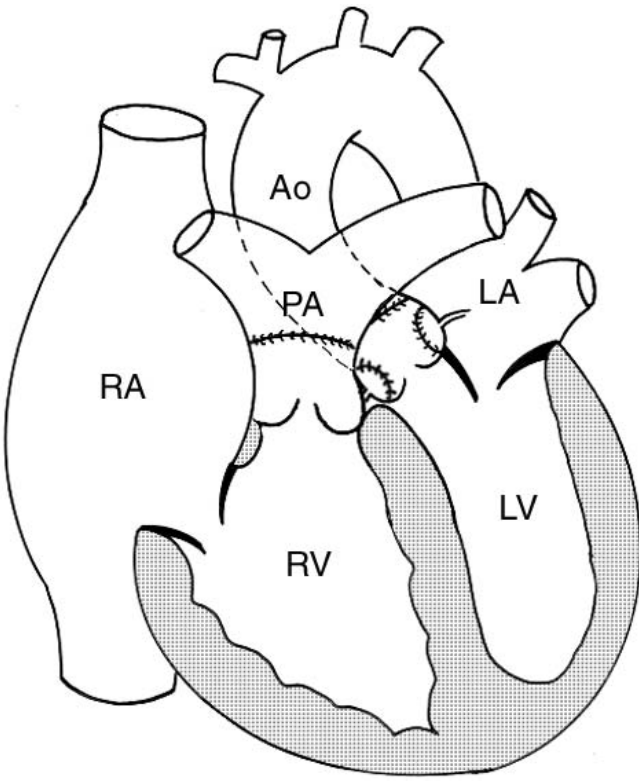
Morphological considerations

In the previous chapter (Chapter 25A), the basic anatomy of transposition of the great arteries in its simple and complex expressions was examined in detail. We and others have thoroughly reviewed elsewhere those morphological features that both occur with and complicate hearts with transposition of the great arteries.[14–22] Any number of anatomic factors have been implicated as potential risk factors for the arterial switch operation including unusual coronary artery patterns, associated ventricular septal defect, obstructive anomalies of the aortic arch, and right ventricular hypoplasia. Many of these factors as we will see were neutralized by one or more institutions as they gained increasing experience with the arterial switch operation.

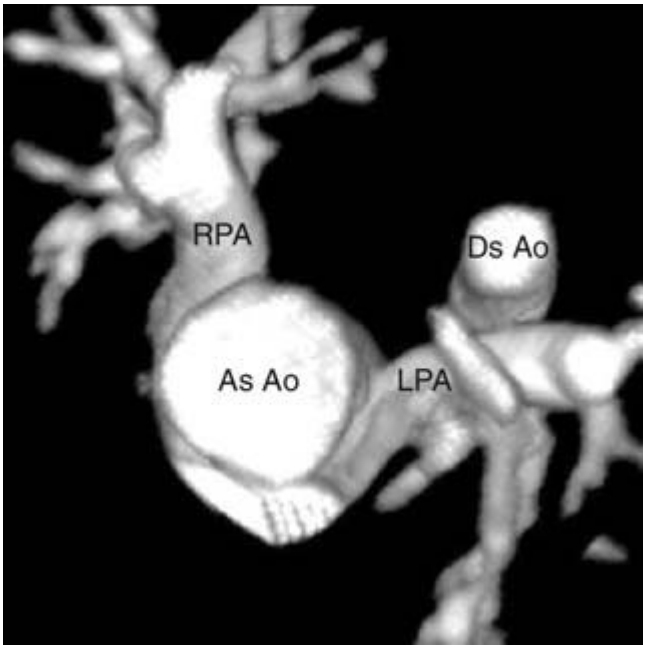
The coronary arteries

The aortic origin and epicardial distribution of the coronary arteries in hearts with complete transposition of the great arteries have been cataloged for many, many years, indeed far before, but perhaps in anticipation of, successful arterial repair.[23,24] Before the first successful arterial switch operation, the coronary arteries were most vulnerable to injury during the Rastelli operation when a conduit was interposed between the right ventricle and the pulmonary arteries. Anomalous origin of the left anterior descending coronary artery originating from the right coronary artery and coursing in front of the transposed aorta was of course vulnerable to injury during the right ventricular surgery, as were the large infundibular branches and accessory anterior descending branches, concerns applicable as well to the patient with tetralogy of Fallot. But once the arterial switch became a reality, a tremendous interest in the coronary arteries was rekindled. This interest focused on the nomenclature applied to the aortic origin of the coronary arteries; the many abnormalities of aortic origin and epicardial course; stratification of outcome of arterial switch operation by coronary artery anomaly; preoperative recognition of the coronary artery anatomy, especially that egregious condition, the so-called intramural coronary artery; surgical maneuvers to deal with specific coronary artery abnormalities; sequelae of myocardial ischemia including assessment of wall motion abnormalities, and late follow-up; and unique abnormalities of the coronary circulation in the patient with transposition including anomalous origin of the left coronary artery from the main pulmonary trunk.[14,17,25–72]

The coronary arteries in transposition almost always originate from the posterior facing sinuses of the aortic valve.[14,17,25–75] But the nomenclature addressing coronary artery origin is more complex than the designation of right coronary artery and left coronary artery as in the normal heart with levocardia, atrial situs solitus, concordant atrioventricular and ventriculoarterial connections. Even to this day there is not unanimity of opinion of coronary artery designation although many now use the so-called Leiden convention (Fig. 25B-2).[51,52,58] However, even using this convention, it became apparent that subtle variations in coronary artery origin in relation to the aortic commissure, multiple coronary ostia, and certain patterns of single coronary artery could complicate the arterial switch operation. Indeed, early in the accumulating arterial switch experience, some advocated the so-called arterial switch operation without coronary artery relocation using the so-called Damus–Kaye–Stansel maneuver (see later in this chapter). This surgical maneuver was used in those patients when the surgeons considered specific coronary artery anatomy as a particularly significant risk: i.e. an intramural coronary artery; or side-by-side great arteries. In this surgical approach, the main pulmonary trunk is divided and a connection between the proximal main pulmonary trunk and ascending aorta is made, thus providing a non-obstructed systemic outlet. To achieve a biventricular repair the ventricular



A



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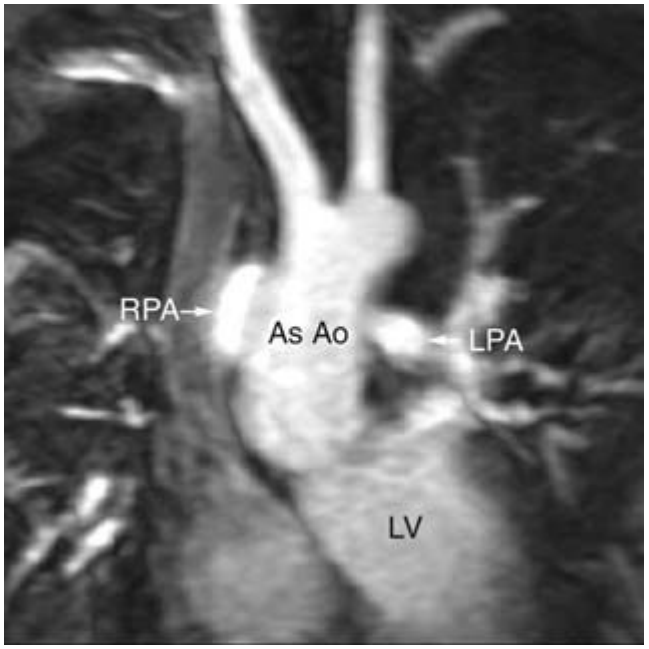


C

Fig. 25B-1 Arterial switch operation. Illustration (**A**) and contrast-enhanced MR angiograms (**B**, **C**) showing the result of arterial switch operation. The ascending aorta (Ao) and main pulmonary artery (PA) are divided and the coronary arteries are transferred to the pulmonary arterial root. The great arteries are sutured in a switched position. In **B** and **C**, both branch pulmonary arteries (LPA and RPA) are mildly compressed and stretched as they pass backward around the ascending aorta (As Ao). Ds Ao, descending aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

septal defect is closed to the pulmonary valve and continuity between right ventricle and distal pulmonary trunk is achieved usually with an extracardiac conduit.

The marked variability in both the orientation of the great arteries and the coronary artery origins in patients with complete transposition has been well documented in both post-mortem, angiographic and echocardiographic investigations.[14,17,25–75] This variability has led to a number of attempts at nomenclature but a system combining accurate detailed cataloging of the variations plus a comprehensive but simple shorthand annotation, has been elusive. Many groups use the Leiden convention (Fig. 25B-2)[51,52,58] but this only refers to the origin of the coronaries from the aortic sinuses. The classification systems and various terminologies that have been proposed are discussed in detail elsewhere.[23,25,49,51] There are three important components of the coronary artery anatomy for the

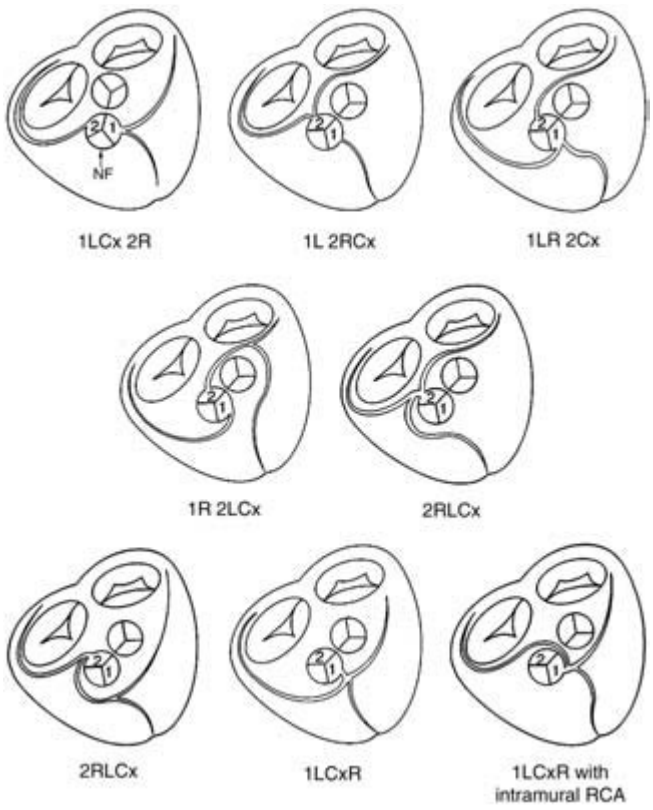


Fig. 25B-2 Nomenclature and variations of origins and courses of coronary arteries in complete transposition of the great arteries. Coronary sinuses are named as observed from the nonfacing sinus (NF) of the aortic valve. The aortic sinus on the observer's right-hand side is called "right-hand facing sinus" or "sinus 1." The aortic sinus on the observer's left-hand side is called "left-hand facing sinus" or "sinus 2." Coronary arteries: L, left anterior descending; Cx, circumflex; R, right. 1LCx 2R pattern is the most common type seen in *c*. 70% of cases. The second most common form is 1L 2RCx and is commonly seen when the great arteries have a side-by-side relationship.

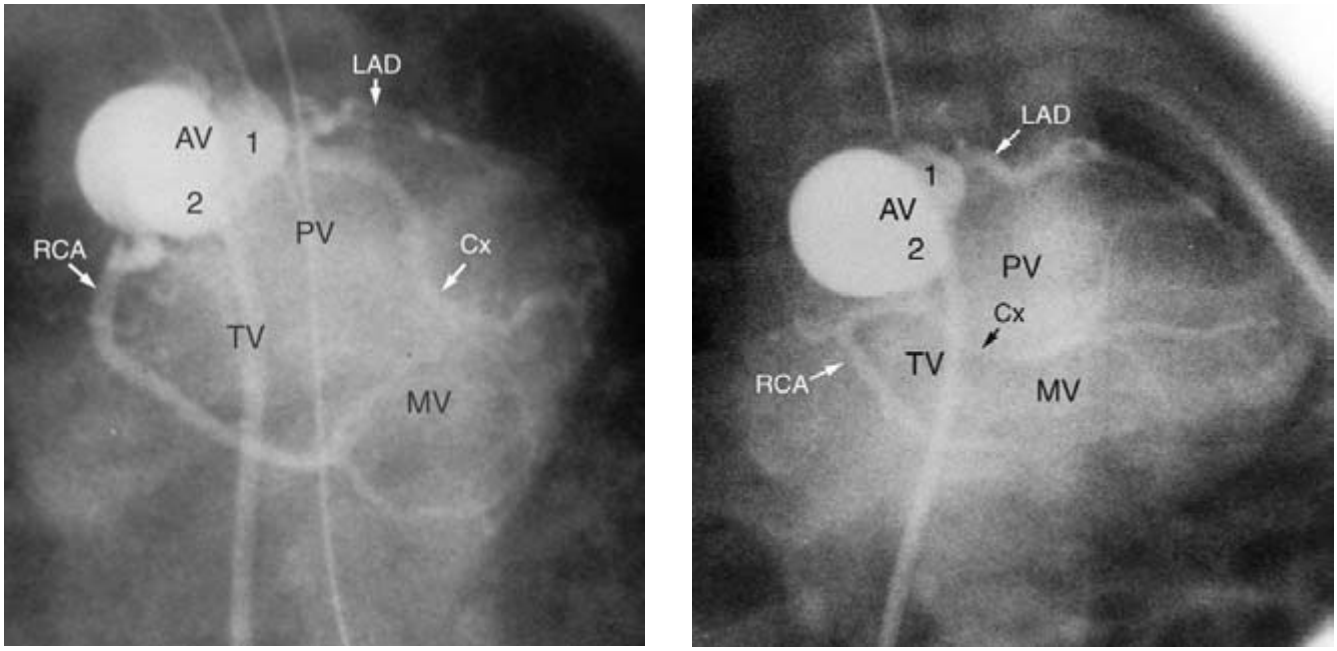
surgeon: (1) the relationship of the great arteries (and thus the designation of the sinuses); (2) the location of the coronary artery origins within one or both sinuses; (3) the epicardial course of the proximal vessels. When these three components are taken into account, the possible variations in the coronary artery anatomy are enormous, although as pointed out by Wernovsky and Sanders,[37] nine types account for *c*. 95% of all patients with transposition of the great arteries.

Relative to the pulmonary artery, the aorta may be anywhere from right posterior to right anterior, to left anterior. Gittenberger-de Groot[51] used the terminology of "facing" sinuses to refer to the two sinuses facing the pulmonary artery, and proposed the term "nonfacing" to refer to the third sinus rather than using the term "noncoronary," and we agree with this designation (Fig. 25B-2). Like Wernovsky[37] and Angelini and colleagues[27] we prefer to label the sinuses as "facing" based on the great artery orientation using anatomically correct descriptive terms such as anterior and posterior facing sinuses, left and right facing sinuses, left anterior and right posterior facing sinuses, etc., rather than using alphanumeric designations.

As no one shorthand system allows information on all three aspects of coronary anatomy to be neatly encoded, again, like Wernovsky[37] and Angelini[27] we find that a brief verbal description of an individual's anatomy, often supplemented by a simple diagram, to be of most help to the surgeons. Information on great artery positions and the surgically relevant coronary anatomy can be obtained from both echocardiography[32,35–37] and angiography. The anatomy as displayed echocardiographically can be represented diagrammatically as if the great arteries are seen in cross-section as viewed from the apex of the heart, equivalent to a parasternal short axis view.[32] The "laid-back" balloon occlusion aortogram as described by Mandell *et al.*[45] and as critically evaluated in Toronto[46] displays the anatomy in a somewhat similar fashion (Fig. 25B-3). In contrast, conventional aortography filmed in a combination of RAO/LAO or PA/lateral projections, displays the anatomy of the great arteries and the coronaries as if the viewer were looking at the chest wall of the patient. Diagrammatic representations of these two general projections have been compared by Wernovsky.[37] Whatever imaging modality or projection is used to obtain the relevant information, we prefer to display the information two-dimensionally as if viewed from directly in front of the patient.[32,37,49,51,53]

In transposition of the great arteries, the majority of patients have a right anterior aorta relative to the pulmonary artery as demonstrated in the post-mortem study and literature summary of Gittenberger-de Groot[51,52] and since then, by Smith,[60] and Angelini and their respective colleagues.[27] A position of the aorta to the right of the pulmonary artery ("side by side great arteries"), a rightward anterior aorta, or an aorta directly in front of the pulmonary artery ("AP great arteries"), accounts for the vast majority of patients. A rightward posterior aorta (so-called posterior transposition) is well recognized[14,17,76–85] as is a leftward anterior (so-called L-malposed) aorta[66–89] amongst patients with atrioventricular concordance, but ventriculoarterial discordance.

Gittenberger-de Groot[51] studied the alignment of the "facing" or "interarterial" commissure between aorta and pulmonary artery. All 103 specimens had two aortic sinuses facing the pulmonary artery but there was perfect alignment between the facing commissures in only two-thirds of these. An additional group had "minor" malalignment but 19% had "major" malalignment which was not especially related to great artery positions. They suggested that this malalignment could increase the complexity of coronary transfer if attention was not paid to planning the excision of pulmonary sinus wall to create space for the transferred "button." The coronaries almost always arise from the facing aortic sinuses. In reviewing the published series to date together with their own specimens, Gittenberger-de Groot[51] only found two cases where a coronary originated from the nonfacing aortic sinus.[23] Origin of a coronary artery from the pulmonary artery has been reported in a patient with transposition.[40] The coronaries usually arise from the mid point of the facing sinuses, usually just below the sinotubular ridge[51] although this group also reported 5 of their 103 cases having coronaries arising above the sinotubular ridge. Within a sinus, the most common displacement of a coronary origin is toward the facing commissure and coronary origins have been observed that actually involve the commissure. Gittenberger-de Groot[51] denoted the origin as "ectopic" if it was displaced more than half the distance from sinus midpoint to the facing commissure. Angelini and colleagues[27] refers to these displaced origins as "commissural" origins and noted that there was some degree of displacement in 30% of their cases where there was a rightward



A B

Fig. 25B-3 Examples of coronary arterial anatomy shown in laid-back aortograms. **A**. 1LCx 2R pattern. **B**. 1L 2RCx pattern. AV, aortic valve; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; MV, mitral valve; PV, pulmonary valve; RCA, right coronary artery; TV, tricuspid valve.

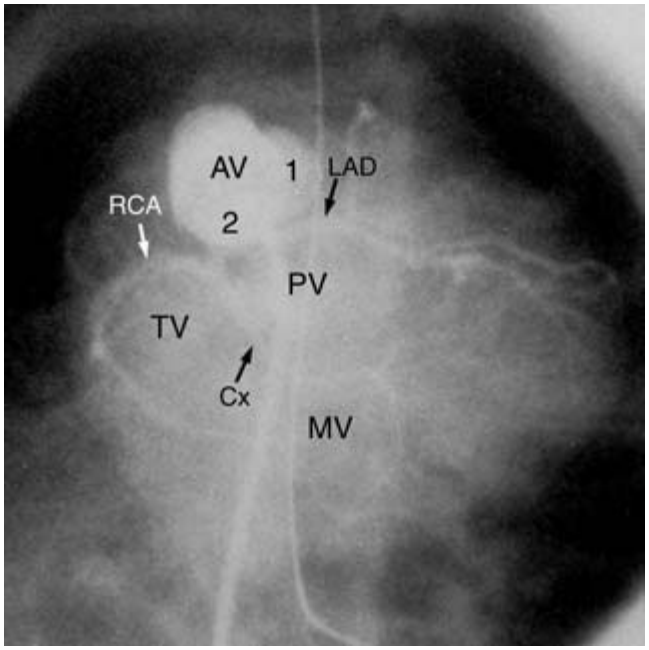


Fig. 25B-4 Single coronary artery with intramural course of left anterior descending coronary artery. Laid-back aortogram shows a single coronary artery arising from the sinus 2 or left-hand sinus. It bifurcates into the left anterior descending coronary artery (LAD) and the common stem for the right coronary (RCA) and circumflex (Cx) arteries. The left anterior descending coronary artery has an intramural segment as it courses leftward along the aortic sinus wall. AV, aortic valve; MV, mitral valve; PV, pulmonary valve; TV, tricuspid valve.

anterior aorta and two coronaries from facing sinuses. Obviously, with such displacement, there is a risk of an oblique origin and proximal course, including intramural or interarterial course. Gittenberger-de Groot[51,52] noted an intramural course in 3% of their cases with all being interarterial but an intramural component may be present with vessels arising from midpoints of facing sinuses, or above the sinotubular ridge (Fig. 25B-4).[27] While an interarterial course does not of itself equate with an intramural component, the chances of such a course being intramural are high.[41,51,52] With a rightward anterior aorta, approximately two-thirds of patients will have two coronaries from facing sinuses with a typical branching pattern and distribution (so-called "usual" coronaries). The next most common pattern is for the right coronary artery from the right anterior facing sinus, to give a circumflex which travels a retropulmonary course. Beyond that, the variations are almost endless. Note should be made that there is general agreement that in patients with side by side great arteries, there is an increased incidence of these unusual patterns. Several years ago Sauer and Gittenberger–de Groot presented an elegant review of the anatomic types of transposition of the great arteries and the various coronary artery patterns.[90] Even more recently Li and her colleagues working with Professor Robert Anderson addressed those subtle features of coronary arterial origin that could affect the outcome of the arterial switch procedure.[91] They found in 20% of hearts unusually high take off, a paracommissural orifice or a tangential origin of the coronary arteries, all features which could cause technical difficulty in coronary artery transfer.[91]

Among other considerations for an arterial switch operation, the morphologic left ventricle must be of adequate size, wall thickness, and function to support the systemic circulation.[92–95] As will be discussed later in this chapter, the left ventricle of

some patients must be prepared or retrained before the arterial switch operation can be safely performed. But there are other anatomic issues as well. Uemura and his colleagues concluded that a non-stenotic bicuspid pulmonary valve was not a contraindication to the arterial switch operation.[96] This group proceeded to the arterial switch repair in 6 patients with an adequate diameter of a bicuspid pulmonary valve (> 100% of the calculated normal aortic orifice). Postoperative catheterization (*c.* 8 months after the procedures) showed no pressure gradient between the left ventricle and the neoaorta except for a 34 mmHg difference in 1 patient who had undergone simultaneous subpulmonary myotomy. Echocardiography (7 years later in the patient with the longest follow-up) has shown no more than slight regurgitation across the bicuspid neoaortic valve, with no progressive increase of blood velocity across the valve. They concluded on the basis of this relatively modest follow-up interval that the arterial switch procedure remains an option of choice for patients with a bicuspid pulmonary valve, providing there is no severe subpulmonary stenosis. Clearly a longer follow-up with the abnormal pulmonary valve in the systemic circulation will be necessary to confirm this conclusion. Wernovsky and his colleagues at the Boston Children's Hospital also addressed the results of the arterial switch procedure in patients with transposition of the great arteries and abnormalities of the mitral valve or left ventricular outflow tract.[97] In their early experience with 290 patients undergoing the arterial switch and operated between January 1983 and October 1989, 30 (10.3%) had abnormalities of the mitral valve or left ventricular outflow tract. These included isolated pulmonary valve stenosis in 9 patients, dynamic subpulmonary stenosis in 5, anatomic or fixed subpulmonary stenosis in 7, abnormal mitral chordal attachments in 2, or a combination of anomalies in 7. There were 2 early deaths, 1 in a patient with unrecognized mitral stenosis and subpulmonary (neoaortic) membrane and 1 late death due to coronary artery obstruction.[97] Of the patients with isolated pulmonary stenosis only one required a pulmonary valvotomy. Those patients with anatomic subpulmonary obstruction due to accessory atrioventricular valve tissue or to a subpulmonary membrane did very well following resection of the obstructing tissue. Only those patients with a combination of abnormalities that included obstruction due to posterior deviation of the infundibular septum had significant residual outflow tract obstruction. Similar findings and conclusions were published by Sohn and colleagues.[98] Both groups caution about using the preoperative left ventricle-to-pulmonary artery pressure gradient as this may overestimate the severity of the obstruction because of the excessive pulmonary blood flow inherent to transposition physiology.[97,98] Kovalchin and his colleagues have assessed from the pathology and clinical perspectives pulmonary valve eccentricity in specimens and patients with complete transposition of the great arteries.[99] They found that in many specimens of hearts with transposition of the great arteries with or without ventricular septal defect, the pulmonary valve leaflets had unequal cusp sizes which resulted in eccentric closure. Further analysis showed that the right cusp was usually the smallest and the posterior cusp was usually the largest and was anatomically related to the membranous ventricular septum and anterior leaflet of the mitral valve. They speculate that such pulmonary valve eccentricity may be one reason for aortic regurgitation after the arterial switch operation.[99]

Ventricular hypoplasia in some series has been considered a risk factor for the arterial switch procedure.[100–104] Indeed, some have asked whether a high-risk biventricular repair is always preferable to conversion to a single ventricle repair.[105] This consideration is certainly germane to the patient with unbalanced ventricles considered for the arterial switch. Perhaps left ventricular hypoplasia is less forgiving as there are any number of maneuvers that one can employ to unload the right ventricle: fenestration of the atrial septum; fenestration of the ventricular septal defect patch, or in those infants older than a few months and low pulmonary vascular resistance, consideration of a bidirectional cavopulmonary shunt. Right ventricular hypoplasia can occur in some patients where the tricuspid valve annular dimension is normal or nearly so. In this situation, straddling and overriding of the tricuspid valve contributes to underfilling of the right ventricle. In consideration of tricuspid valve hypoplasia, how small is too small to consider a biventricular repair? Rebeyka[106] in discussion of a recent paper by Serraf and his colleagues from the Marie Lannelongue hospital suggests that a tricuspid valve *Z*-value ≥ 4 would be consistent with a favorable outcome for a biventricular repair. He indicated that this would adhere to the guidelines of George Trusler who suggested that a tricuspid valve orifice diameter measured intraoperatively at least two-thirds of normal would permit a biventricular repair. A number of mitral valve anomalies occur in patients with complex transposition with the potential for complicating a biventricular repair.[21,22] Fraisse and colleagues from their review of the literature state that mitral valve anomalies are identified and may complicate arterial repair in from 2.8% to 5% of patients. Also they state that in autopsy studied, the incidence of mitral valve anomalies is considerably higher, approaching 30%.[106A]

Outcome analysis in the era of the arterial switch operation

One of the obvious disadvantages to atrial repair of transposition of the great arteries was the attrition and morbidity from birth through initial palliation until the atrial repair could be carried out (see Chapter 25A). Despite a very aggressive approach to palliate even moderate hypoxemia in the era of the Mustard operation at the Toronto Hospital for Sick Children, the attrition amongst potential Mustard patients was still substantial, about 11%.[107–109] In the era of the arterial switch operation, there is still some attrition before the arterial switch operation can be performed, but in Toronto this is substantially less than in the Mustard era.[110] We reviewed all neonates with transposition of the great arteries and a patent foramen ovale who died before arterial switch surgery between 1988 and 1996.[110] Of 295 neonates with simple transposition of the great arteries, we identified 12 (4.1%) neonates who died before the arterial switch procedure, and in 11 of the 12, the cause of death was attributed to the sequelae of profound hypoxemia from inadequate atrial mixing. Contributing factors were prematurity, severe respiratory distress syndrome, and persistent pulmonary artery hypertension of the newborn. None of these patients was diagnosed prenatally, although it is likely that at least some of these patients had fetal ductal constriction and a very restrictive arterial duct as shown some years later by Maeno and his colleagues.[111] Chantepie and colleagues carried out a similar, but collaborative study.[112] In five French centers of pediatric cardiology, data of all the neonates with isolated transposition of the great vessels who died before arterial switch operations between January 1986 and June 1996 were obtained from

reviewing hospital files, echocardiography records and autopsy reports. Among 199 neonates with transposition of the great vessels, 20 (9.9%) died before surgery. The death was related to intracranial haemorrhage in 1 premature neonate, severe and early hypoxemia in 13 full-term patients (group A) and later sudden collapse in 6 patients (group B). In group A, the symptoms occurred within 20 min after the birth and included cyanosis (n = 12), acute respiratory distress (n = 8), and shock (n = 4). Despite assisted ventilation (n = 13), bicarbonate infusion (n = 12), prostaglandin E_1 (n = 7), inotropic drugs (n = 5) and balloon atrioseptostomy (n = 7), death occurred at the median age of 5 h. The patent foramen ovale was absent or tiny in 10 patients, normal in one patient and not specified in 2 patients. The ductus arteriosus was patent in 10 patients and not specified in 3 patients. In group B, the neonates were initially in a good hemodynamic condition. Unexplained death occurred between 2 and 5 days after the birth: 1 infant with a large patent foramen ovale did not receive prostaglandin E_1, 4 patients died a few hours after an angiographic study or a balloon atrioseptostomy was performed in a catheterization laboratory, and 1 child suffered from a cerebral anoxia owing to a nuchal cord. This group concluded that the high preoperative mortality rate in isolated transposition of the great vessels is mainly owing to absent or small atrial shunt, and furthermore these findings suggest that only prenatal diagnosis of transposition of the great vessels with immediate balloon atrioseptostomy could avoid a fatal outcome. There is some disagreement in the literature as to whether prenatal recognition of transposition of the great arteries leads to better outcome of the arterial switch procedure.[113,114] Kumar and colleagues suggest that prenatal recognition leads to an improved status before the arterial switch procedure, but does not confer any appreciable difference in surgical mortality.[113] Bonnet and his colleagues conclude that prenatal recognition of transposition of the great arteries does confer an advantage as to outcome of the arterial switch procedure.[114] The study of Lupoglazoff and colleagues does not lend support to the inference that prenatal recognition of transposition of the great arteries does in fact confer an advantage.[115]

Attempts to logically and thus anatomically correct transposition of the great arteries began nearly 50 years ago with the pioneering efforts of Bjork and Bouckaert in 1954, Mustard and his colleagues in 1954, Kay and Cross in 1955, and Idriss and colleagues in 1961, amongst others.[4–9] Some of the pioneering operations were very inventive to say the least.[6,8,9] Mustard and his colleagues operated on 7 patients, unfortunately with no survivors.[7] In several of the patients operated by Mustard a striking discrepancy between the diameters of the aorta and the pulmonary trunk led to the abandoning of the arterial switch attempt, and in others only one coronary artery was surgically transposed, usually the left.[10,11] May 4, 1975 should be a day celebrated by those who care for the patient with congenital heart disease.[11] On this date, Jatene and his colleagues operated on a 3-month-old girl with complete transposition of the great arteries with a large ventricular septal defect. She underwent an arterial switch operation with relocation of both coronary arteries and via a right ventriculotomy closure of the ventricular septal defect. Sadly she died on the third postoperative day from renal failure and hyperkalemia, before peritoneal dialysis was begun. The post-mortem examination showed that the anatomical repair was intact.[11] Just 4 days after the first operation Jatene and his colleagues operated on a 42-day-old boy with complete transposition of the great arteries with a large ventricular septal defect. This infant survived the arterial switch operation, relocation of both coronary arteries, and closure of the large ventricular septal defect. Ten months after the operation he was thriving and had gained 4.6 kg. Just as the Blalock–Taussig shunt, the Blalock–Hanlon atrial septectomy, the Glenn operation, the Norwood procedure, the Damus–Kaye–Stansel procedure, the Fontan procedure have been assimilated into the "technospeak" of pediatric cardiology and cardiovascular surgery, the Jatene operation has rightly assumed this status as well.

Castaneda and his colleagues pointed out that Jatene recognized early in his experience that a left ventricle that has developed for some time in the low-resistance pulmonary circuit could fail acutely following the arterial switch procedure as the left ventricle in this situation would not have an adequate mass to support the systemic circulation.[75,116] For this reason, Jatene recommended the arterial switch procedure be performed in those patients with transposition of the great arteries with either a large ventricular septal defect or a large patent arterial duct.[11,116] The reality for patients with complete transposition of the great arteries is that only about 20% of all such patients have a large ventricular septal defect or a large patent arterial duct. This was clearly evident from the natural history studies cited in the previous chapter, mainly the contribution from Liebman, Cullum and Belloc.[117] To overcome this obstacle then for the majority of patients with transposition of the great arteries, Yacoub and his colleagues developed a two-staged approach to anatomic repair.[118,119] The initial stage was to prepare the left ventricle by banding the pulmonary artery after a balloon atrial septostomy had been performed.[118,119] Because this could result in severe hypoxemia by reducing the effective pulmonary blood flow, banding of the pulmonary trunk was usually combined with the performance of a systemic-to-pulmonary arterial shunt. The second stage was then to take down the arterial shunt, close the atrial septal defect, and perform the arterial switch operation with coronary artery relocation. In the early days of the two-staged anatomic repair, a variety of investigations were used to determine if an adequate left ventricular mass was achieved, including the use of vectorcardiography and later the shape and position of the interventricular septum from cross-sectional echocardiography.[120–122] The two-staged approach to anatomic repair, while certainly logical, constituted some hazard to the early survival of these patients.[118–123]

From 1975 to the early 1980s, many centers began tentatively introducing the arterial switch operation primarily for patients with transposition of the great arteries and large ventricular septal defect where the early and longer term outcomes of atrial repair were clearly disappointing, at least in comparison to the results of atrial repair for transposition of the great arteries and intact ventricular septum[124–127] (see also Chapter 25A: Figs 25A-7, 25A-8). Castaneda and his colleagues at the Children's Hospital in Boston pioneered from the 1970s early corrective surgery for many forms of congenital heart disease, eschewing the more commonly used two-staged approach of initial palliation with later repair. It should therefore come as no surprise that he advocated anatomical repair of simple transposition of the great arteries in the neonate, reasoning correctly that the left ventricle of the neonate is well suited for systemic function as it supported systemic pressures during gestation and throughout the first weeks of life until the pulmonary vascular bed remodeled.[116] From May 1983 through December 1, 1983, 14 consecutive neonates underwent an arterial switch operation

at a mean age of 6.6 days and a mean weight of 3.4 kg at the Children's Hospital in Boston, with 1 surgical death.[116] These data were presented at the 20th annual meeting of the Society of Thoracic Surgeons held in San Antonio, Texas from January 23–25, 1984, just about 20 years ago. Thus began the era of the arterial switch operation for the neonate with complete transposition of the great arteries.

The management of the neonate with complete transposition of the great arteries began to change as well, coincident with neonatal arterial repair. Those very hypoxemic neonates were treated with an E-type prostaglandin and balloon atrial septostomy [128–131] (see Chapter 25A). Rather than transfer the critically ill neonate to the catheter laboratory, there was increasing experience with the performance of balloon atrial septostomy[132] under echocardiographic guidance in the neonatal intensive care unit.[133–135] The imaging modalities also began to change, and many babies with simple and complex transposition of the great arteries were sent to the operating theater for arterial switch surgery on the basis of echocardiographic examination alone.[136–141] At first this seemed to some like heresy, but again, with increasing experience and confidence, most babies with transposition do not require angiographic imaging. Those babies with unbalanced ventricles, multiple or Swiss cheese-type of ventricular septal defects, or those with an unusual coronary artery pattern may still be referred for angiographic imaging.[17,141] Over the past decade there has been an interest in standardizing the preoperative management of the neonate with transposition, acknowledging the morbidity associated with invasive investigations.[136,139]

For those centers with a large and rewarding experience with atrial repair of transposition of the great arteries, there was considerable apprehension in adopting a new and potentially risky procedure for the patient with transposition. Many could not duplicate the excellent results from Boston, or Leiden, or indeed from other centers.[116,142,143] In 1984, Stark in a rhetorical editorial asked of patients with transposition of the great arteries: which operation?[144] At this time there were any number of operations for the patient with transposition of the great arteries: atrial repair of the Mustard or Senning types,[12,13] the Jatene operation,[10,11] the two-stage anatomic repair of Yacoub,[118,119] the Damus–Kaye–Stansel of anatomic correction without coronary relocation,[145–148] the operation of Nikaidoh of aortic translocation and biventricular outflow tract reconstruction,[149] the anatomical correction of transposition by the method of Bex and his colleagues,[150] the Rastelli operation[151–153] (see Chapter 25C), and the operation suggested by Aubert and his colleagues.[154] In the Bex operation, the pulmonary valve is sacrificed and the entirety of the muscular aortic root (including about 2.0 mm of the subaortic infundibulum), the aortic valve and coronary arteries are completely mobilized, slightly rotated and sutured to the pulmonary annulus. The main pulmonary artery is then sutured directly to the right ventricle. Rubay and colleagues asked in 1988, "To switch or not to switch?" and asked whether one should employ the Senning as an alternative to the arterial switch.[155] We are aware that evolution results from both internal and external forces, and this is likely true for the introduction of new surgical procedures. The singular accomplishment of Jatene and his colleagues was globally recognized by those caring for the patient with complete transposition of the great arteries.[10,11] This was the external force. The internal force was the scrutiny of our own Mustard results in the face of Jatene's accomplishment and then to critically examine our own Mustard results at least initially in the patient with transposition and large ventricular septal defect. With the attrition before the Mustard operation, the early and disappointing late results for atrial repair and ventricular septal defect closure in the patient with complex transposition, the evolution to arterial repair in this group was inevitable.[74,107–109]

As an institution grapples with the evolution from one form of surgical therapy to a newer and bolder form of therapy, what are the scientific, ethical, and logistical considerations in introducing a new operation? This question has been asked by Bull and her colleagues of the Great Ormond Street Hospital for Sick Children.[156] We are reminded that there is not a Federal Drug Administration agency (USA) or Health Protections Branch (Canadian) to oversee the implementation of new surgical procedures. Bull and her colleagues have attempted to answer this question by analyzing the outcomes of 325 consecutive neonates with simple transposition of the great arteries admitted before, during, and after the preferred management changed from the Senning operation to the arterial switch (1978–98); and 100 consecutive neonates requiring a different neonatal open heart operation that did not change in that period.[156] The mortality before and early after operation reconstructed sequentially as the series evolved and retrospectively once the series was complete; actuarial survival associated with the different treatment strategies was calculated. For both the transposition and the comparison group, early mortality in 1998 was lower than in 1978. During that period, however, there was a phase temporally related to the adoption of the switch operation in which early mortality for transposition increased. Actuarial survival of recent patients with "intention to treat" with arterial switch is superior to those with intention to treat with the Senning operation, as predicted when the switch operation was first adopted. A period of increased hazard for individual patients may occur when a specialist community, a particular unit, and an individual surgeon are all learning a new technique concurrently. Obtaining informed consent during this time of uncertainty is helped by clarity about the objectives of treatment and availability of relevant local and international data. Any number of publications in the late 1980s and early 1990s seemed to indicate that for the patient with simple transposition, arterial repair had a higher mortality than atrial repair with the exception of few centers.[38,102,127,157,158] Yet the quest for anatomical correction of transposition in its simple and complex forms continued despite a prolonged learning curve for many institutions. The reality of baffle-related problems, right ventricular dysfunction and failure, tricuspid regurgitation, debilitating rhythm disturbances, sudden death, all realities for the survivors of the Mustard or Senning repair (see Chapter 25A), were the impetus to overcome the technical problems of the arterial switch procedure and to define excellent surgical results. Data from Toronto which were portrayed in Figs 25A-7 and 25A-8 resonated strongly in the evolution from atrial to arterial repair for transposition of the great arteries.

As one surveys the early literature devoted to arterial switch surgery, the focus of many of the papers were on technical factors devoted to coronary transfer, mobilization of the pulmonary artery, shape of patch used to close the explanted coronary ostia, and to identify so-called risk factors: coronary artery anatomy, spatial relationships between the great arteries and associated malformations. Quaegebeur and his colleagues from Leiden reported in 1986 on the outcomes of 66 patients including 23 with

transposition and intact ventricular septum, 33 with transposition and large ventricular septal defect, and 10 with double-outlet right ventricle with subpulmonary ventricular septal defect who underwent the arterial switch procedure from 1977.[57] Eight patients died including 1 with transposition and intact ventricular septum, 6 with transposition and large ventricular septal defect, and 1 with double-outlet right ventricle. Including the hospital deaths, the actuarial survival rate for the entire group was 81%. Incremental risk factors for death included low birth weight, transposition and large ventricular septal defect, double-outlet right ventricle with subpulmonary ventricular septal defect, and a large patent arterial duct. In this series neither coronary artery anatomy nor position of the great arteries were risk factors. Castaneda and his colleagues reported in 1988 the early results of the Congenital Heart Surgeons Study of 187 neonates with simple transposition entered into a 20-institution comparative study between January 1, 1985 and June 1, 1986.[159] Three surgical protocols were used by the participating institutions: Mustard atrial repair, Senning atrial repair, and arterial switch operation. Overall survival among the 187 patients was 81% at 1 year. The only risk factors for death were low birth weight, date of entry into the study (earlier date) and an arterial switch protocol in the group of institutions identified as high risk for repair.[159] Neither an atrial repair nor arterial repair was a risk factor *per se*, although the Mustard operation had the lowest surgical mortality. According to the multivariate equation, the 12-month survival rate of a patient with a birth weight of 3.4 kg then entered into atrial or arterial switch protocols (excluding those high risk arterial switch institutions) is 92%. Norwood and his colleagues reported later in 1988 the outcomes of 466 neonates with transposition of the great arteries entered into the 20-institutions of the Congenital Heart Surgeons Study.[160] Seventy-three per cent of the patients were < 48 h old when entered into the study. Two hundred and twelve of these underwent an arterial switch repair in 16 of the 20 institutions and the 1-week, 1-year, and 2.5-year survival rates were 82%, 79%, and 78%, respectively.[160] The usual coronary artery anatomy was present in 67% of the patients. Six of the 16 participating institutions were identified as low risk and the 1 week, 1 year, and 2.5 year survival rates for patients with simple transposition were 96%, 91% and 90%, respectively. For transposition with large ventricular septal defect, the survival rates were somewhat lower at 84%, 83%, and 83%. Risk factors for death in these low risk institutions were older age at operation for those with simple transposition (> 14 days of age) and transposition with ventricular septal defect. Among the entire cohort of patients, freedom from reoperation for pulmonary outflow obstruction at 1 week and 1 year was 99% and 89%, respectively. Also in 1988, Planche and his colleagues reported on the outcomes of 120 neonates undergoing the arterial switch operation.[143] One hundred and ten of these had simple transposition (mean age at operation 7.8 ± 3.5 days) and 10 had transposition with large ventricular septal defect (mean age at operation 17.9 ± 8.3 days). The perioperative mortality for the entire series was 8.3% and 5.4% for the last 110 patients, with no deaths in the group with transposition with large ventricular septal defect. There were 2 late deaths from myocardial infarction, both occurring in the second postoperative month.[143] Two additional patients required reoperation for pulmonary outflow tract obstruction. At the time of this report, all were asymptomatic, had normal left ventricular function, no ischemic problems and were not receiving any medication.[143] In 1989, Di Donato and his colleagues reported the Boston Children's Hospital experience with the arterial switch operation for transposition with large ventricular septal defect.[161] Between January 1983 and December 1987, 62 patients with transposition with large ventricular septal defect or double-outlet right ventricle with subpulmonary ventricular septal defect underwent anatomic repair, with 3 hospital deaths (4.8%) but no deaths occurred in the 18 operated neonates. There were 3 late deaths, 1 secondary to coronary obstruction and 2 to pulmonary vascular obstruction.[161]

Other reports of outstanding results of the arterial switch procedure were being continually published. Lupinetti and his colleagues described in 1992 the early and intermediate-term results in 126 patients who underwent arterial repair.[162] The arterial switch operation was performed at a median age of 6 days with 76 patients operated on in the first week of life. The usual coronary artery anatomy was present in 89 patients (71%). Simultaneous procedures included closure of ventricular septal defect in 35 patients, and repair of interruption of the aortic arch in 2, and coarctation of the aorta in 5. Hospital mortality was 7 of the 126 patients (5.5%) and 3 deaths among the most recent 100 patients. The actuarial survival at 5 years including operative mortality was 92%. Reconstruction of the pulmonary artery with a single pantaloon patch substantially reduced the requirement for reoperation for pulmonary outflow tract obstruction.[162] Serraf and his colleagues from the Marie Lannelongue Hospital in France reported the outcomes of 64 consecutive neonates with transposition and ventricular septal defect operated upon from January 1985 to March 1992.[163] Seventeen patients had an associated coarctation, 15 of whom underwent single-stage repair through a median sternotomy. For the entire cohort, the mean age at operation was 18.5 ± 12 days, and the mean weight 3.3 kg. The hospital mortality was 9.3%, with 4 late deaths. The actuarial survival and freedom from reoperation at 5 years were 81% and 84.6%, respectively.

Also in 1992 Kirklin and his colleagues extended the observations of the Congenital Heart Surgeons Study with information about the outcome and follow-up of 513 patients with simple transposition or transposition with ventricular septal defect entering for diagnosis and treatment at < 15 days of age and undergoing an arterial switch repair.[102] The 1-month, 1-year and 5-year survival rates were 84%, 82%, and 82% respectively. The hazard function for death had a rapidly declining single phase that approached zero by 12 months after surgery. Among the 8 patients who died ≥ 3 months after surgery, 4 had severe ventricular dysfunction likely related to imperfect coronary transfer. A coexisting single ventricular septal defect was not a risk factor for death, but multiple ventricular septal defects were a risk factor for death after arterial switch repair as were important coexisting noncardiac anomalies. Origin of the left main coronary artery, only the left circumflex coronary artery or the left anterior descending coronary artery from the right posterior sinus (sinus 2) was a risk factor that was even stronger when an intramural course was present. In addition to these coronary patterns that were risk factors, certain procedural, operative factors including longer global myocardial ischemic times and total circulatory arrest time were also shown to be risk factors.[102]

We commented in the previous chapter on the results of atrial repair of transposition of the great arteries by the participating members of the Pediatric Cardiac Care Consortium (PCCC) between 1984 and 1994.[158] Of the 1542 patients with transposition of the great arteries enrolled in this study, an arterial switch

was performed in 613 patients, of whom 118 died (19.3%). Five hundred and eighty-five switches (95%) were performed in infants and children and 99% of the deaths occurred in these groups.[158] The authors of this summary conclude that "the data from the PCCC has overall mortality rates that are higher than most other centers. As a group, infants undergoing arterial switch operation in the institutions comprising the PCCC had a mortality rate of 20%."[158] This outcome was certainly less favorable than the results published from a single institution series in the same era, but in some respects was comparable, though still somewhat higher than reported by Kirklin and his colleagues for the Congenital Heart Surgeons Study in 1992.[102]

With the passage of time, many centers were now achieving excellent surgical results with the arterial switch operation in neonates with transposition and intact ventricular septum, in those patients with complex forms of transposition as well as in patients with the Taussig–Bing form of double-outlet right ventricle and other forms of double-outlet ventricle. Wetta and colleagues reported in 2001 their excellent results in the arterial switch operation for 105 patients with complex forms of transposition including 77 with ventricular septal defect, 22 with the Taussig–Bing form of double-outlet right ventricle and 6 patients with other forms of double-outlet ventricle.[164] The median age at operation was 24 days. Aortic arch obstruction was identified in 25 patients, 13 of whom underwent arch repair before the arterial switch operation. The usual coronary artery pattern was identified in 59% of the cohort, and in 6 patients at least one coronary artery had an intramural course. There were 5 hospital deaths (4.7%) and 4 late deaths, 2 of which could be attributed to coronary artery anomalies.[164] The median duration of follow-up was 72 months, and 14 patients underwent 15 reoperations, 8 of which were for right ventricular outflow tract obstruction or neopulmonary stenosis. Survival after 12 years was 91.6% and freedom from reoperation was 82.6%. There were no identifiable risk factors for early death or need for reoperation. At latest follow-up, 87% were in New York Heart Association (NYHA) class I, and 13% class II and/or required medication.[164]

Pretre and his colleagues recently published (2001) the excellent results for arterial switch surgery as conducted at the Hopital Laennec-Necker in Paris.[100] They reviewed all 432 neonates (mean age at operation 7 days, mean weight 3.25 kg) who underwent an arterial switch operation between 1987 and 1999. The mean follow-up was 4.9 years and follow-up was complete in 412 patients. A ventricular septal defect was present in 130 patients and the ventricular septum was intact in 302 patients. Aortic arch obstruction was found in 34 patients. For the entire cohort, survival probability at 10 years was 93.7%. Of the 26 patients who died, 20 ocurred early and 6 after discharge. When stratified by early operation (108 patients operated up to March 1992) and recent operation (324 patients) to analyze mortality trends over time, the mortality in the earlier era was 13% and in the more recent era surgical mortality was 5% ($P < 0.0001$). Risk factors for death included early experience, low weight, associated cardiovascular malformations especially right ventricular hypoplasia or aortic arch obstruction, and difficult coronary artery patterns. The risk from unusual coronary artery patterns was greatly reduced in the more recent era. Thirty-six coronary events occurred in 34 patients and included 16 fatal and 9 nonfatal myocardial infarctions, and 14 reoperations on the coronary arteries, as well as reoperations because of pulmonary artery stenosis, re-coarctation, etc. Freedom from reoperation at 10 years was 79%. De Leval has written a very thoughtful commentary to this paper entitled: "lessons from the arterial switch operation."[100A] In his commentary, he discusses three scientific and ethical issues germane to the arterial switch operation, but to other surgical innovations as well. These include the issue of therapeutic innovation, learning curves, training, and mentoring and finally knowledge about the long-term outcomes of the arterial switch operation.

From the earliest experiences with the arterial switch experience, there have been ongoing attempts to address those risk factors for early and late mortality and the need for reoperation. In many of the papers cited in the previous sections, we have seen early surgical mortality reduced over time and less requirement for reoperation/reintervention. In the early era of arterial switch surgery, important coronary anomalies, especially those with an intramural course among others, side-by-side great arteries, right ventricular hypoplasia, associated ventricular septal defect, and aortic arch obstructive anomalies were identified by one or more groups as risk factors for early surgical death. Mayer and his colleagues from the Boston Children's Hospital identified in 1990 a number of coronary artery patterns among the 314 patients with the intent to perform an arterial switch operation that were associated with increased surgical mortality or led to abandoning the arterial switch and the performance of a Senning operation.[64] The single right coronary artery was perhaps the most important risk factor for early mortality in this series.[64] This experience was extended in 1995 by Wernovsky *et al.* to include 470 patients operated upon between 1983 and 1992.[165] An intact (or virtually intact) ventricular septum was present in 278 of 470 (59%); a ventricular septal defect was closed in the remaining 192. Survivals at 1 month and 1, 5, and 8 years among the 470 patients were 93%, 92%, 91%, and 91%, respectively. The hazard function for death (at any time) had a rapidly declining single phase that approached zero by 1 year after the operation. Risk factors for death included coronary artery patterns with a retropulmonary course of the left coronary artery (two types) and a pattern in which the right coronary artery and left anterior descending arose from the anterior sinus with a posterior course of the circumflex coronary. The only procedural risk factor identified was augmentation of the aortic arch; longer duration of circulatory arrest was also a risk factor for death. Earlier date of operation was a risk factor for death, but only in the case of the senior surgeon. Reinterventions were performed to relieve right ventricular and/or pulmonary artery stenoses alone in 28 patients. The hazard function for reintervention for pulmonary artery or valve stenosis revealed an early phase that peaked at 9 months after the operation and a constant phase for the duration of follow-up. Incremental risk factors for the early phase included multiple ventricular septal defects, the rapid two-stage arterial switch, and a coronary pattern with a single ostium supplying the right coronary and left anterior descending, with a retropulmonary course of the circumflex. The need for reintervention has decreased with time. The arterial switch operation can currently be performed early in life with a low mortality risk (< 5%) and a low incidence of reintervention (< 10%) for supravalvular pulmonary stenosis. Their analyses indicate that both the mortality and reintervention risks are lower in patients with less complex anatomy.[165,165A]

Hutter and his colleagues have also addressed the influence of coronary anatomy and reimplantation on the long-term outcome of the arterial switch.[166] They reported the outcome

of the arterial switch operation in 170 patients stratified by coronary artery anatomy.[166] In 133/170 patients, coronary artery anatomy consisted of a left anterior descending and circumflex artery from the left sinus and the right coronary artery from the right or posterior sinus. The left coronary had an intramural initial course in two of these patients. Fifteen patients had the anterior descending from the left and circumflex and right coronary artery from the right sinus; 8 had the left anterior descending and right coronary artery from one sinus and circumflex artery from the other; 4 had single ostium; and 3 had three separate ostia. Four patients had complex patterns and 4 patients had a supra commissural coronary. To date, follow-up angiography was performed in 59 patients. Surgical coronary sequelae were found in 5 patients. Two patients had an occluded left ostium. Initially, they were asymptomatic but showed polymorphic ventricular extrasystoles on ECG and moderate left ventricular dysfunction with large irreversible perfusion defects on scintigraphy. Both patients developed ventricular fibrillation at the age of 14 years. One patient did not survive. The other patient required implantation of a defibrillator. One patient had an occluded right coronary artery, 1 patient has stenosis of the right ostium and 1 patient has multiple tortuous collaterals without obstruction of a major branch. In the latter 3 patients, coronary sequelae were not suspected on ECG, echocardiography, or scintigraphy and were only found on follow-up angiography. Retrograde collateral flow was noted in all three occluded coronaries. Left ventricular dysfunction, with normal coronaries, was noted in 3 patients. All of these patients had perioperative ischemia suggesting failure of myocardial protection. Two are now asymptomatic with mild left ventricular dysfunction. One patient continues to have severe myocardial dysfunction and secondary aortic insufficiency. A Ross-like procedure was performed placing the original aortic valve in the neoaortic root. Coronary artery anatomy did not influence early survival or late coronary sequelae. Thus in this modest series abnormal coronary anatomy was not a determinant of outcome. Surgical coronary obstruction is independent of original anatomy, and as this group demonstrated it can be almost silent and is potentially fatal. They suggest that follow-up angiography should be considered in all patients after the arterial switch operation. Hutter and his colleagues have recently extended these observations to 195 patients undergoing the arterial switch operation between 1977 and June 2000.[166A] The overall perioperative mortality was 15%, but the mortality rates dropped in the last 5 years of their experience to 4% for complex transposition and 0% for simple transposition. There were 2 late deaths, 1 due to persisting pulmonary hypertension and 1 died with ventricular fibrillation secondary to coronary artery pathology. The most frequent complication in this series was pulmonary stenosis, necessitating 45 reinterventions in 26 patients. Aortic valve incompetence was absent or trivial in 146 patients and was severe in 1 patient. At the last follow-up, 145 patients were in NYHA class I and 4 patients were in class II. Of the 61 patients who underwent post-switch coronary arteriography, important coronary sequelae were found in 5 patients. Interestingly, the authors state there was no relationship to the initial coronary anatomy. In their analysis of those factors contributing to postoperative pulmonary outflow tract obstruction, they found that the use of a conduit and the material of the patch were the important factors. Their experience with the two-stage switch was disappointing with an early mortality of 9 of 31 patients (29%).

Tamisier and his colleagues found in their experience reported in 1997 that coronary patterns with coronary arteries coursing between the great arteries was a risk factor for adverse coronary events.[101] A similar conclusion based on a smaller series was reached by Day and colleagues in 1992.[167] Scheule and his colleagues from the Boston Chidren's Hospital reported on the outcomes of the arterial switch operation in patients with a single coronary artery.[176A] Between January 1983 and June 2000, 844 patients underwent the arterial switch operation at the Boston Children's Hospital, and 53 (6.3%) had a single coronary artery.[176A] Thirty-five patients had a single right coronary artery with the left coronary artery posterior to the pulmonary trunk in 27. Eighteen patients had a single left coronary artery, and in 16 of these the right coronary artery was anterior to the aorta. Six of the total 7 patients patients who died had a single right coronary artery, all dying before 1992. Survival for all patients was 91% at 6 months, and 87% at 1, 5, and 10 years after the arterial switch operation. Survival in this series was lower for those with a single right coronary ostium with the left coronary artery posterior to the pulmonary trunk. Freedom from reintervention for the entire series was 92% at 1 year, 86% at 5 years, and 82% at 10 years after the arterial switch operation, with lower rates of reintervention for those with a single left coronary ostium with the right coronary artery anterior to the aorta.[176A] Similar improvement was shown at the Toronto Hospital for Sick Children and published by Shukla, Freedom and Black.[176B] A meta-analysis of coronary artery pattern and mortality following the arterial switch operation was reported by Pasquali and her colleagues.[171] From an analysis of 1935 patients from 9 single centers, they found that coronary artery looping around the great vessels was associated with a 40% increase in mortality. They also reported that single coronary artery anatomy which also looped around the great vessels was associated with a threefold mortality increase. They also found that patients with an intramural coronary artery had the greatest mortality in this meta-analysis.[171]

The Congenital Heart Surgeon Study identified multiple ventricular septal defects as risk factor for death after the arterial switch operation, and the management of thee patients remains difficult, especially those with a Swiss cheese septum.[102] Belli and his colleagues from the Marie Lannelongue Hospital reported on the outcomes of 45 patients with the challenging combination of transposition and multiple ventricular septal defects operated on between January 1988 and December 1998.[168] The median age at operation was 50 days and the median weight 4 kg. Eighteen patients (40%) had undergone previous palliation including 17 pulmonary artery banding procedures, 7 associated with coarctation repair, and 1 isolated coarctation repair.[168] The ventricular septal defects involved the perimebranous septum in 24 patients, the trabecular septum in 95% of the patients, so-called "Swiss cheese" defects were identified in 8 patients (18%), the inlet septum in 7 patients, and the infundibular septum in only 2 patients. The initial approach to repair the multiple ventricular septal defects was via a right atriotomy which was sufficient in 15 patients. Ventricular septal defects were closed through a right ventriculotomy in 13 patients, 6 via the pulmonary artery, 1 via the aorta, and in the remaining 10 patients a combined approach was used. Only 1 patient required an apical left ventriculotomy. There were 5 hospital deaths and there were 3 late deaths. Several patients required secondary pulmonary artery banding because of failure to adequately close the ventricular septal defects. This

group recommended that a single-stage repair be carried out if aortic or subaortic stenosis were present, or if there was evidence of a coronary artery coursing between the great arteries. They would advocate a two-staged approach if there were truly multiple ventricular septal defects of the Swiss-cheese type, and an aortic arch requiring a complex repair.[168]

Aortic arch obstruction has been implicated by some as a risk factor for early death after the arterial switch operation.[102] Yet Comas and his colleagues showed that aortic arch obstruction did not influence the outcome of arterial switch surgery in 28 patients with the Taussig–Bing malformation.[169] A similar conclusion was reached a few years earlier by Serraf and his colleagues,[170] and more recently in a modest series from Tchervenkov and his colleagues.[171A] Lacour-Gayet and his colleagues from the Cardiac Surgery Department of Professor Claude Planche at the Marie Lannelongue Hospital reported in 1997 the outcomes of 103 patients who underwent biventricular repair of conotruncal anomalies associated with aortic arch obstruction.[172] Excluding those 10 patients with common arterial trunk, 1 with double-outlet left ventricle, and 1 with tetralogy of Fallot, the conotruncal anomalies included 15 patients with transposition of the great arteries with intact ventricular septum, 44 with transposition and large ventricular septal defect, and 32 patients with double-outlet right ventricle and subpulmonary ventricular septal defect. Eighty-nine patients underwent an arterial switch operation, and since 1990 the favored approach was a one-stage repair which was performed in 48 neonates, including 38 with transposition and ventricular septal defect, or double-outlet right ventricle with subpulmonary ventricular septal defect, and 10 with transposition of the great arteries with intact ventricular septum. The hospital mortality for the entire cohort was 12% for the one-stage repair and 20% for the two-stage repair. For those 48 patients with transposition or double-outlet right ventricle undergoing a one-stage repair, there were 4 early deaths (8.3%). Of those with the same anatomy undergoing the two-stage repair, 9 of 43 died (20.9%). There were 6 late deaths and a number of patients required reoperation/reintervention for either right ventricular outflow tract obstruction or recurrent coarctation of the aorta.[172] Interestingly, one study identified female gender as a significant risk factor for adverse outcome in both a univariate and multivariate analysis.[173] This has not been identified by other groups as a risk factor for early mortality.[38,174,175]

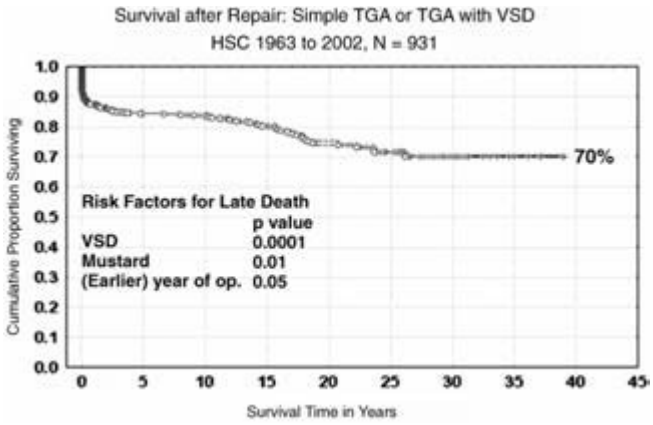
With increasing experience with the arterial switch operation, many of these factors have been effectively neutralized. While the Congenital Heart Surgeons Study identified so-called high and low risk institutions for those conducting an arterial switch protocol, this was not invariably related to volume.[102] Conte and his colleagues from Copenhagen have demonstrated that with an early surgical mortality of 2.6% (1 death in 39 consecutive patients) that the arterial switch is no longer a challenge in some small centers.[176] There is some evidence to suggest, however, that length of stay after neonatal arterial repair is inversely correlated with institutional volume.[177] In 2001, Brown and his colleagues analyzed the outcomes of arterial switch surgery in 201 consecutive patients operated on between September 1986 and December 1999.[173] The overall early surgical mortality was 19 of 201 patients (9.5%), with 5 late deaths (2.7%). When stratified by earlier era of operation and recent era, the mortality in the earlier era was 27.6% (8 of 29) declining to 6.4% (11 of 172). One-month, 1-year and 5-year actuarial survival rates were 90.4%, 87.9%, and 87.9%%, respectively, and freedom from reoperation at 3 and 5 years was 97.5% and 93.3%, respectively. The risk factor for surgical death in the earlier era was coronary artery patterns (usual vs. retropulmonary left coronary artery) and in the more recent era, preoperative instability.[173] Daebritz and her colleagues carried out a similar analysis for their arterial switch experience in 312 patients operated between 1982 and 1997.[175] Survival for the entire cohort was 95%, 92%, and 92% after 30 days, 5, and 10 years, respectively. Operative survival improved to 97% after 1990. They identified as risk factors for operative mortality complex anatomy, complex coronary artery patterns, and prolonged bypass time. Determinants of late mortality included coronary artery distribution, position of great arteries, bypass time and aortic coarctation. Freedom from reoperation was 100%, 96%, and 94% after 1, 5, and 10 years respectively. No preoperative anatomic parameter in this series correlated with long-term morbidity.

Some patients with simple transposition present beyond the first month of life, are severely premature or because of adverse cerebral vascular events with intracerebral hemorrhage or because of other medical conditions had to have the arterial switch postponed. There is no agreement as to the latest age at which an arterial switch operation can be safely performed in the patient with transposition and an intact ventricular septum. Some of the earlier reports suggested that an arterial switch beyond the first 2–3 weeks of age increased the risk for early surgical mortality.[102] Davis and others have certainly reported successful arterial switch procedures in patients 21 days of age or older.[178,179] Davis and his colleagues conclude that the arterial switch procedure can be carried out safely as a primary procedure for patients up to 1 month of age and probably up to the age of 2 months. Yacoub and his colleagues pioneered the two-staged approach to anatomic correction of simple transposition of the great arteries and an initially unprepared left ventricle.[118,119] After an initial balloon atrial septostomy, the first stage consisted of banding of the pulmonary trunk to increase ventricular afterload and ultimately left ventricular mass combined with the construction of a systemic-to-pulmonary artery shunt, the latter to maintain satisfactory systemic arterial oxygen saturations. Yacoub and his colleagues and others showed that this maneuver decreased the actual pulmonary blood flow, but did not reduce the effective pulmonary blood flow.[118–122] The time between the first and second stages in Yacoub's experience ranged from 5 weeks to 9 months.[118,119] In this experience reported in 1980 there was a high incidence of severe cyanosis, respiratory and cardiac failure, with substantial early mortality.[119] Sidi and his coworkers in 1983 reviewing their experience of preparing the left ventricle for the arterial switch procedure noted the development of acute or chronic left ventricular dysfunction in 50% of their patients and severe hypoxemia in another 25%.[180] It has been suggested that the sudden increase in left ventricular pressure resulting from the banding leads to acute myocardial dysfunction and that the magnitude of cardiac decompensation correlates to the severity of the banding.[180] In trying to "fine-tune" this maneuver, Ilbawi and his colleagues found that avoidance of severe pulmonary artery banding decreases the incidence of postoperative myocardial dysfunction and that a moderate degree of pulmonary artery banding and volume overload provide the most stimulus for acquisition of left ventricular growth and mass.[123] Two years after the recommendations of Ilbawi and colleagues, Jonas and his colleagues reported the rapid, two-stage arterial switch operation for transposition of the great arteries and intact ventricular

septum beyond the neonatal period.[181] They showed in their initial report on 11 patients that the left ventricle can be prepared by a surprisingly short interval period (median 9 days) between a first-stage preparatory operation (pulmonary artery band with or without a shunt) and a subsequent second-stage arterial switch procedure. Serial two-dimensional echocardiography showed that left ventricular mass increased by a mean of 85% during this short interval. Mean left ventricular–right ventricular pressure ratio as measured by cardiac catheterization increased from 0.5 ± 0.08 a median of 7 days before the first stage to 1.04 ± 0.29 a median of 7 days after the first stage. One patient underwent a Senning procedure because of an intramural left coronary artery. The other 10 patients underwent an arterial switch, with no early deaths. The median length of hospitalization after the arterial switch was 8 days. There was 1 late death at 5 months. No patient was initially thought to have abnormal ventricular function, although trivial to mild aortic regurgitation has been commonly observed with color flow mapping. These results have encouraged this group to offer a two-stage arterial switch procedure to appropriate infants with an interval period of *c*. 1 week. Furthermore they suggest that when both stages are performed at one hospitalization, there are important psychosocial, logistic, and financial advantages.[181] This early experience and observations about the rapid two-stage arterial switch operation was extended by Boutin and her colleagues in two consecutive papers published in *Circulation* in 1994.[182,183] She and her colleagues showed using serial echocardiographic evaluations that the mean percentage increase in left ventricular mass from the time of banding to the arterial switch was 96%, 95% of which was achieved in the first 7 days.[182,183] The left ventricular ejection fraction fell significantly by 12 h after the banding, but returned to the pre-banding level by 3.5 days after the banding. The recovery in left ventricular function occurred rapidly coincident with compensatory hypertrophy. In the companion paper, Boutin and her colleagues evaluated in patients who had undergone the rapid two-stage arterial switch left ventricular systolic mechanics late after an acute pressure overload stimulus in infancy.[182] When parameters of function were compared between patients undergoing a primary arterial switch procedure and the rapid two-staged approach, systolic dysfunction due to a higher afterload and lower contractility was observed in the two-stage group. Of concern was that contractility below the limits of normal was seen in 25% of the two-stage arterial switch group compared to 3% of the primary arterial switch group.[182] They also found that a very high peak rate of hypertrophy and severe left ventricular dysfunction after banding predicted a greater reduction in late contractility. In 1995, Iyer and his colleagues demonstrated that serial echocardiography provided reliable information for decision making in the rapid two-stage arterial switch operation.[184] This group found that echocardiographic examinations provided information about increase in left ventricular mass, left ventricular posterior wall thickness, left ventricular end-diastolic internal diameter towards normal, and also could demonstrate the acquisition of circular left ventricular configuration with the interventricular septum contracting in synergy with the left ventricular mass. All of these parameters could be used to predict a successful outcome.[184] Lacour-Gayet and his colleagues have taken a similar approach to left ventricular retraining as documented in their publication in 2001.[185] Between January 1992 and January 2000, left ventricular retraining was attempted in 22 patients with simple transposition and an intact ventricular septum. They used as indications for left ventricular retraining a combination of factors including age > 3 weeks, a "banana-shaped" contour of the interventricular septum, and a left ventricular mass < 35 g/m^2. The mean age at retraining was 3.2 months, and the second stage was carried out in 19 patients at a mean delay of 10 days, with a mean left ventricular mass of 50 g/m^2. One patient died after the first stage of mediastinitis. There were no early surgical deaths after the second stage, but there was one noncardiac late death in this group. With a mean follow-up of 25 months all the patients are in NYHA class I, with a mean left ventricular shortening fraction of 39%.[185] Foran and his colleagues advocate a primary arterial switch operation for transposition of the great arteries with intact ventricular septum in infants older than 21 days.[179] Furthermore they suggest that a primary arterial switch operation may be appropriate treatment for infants with simple transposition 2 months old, regardless of preoperative echocardiographic variables and that the upper age limit for which primary switch is indicated in these patients is not yet defined. Other maneuvers have been used to support acutely the failing left ventricle after a late arterial switch operation including extracorporeal membrane oxygenator (ECMO) and left ventricular assist device.[178] Finally, some have advocated a temporary intraoperative pulmonary banding to determine whether a patient presenting late is a candidate for a primary arterial switch procedure.[186] Dabritz reported on 5 patients with simple transposition presenting late with low left ventricular pressure with a pulmonary to systemic pressure ratio of 0.2–0.5 in whom echocardiography showed a banana-shaped left ventricle with left ventricular wall thickness as low as 3 mm. These patients underwent a trial of pulmonary artery banding to systemic pressure for 15–30 min. As this increase in workload was tolerated well with an anticipated decrease of oxygen saturation but without hemodynamic disturbances anticipated, the arterial switch operation was performed immediately. The postoperative course was uneventful in all 5 patients, although catecholamine dependence was prolonged and 3 patients received enoximone. There were no severe complications. Echocardiography showed an increase in posterior wall thickness from 3 to 6 mm after 19 days in 1 infant. On the basis of this experience they concluded that some of the children, assigned for a "two-stage" arterial switch operation, may tolerate a primary anatomic repair up to an age of at least 3 months. This subgroup can be selected by a trial of pulmonary artery banding.[186] Some patients with transposition of the great arteries and an intact ventricular septum will develop dynamic subpulmonary outflow tract obstruction, thus preparing the left ventricle for a late arterial switch procedure.[17,187–190]

It might be helpful to summarize and put into perspective the Toronto Hospital for Sick Children's surgical experience with transposition of the great arteries with or without ventricular septal defect arteries between the years 1963 to December 31, 2001. These years embrace the Mustard era (May 1963, see Chapter 25A) with our conversion to the arterial switch approach for neonates in the late 1980s, to the present time. This data analysis focuses on 931 infants, children and adults with transposition of the great arteries with or without ventricular septal defect. We have excluded 147 patients from this analysis, the majority of these with more complex forms of transposition, often with left ventricular outflow tract obstruction and/or other confounding lesions (see also Chapter 25C). Of the 931 patients

A



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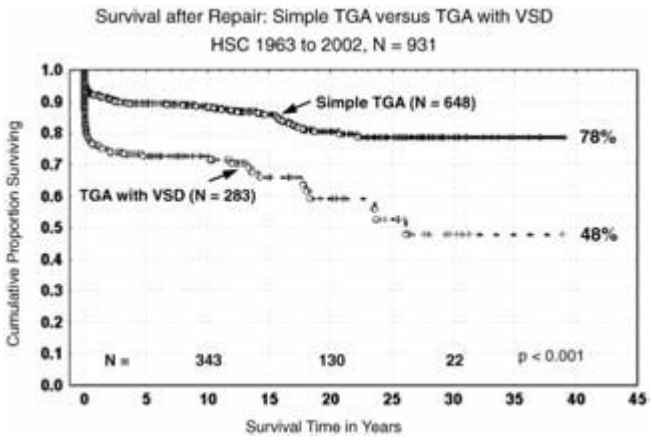


C

Fig. 25B-5 Outcomes after surgical repair of simple forms of complete transposition of the great arteries. **A**. Operative risks for simple transposition of the great arteries. This includes Mustard and switch protocols. **B**. Survival after repair of simple transposition and transposition with ventricular septal defect. **C**. Survival after repair: simple transposition vs. transposition with ventricular septal defect.

(86% of the entire cohort), 648 had "simple" transposition and 283 had an associated ventricular septal defect. The overall operative risk for the 931 patients is depicted in Fig. 25B-5A. Survival after repair for the 931 patients is shown in Fig. 25B-5B with an overall late survival of 70% (see also Figs 25B-11 to 13). Risk factors for late death included those patients with ventricular septal defect, those who had undergone the Mustard operation, and earlier year of operation. When long-term survival is stratified by type of operation, long-term survival for the 438 patients undergoing the Mustard operation was 67% compared to 84% of those who underwent the arterial switch ($P = 0.26$). The reoperation rate was less for those who had undergone the Mustard operation vs. the arterial switch ($P = 0.00009$). We have discussed in Chapter 25A the important differences in survival between patients with "simple" transposition and those with an associated ventricular septal defect who had undergone the Mustard operation (Fig. 25B-5C), with 78% long-term survival for those without a ventricular septal defect compared to only a 48% long-term survival for those with a ventricular septal defect. The outcomes are different depending on the surgical strategy and thus the era in which surgery was performed. The long-term survival for 366 patients with simple transposition undergoing Mustard's operation was 78%, while for 282 patients who underwent the arterial switch procedure it was 89% ($P = 0.69$). When the two strategies are compared for the patient with transposition of the great arteries and ventricular septal defect, the difference is striking. The long-term survival for the 211 patients with transposition of the great arteries and ventricular septal defect who had undergone the arterial switch was 77%, compared to the 31% survival for the 72 patients who had undergone the Mustard repair ($P = 0.00001$). One of the interesting observations about these data is the importance of the ventricular septal defect in those patients undergoing the arterial switch operation. Many more patients with transposition of the great arteries undergoing the arterial switch required closure of the ventricular septal defect than patients who underwent the Mustard procedure. This is explained by the fact that patients undergoing the Mustard operation in our institution were often a year of age or older, and by that age the ventricular septal defect had either closed or had become hemodynamically insignificant (see also Chapter 3).

Finally, the Congenital Heart Surgeons Study has just again extended its observations on the outcomes of 829 neonates with complete transposition of the great arteries 12–17 years after repair.[190A] Twenty-four institutions entered 829 neonates age less than 15 days in this prospective study. The diagnosis was simple transposition ($n = 631$), transposition with ventricular septal defect ($n = 167$), transposition with ventricular septal defect and pulmonary stenosis (TGA/VSD/PS) ($n = 30$), or transposition with pulmonary stenosis ($n = 1$). Repair was by arterial switch ($n = 516$), atrial repair (Senning = 175, Mustard = 110) or Rastelli ($n = 28$). Time-related events were analyzed by parametric hazard function modeling and incremental risk factors for mortality, re-intervention, and late functional assessment were sought. For the entire cohort, survival estimates at 6 months, 5, 10, and 15 years are 85, 83, 83, and 81%, respectively. The hazard function for death after repair has two phases: an early rapidly declining phase and an ongoing constant one. Constant phase mortality is less likely after the arterial switch operation and in children with simple TGA. During follow up, at

least one re-intervention was required in 167 children (pacemaker, $n = 35$; percutaneous intervention, $n = 32$; baffle re-intervention, $n = 27$; re-operation, $n = 125$). Freedom from re-intervention at 6 months, 5, 10 and 15 years is 93, 82, 77, and 76%, respectively. Of survivors, 87% have been followed up to the last 3 years, including an assessment of functional ability of 562 children (83%). Functional class 15 years after repair is class I in 76%, II in 22%, III in 2%. The proportion in functional class I decreased over time. Psychosocial deficits, especially learning disorders, are prevalent. On the basis of this experience they concluded that survival 15 years after transposition repair is good with most children functioning well. Surgical results are best after an arterial switch operation. There is an ongoing risk of death that is less after the arterial switch operation. With the exception of Rastelli patients, the likelihood of survivors needing re-intervention after 5 years is low.

Other types of arterial switch operations

Damus, Kaye and Stansel operation

Damus, Kaye and Stansel all proposed a type of arterial repair for complex forms of transposition without coronary artery transfer (Fig. 25B-6).[145–148] This operation was suggested in 1975 as an alternative to the classic arterial switch operation in those patients with side-by-side great arteries or in those with a concerning pattern of coronary artery anatomy.[145–148] As stated earlier in this chapter, the basic concept of this operation was to baffle the left ventricle through the ventricular septal defect (which was often subpulmonary) to the pulmonary trunk; the main pulmonary trunk is then divided and the proximal portion of the main pulmonary trunk is then anastomosed to the aorta in an end-to-side fashion; finally a conduit is interposed between the right ventricle and distal pulmonary trunk.[145–148,191–196] The patent aortic orifice was initially left in continuity with the right ventricle, with the presumption that systemic pressure in the aorta would keep the aortic valve from opening. There were few data then, but there are considerable data now that the pulmonary valve seems to function well in the systemic circulation, experience gleaned from the classic arterial switch experience and from the Norwood–Fontan experience in the patient with the hypoplastic left heart syndrome.[197,198] The Damus–Kaye–Stansel operation achieved a type of anatomic repair without coronary relocation,[145–148,191–196] and a number of case reports and several series utilizing this approach have been published.[146,191–196] The detracting features of this operation are that a conduit is utilized and clearly this would necessitate repeated reinterventions. Also in some patients thrombus formation occurred in the aortic root, forcing the question should the aortic root be closed?.[195] We also documented systolic aortic regurgitation in a patient with double-outlet right ventricle palliated with a Damus–Kaye–Stansel procedure.[199] Like most centers as we gained experience with the classic arterial switch operation and complex patterns of coronary artery anatomy once considered at high risk, this approach for complex transposition or Taussig–Bing anomaly has been largely abandoned.[196] We still find the proximal pulmonary artery–aortic connection as a valuable adjunct to the palliation of the "single" ventricle malformation with systemic outflow tract obstruction (see Chapter 36).

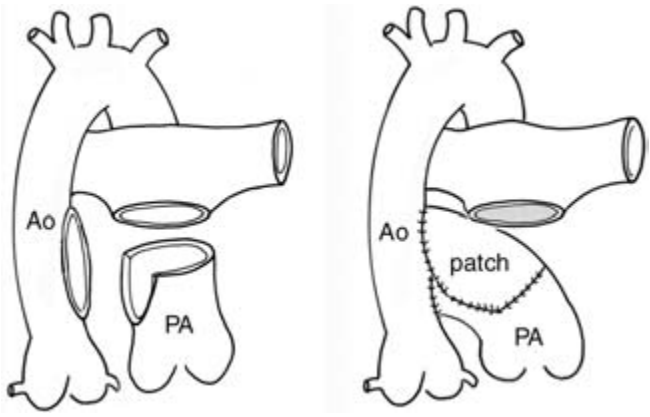


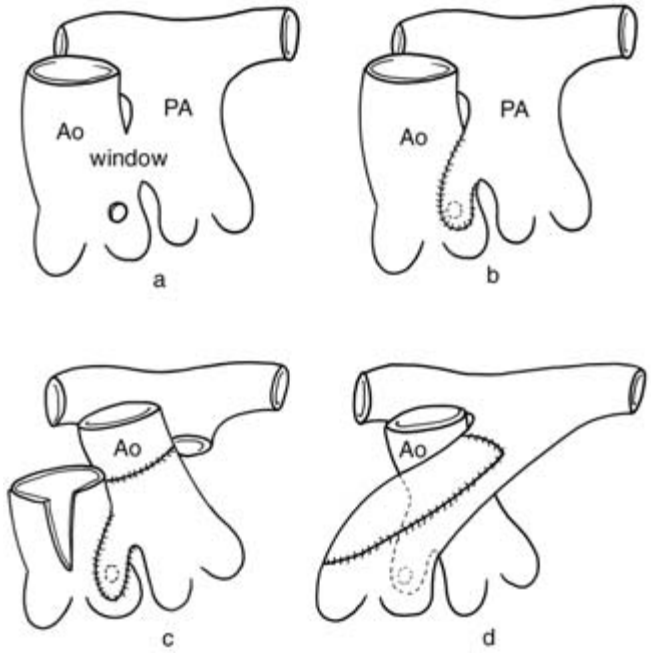
Fig. 25B-6 Damus–Kaye–Stansel operation. The pulmonary artery (PA) is divided and the proximal part of it is anastomosed, end-to-side, to the ascending aortic root (Ao). The pulmonary artery confluence is closed if a shunt is to be created for the pulmonary circulation, or it is connected to a conduit if a biventricular repair is possible.

Aortic translocation and biventricular outflow tract reconstruction

In 1984, Nikaidoh published a new surgical repair for transposition of the great arteries, ventricular septal defect, and pulmonary stenosis.[149] This innovative approach was a departure from the Rastelli operation conceived of and published nearly 15 years earlier[151–153] (see also Chapter 29C). This operation achieves an anatomic repair that utilizes aortic root mobilization and transfer combined with reconstruction of both right and left ventricular outflow tracts.[149] The one potential advantage of this approach is that with the mobilization of the aortic root with the coronary arteries intact, it obviates the need for coronary artery transfer and the hazard of ostial stenosis, etc.[149] However, the reconstructed right ventricular outflow tract is devoid of functioning valve tissue and free pulmonary regurgitation results.[149] This operation is similar in concept to that published by Bex and his colleagues a few years earlier.[150] Subsequent to these initial reports there seems to have been little enthusiasm for these procedures although there are several other reports of similar operations.[200–202] Others have advocated an arterial switch combined with a Ross-Konno type of operation in the patient with transposition, an intact ventricular septum, and severe and unresectable left ventricular outflow tract obstruction. This transfers the native aortic root and coronary arteries to the morphologically left ventricle combined with an infundibular patching to widen the left ventricular outflow tract. This is similar in concept to the operations of Bex and Nikaidoh, but the homograft valve in the right ventricular outflow tract provides a degree of competency.

Anatomic repair of transposition of the great arteries with intact ventricular septum and fixed left ventricular outflow tract obstruction

Anatomic repair with coronary transfer can be achieved in some patients with transposition of the great arteries, an intact ventricular septum, and fixed forms of left ventricular outflow tract obstruction.[97,98] Some patients with this anatomy are perhaps better served with an atrial repair in combination with attempted resection of the offending left ventricular outflow



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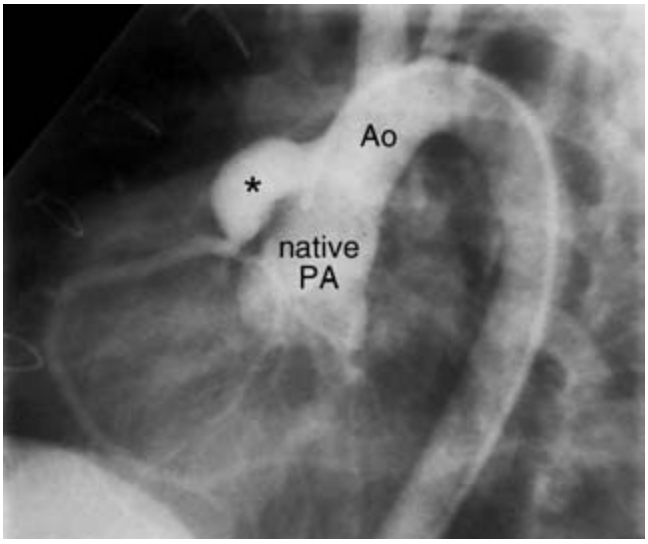

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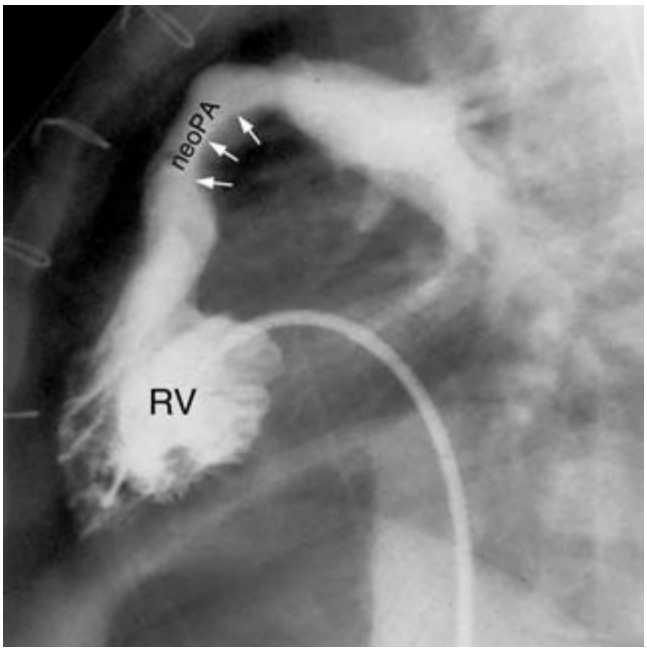

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Fig. 25B-7 Aubert operation. **A**. Illustration shows the procedure. An aortopulmonary window is created (a) and the coronary artery is diverted into the pulmonary artery (PA) through the window (b). Then, the great arteries are switched (c and d). **B**. Aortogram shows the single coronary artery connected to the aorta through a tunnel (asterisk). **C**. Pulmonary arteriogram shows deformity and narrowing (arrows) of the posterior part of the neopulmonary artery (neoPA). Ao, aorta; RV, right ventricle.

tract tissue with or without a left ventricular-to-pulmonary artery conduit. Jex and his colleagues advocate creating a ventricular septal defect and then carrying out a Rastelli procedure to treat this combination of malformations.[202] They reported the successful outcome of this approach in a 6-year-old boy with transposition of the great arteries, an intact ventricular septum, and severe left ventricular outflow tract obstruction. The child had been previously palliated with a balloon atrial septostomy and a Blalock–Taussig shunt. Preoperative investigations revealed a pressure ratio between the left and right ventricles of 1.6/1 and angiographically a very severe tunnel-form of subpulmonary obstruction. A 20-mm ventricular septal defect was created and then a Rastelli procedure was performed with excellent postoperative hemodynamics.[202] Again, from the subsequent literature, there does not seem to be much support for this approach, but it is an approach to be considered none the less.

The operations of Aubert, Kawada *et al.* and Takeuchi and Katogi

As with the Damus–Kaye–Stansel approach to arterial repair without coronary transfer, others have also reported variants on this theme, with Aubert's operation being successfully performed and reported in 1977 (Fig. 25B-7),[154] and that of Kawada an his colleagues in 1989,[203] and the report from Takeuchi and Katogi in 1990.[204] In the original report in English from Aubert and his colleagues, an aortopulmonary window was created and a patch placed over this and the coronary ostia so that the coronary arteries arose from the new aorta.[154] A 4.2 kg infant, with transposition and ventricular septal defect, was successfully operated on using this technique. These techniques all use an internal tunnel technique to facilitate coronary transfer but eliminate the need for coronary artery reimplantation. Murthy and Cherian further developed the *in situ* method of coronary

transfer.[203A] A modification of these "*in situ*" situations using spiral reconstruction of the great arteries has also been reported.[204A,204B] The apparent advantage of this spiral technique is that the great arteries after repair have a more normal spatial relationship, thus lessening the possibility of pulmonary outflow tract obstruction. It is interesting that the Takeuchi method for treating anomalous left coronary artery from the pulmonary trunk derives from the earlier report of Aubert.[205] Other approaches including the "bay window" technique have been developed to facilitate transfer of complex coronary artery patterns.[205A]

Long-term issues after the classic arterial switch operation with coronary artery transfer

As with any newly introduced surgical procedure, some long-term issues will reflect the technical challenges intrinsic to performing the new procedure. Thus the specific manner in which coronary artery transfer is achieved, the methodology of closing the "buttons" in the original aortic root, maneuvers to facilitate the right ventricular-to-pulmonary artery connection, the era in which the surgery is conducted, etc., may all impact on long-term functional considerations. These functional considerations[206,207] include:

- late death
- neopulmonary valve and artery stenosis
- right ventricular outflow tract obstruction
- supraaortic obstruction
- coronary artery function and myocardial ischemia
- left ventricular function
- aortic regurgitation
- atrioventricular valve function
- cardiac rhythm disturbances
- somatic and neurodevelopmental outcome
- miscellaneous complications.

First, and it is worth emphasizing, the majority of patients following a successful arterial switch operation are active, healthy, free from troublesome rhythm disturbances, are taking no cardiac medications, are usually in NYHA functional class I, and have normal or near normal neurodevelopmental outcome and cognitive function.[208–211] That is not to say, however, that the cardiac examination is entirely normal, as many will have some turbulence across the reconstructed right ventricular outflow tract, and both auscultatory and Doppler evidence of aortic incompetence is fairly common as well. Some patients despite being asymptomatic will demonstrate clinical evidence of myocardial ischemia likely related to problems in achieving coronary artery transfer. Most patients at rest have nearly normal indices of left ventricular contractility and do not demonstrate wall motion abnormalities. Suffice it to say, most of these children have not been challenged with a dobutamine stress test to unmask latent ischemia. We have presented elsewhere in this chapter that some patients undergoing a rapid two-stage arterial repair do demonstrate abnormalities of left ventricular contractility.[182,183] The entire gamut of invasive and non-invasive methodologies has been employed in the survivors of the arterial switch to elucidate sequelae of this surgery.

Late death after the arterial switch operation

Late death after the arterial switch operation is a sad but inevitable reality. The incidence of late death seems to be considerably less than that among patients who survived either atrial repair of transposition of the great arteries (see Chapter 25A), or the Rastelli operation for transposition, ventricular septal defect and pulmonary outflow tract obstruction (see Chapter 25C). Late death has been consistently reported in most series since such data began accumulating, and in the majority of patients it is related to adverse coronary artery events.[38,100–103,125,143,159,160,173–175,212,213] In an early experience from Japan, Tsuda and his colleagues reported in 1992 6 late deaths from a cohort of 59 patients who survived the arterial switch procedure. The late deaths occurred from 40 days to 10 months after the operation and in all patients resulted from acute myocardial infarction.[214] Kirklin and his colleagues also in 1992 reporting for the Congenital Heart Surgeons Study found the hazard function for death had a rapidly declining hazard phase approaching zero by 12 months after surgery.[102] Of the 513 neonates with either simple transposition or transposition with ventricular septal defect, 8 patients died ≥ 3 months after surgery, and in half of these death was likely related to imperfect coronary artery transfer. The mean follow-up interval in this report was 37.5 ± 14.16 months. Of the 1095 patients from the 1200 who survived the arterial switch operation at the Marie Lannelongue Hospital, Losay reported in 2001 of 32 late deaths (2.9%) occurring at a median of 2.68 months after the arterial switch operation.[215] Survival rate for the entire cohort including early mortality was 89% at 1 year and 88% at 10 and 15 years. It was higher in those with simple transposition (92% at the same intervals) than in those with complex transposition who had a survival rate of 81% at 1 year and 80% at 10 and 15 years. Deaths could be attributed to adverse coronary artery events in 9 patients, 3 who experienced sudden death, 3 with ventricular dysfunction, and a wide range of other causes for late death.[215] Late deaths were more common in those with complex transposition (5.9%) than in those with simple transposition (1.7%), and other risk factors for late deaths included those with a major cardiac event in the intensive care unit and when the patient required reoperation. Whether these patients will experience more adverse coronary events as they enter the age range for arteriosclerosis is unclear. However, the topography of the coronary ostia is not entirely normal after the arterial switch operation and whether patients will be predisposed to vascular atheroma and late ostial events is yet to be clarified.

Neopulmonary valve and artery stenosis

Stenosis of the neopulmonary valve and pulmonary arterial stenosis are perhaps the most frequent sequelae of the arterial switch procedure, with a reported incidence from 7% to 40% (Figs 25B-1B, 25B-8).[102,103,142,143,160,162,164,166,175,215–221] With increasing experience with the arterial switch operation and the introduction of the Lecompte maneuver in 1981, this complication began to subside.[222] The Lecompte maneuver obviates the requirement for a prosthetic conduit in the arterial switch, and this procedure has been widely adapted. Nogi and his coworkers from the Toronto Hospital for Sick Children provided in 1998 our institutional experience with the fate of the neopulmonary valve after the arterial switch operation.[223] During a median follow-up of 18 months, 32 patients of the study population of 136 patients (24%) developed supravalvular pulmonary stenosis (Fig. 25B-8), 15 (11%) with associated pulmonary valve stenosis. Nogi's findings showed that the valve annulus was considerably larger in those in whom neopulmonary valve stenosis did not develop compared to those who did develop this complication. Failure of growth of the valve

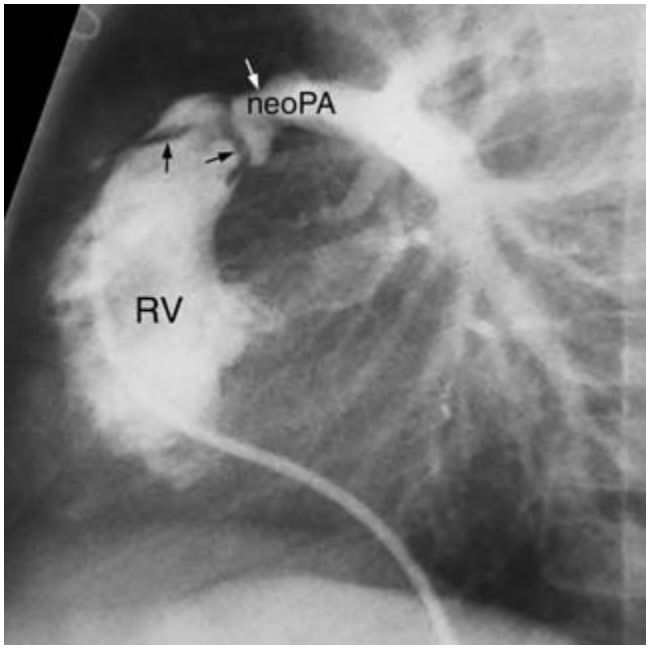


Fig. 25B-8 Supravalvar stenosis (arrow) of the neopulmonary trunk after arterial switch operation. The neopulmonary valve is also stenotic (arrows).

annulus was also seen in those patients with neopulmonary valve and supravalvular obstruction.[223] Nakanishi and his colleagues in 1996 also documented growth of the neopulmonary valve annulus after the arterial switch operation, but less growth occurs in those with history of previous pulmonary artery banding and in patients with an associated ventricular septal defect, both groups associated with an inherent discrepancy in size between the pulmonary and aortic root.[224]

Williams and his colleagues reported in 1997 the incidence and risk factors for outflow tract obstruction from the 23 participating institutions of the Congenital Heart Surgeons Study.[217] These institutions enrolled 514 neonates < 14 days of age with either simple transposition or transposition with ventricular septal defect between January 1, 1985 and March 1, 1989. Sixty-two patients underwent 86 reinterventions for right-sided obstruction (83% free at 10 years) and six for supraaortic obstruction (98% free at 10 years). Pulmonary trunk or pulmonary arterial stenosis or obstruction was associated with lower birth weight, left coronary artery originating from sinus 2, coronary artery explantation away from the transection site, three so-called high risk institutions, use of nonautologous materials for sinus reconstruction, and earlier institutional experience.[217] A risk-adjusted base incidence of 0.5% per year for reintervention continues late after operation.[217] Freedom from distal right-sided obstruction was 95%, 90% and 86% at 1, 5, and 10 years, respectively. Serraf and his colleagues reported in 1995 the Marie Lannelongue experience with reoperation after the arterial switch operation in 753 patients.[219] They reviewed the requirement in these patients operated between March 1983 and July 1994. Sixty-eight of the 753 patients (9.3%) underwent 75 reoperations. Thirty of these underwent early reoperation < 30 days or during the same hospital stay, and 38 underwent late reoperation. Of the 68 patients, 5 required reoperation for subvalvular pulmonary stenosis and 16 for supravalvular pulmonary stenosis. These 21 patients underwent patch plasty repair of the residual obstruction. Univariate analysis revealed risk factors for reoperation for right ventricular outflow tract obstruction including nonneonatal repair, longstanding pulmonary arterial banding, and the specific surgical technique used for pulmonary arterial reconstruction.[219] Multivariate analysis revealed that the only risk factor for reintervention for postoperative pulmonary stenosis was a hypoplastic aortic annulus as compared to the native pulmonary annulus. Losay and his colleagues extended these observations in 2001, reviewing the long-term follow-up issues in the 1095 survivors of the 1200 patients who underwent the arterial switch operation from December 1982 to December 1999.[215] The median follow-up interval was 4.9 years, ranging from 0.5 to 17 years. One hundred and twenty-one reoperations were performed in 103 patients. Freedom from reintervention was observed in 90%, 83%, and 82% of the survivors at 5, 10, and 15 years, respectively.[215] After a rapid declining phase, the hazard function for all reoperations reached a nadir by 3 years, slowly increasing after that. Reoperation for pulmonary outflow tract obstruction was the most frequent cause for reintervention, being required in 43 patients, and reintervention in this group was observed up to 9 years after the arterial switch operation. At last follow-up, a peak systolic gradient ≥ 50 mmHg was observed in only 41 patients.[215] One of the uncommon complications secondary to balloon angioplasty of narrowed pulmonary arteries is the creation of a traumatic aortopulmonary window.[215A]

Right ventricular infundibular obstruction

Many have grouped right ventricular infundibular obstruction with right ventricular outflow tract obstruction, thus including the infundibulum, neopulmonary valve, main and branch pulmonary arteries in the cascade of potential complications after the arterial switch operation. In the data from the Congenital Heart Surgeons Study reported by Williams and his colleagues, right ventricular infundibular obstruction was associated with a side-by-side great artery relationship, coexisting coarctation of aorta, and earlier institutional experience.[217] The morphological substrate for residual right ventricular outflow tract obstruction would predict this late complication, as the right ventricular outflow tract is often intrinsically narrowed, wedged between the infundibular septum and right-sided ventriculoinfundibular fold.[17,225–228] Freedom from so-called proximal (subvalvular) right-sided obstruction was 98%, 96%, and 95% at 1, 5, and 10 years, respectively.[217] Urban and Brecher reported their results in the resection of right ventricular infundibular obstruction in 5 of 78 neonates with simple transposition and 10 of 26 patients with either transposition and ventricular septal defect or double-outlet right ventricle with subpulmonary ventricular septal defect.[225] The early mortality was 7.7%. They asked of the obstructive right ventricular outflow tract: does it matter? The answer from this and other experiences is yes, and that the morphology of the right ventricular outflow tract before the arterial switch, the diameter of the native aortic valve, obstruction of the aortic arch, and a malalignment-type ventricular septal defect should raise the necessity for resection of right ventricular infundibular obstruction.[17,225–228]

Supra-aortic obstruction

This complication is uncommon after the arterial switch operation, occurring in about 0.1% of patients, primarily in those with an initially small ascending aorta, and thus those with a

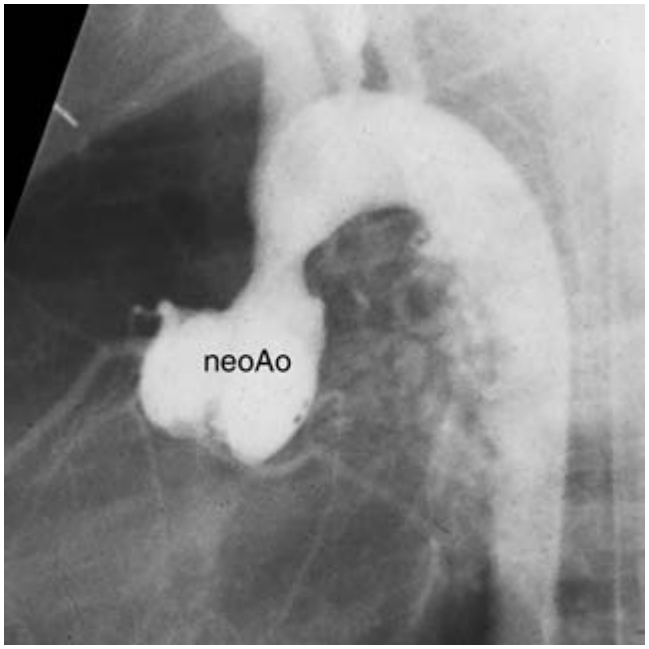


Fig. 25B-9 Supravalvar stenosis of the neoascending aorta (neoAo) after arterial switch operation.

ventricular septal defect, Taussig–Bing form of double-outlet right ventricle ± an obstructive anomaly of the aortic arch (Fig. 25B-9).[215,217] Data from the Congenital Heart Surgeons Study showed that risk-unadjusted freedom from reintervention for left-sided obstruction was 99.3%, 98.9%, and 98.3% at 1, 5, and 10 years, respectively.[217]

Others have documented late development of a thoracic coarctation, likely related to its unmasking by division of the arterial duct at the time of the arterial switch operation.[229] This mechanism was suggested nearly three decades ago by Elseed and colleagues.[230]

Coronary artery function and myocardial ischemia

Perhaps the greatest concern, both early and late, expressed by those caring for patients undergoing the arterial switch operation is the fate of the coronary arteries after transfer.[11,26,30–34,38,39,47,48,57,61,64–66,75,101–103,116,159,160,162–166,173–175,212,214–216] The issue of the impact of residual coronary artery pathology on myocardial function is confounded by the study of Millane and colleagues.[231] In their study of patients who developed late right ventricular dysfunction after atrial repair of transposition, they documented using dipyridamole sestamibi single-photon emission tomography reversible and fixed perfusion defects with concordant regional wall motion abnormalities in the systemic right ventricle 10–20 years after the Mustard repair. They suggested that these abnormalities could be important in the pathogenesis of systemic right ventricular dysfunction.[231] It is unclear whether the failing right ventricle is responsible for these findings, or vice versa. Clearly these observations may confound similar studies conducted in patients after the arterial switch operation.

The early literature focused considerable attention on the coronary issues as reimplantation of the coronary arteries into the neoaortic root was considered the key of the arterial switch operation. Thus, in the first few years after Jatene's initial publication,[11,26,30–34,38,39,47,48,57,61,64–66,75,101–103,116,159,160,162–166,173–175,212,214–216] there was a resurgence of interest in the coronary artery anatomy in patients with transposition; increased interest in the angiographic demonstration of the pertinent coronary anatomy; emphasis on newer angiographic techniques (balloon occlusion techniques and selective coronary arteriography) to both image and profile ("laid-back" or orifice view) the coronary anatomy; and echocardiographic recognition of the diverse coronary artery patterns (Figs 25B-3, 25B-4, 25B-10). There was of course great interest in the specific surgical maneuvers to transfer the usual and uncommon coronary artery patterns, particularly those with a single right coronary artery and a retropulmonary left system and those with an intramural course.[232] While the majority of coronary artery patterns can now be safely transferred, there is still appropriate concern about the influence of coronary artery anatomy and transfer on the long-term outcome of the arterial switch. As shown by Hutter and his colleagues, abnormal coronary anatomy was not a determinant of outcome in their review of 170 patients operated between 1977 and 1999.[166] Severe residual coronary arterial obstruction can be clinically silent, and in this series several patients were found to have important residual coronary pathology in the face of normal electrocardiography, echocardiography, and scintigraphy. For this reason this group recommends that follow-up angiography be considered in all patients after the arterial switch procedure. They did not explore stress-dobutamine studies as a methodology to unmask ischemic damage. Tamisier and his colleagues have also examined how coronary patterns influence later coronary events.[101] In their experience with 236 consecutive arterial switch patients operated by one surgeon reported in 1997, there were 19 deaths, with survival at 1 month, 1 year, and 5 years being 93%, 92%, and 92%, respectively. Coronary events occurred in 26 patients and involved coronary deaths in 11 patients, nonfatal myocardial infarctions in 8 patients, and coronary stenoses or occlusions in

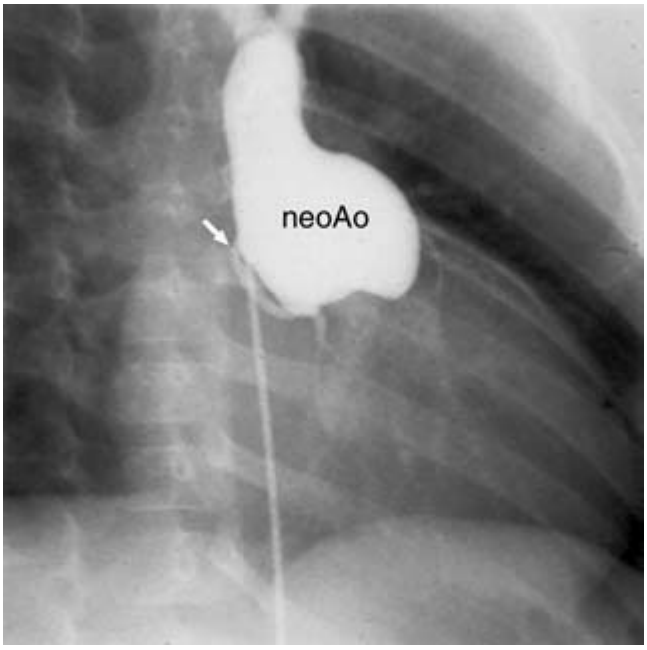


Fig. 25B-10 Narrowing of the proximal right coronary artery (arrow) due to kinking. NeoAo, neoascending aorta.

7 patients. Freedom from coronary events at 1 month, 1 year, and 5 years was 94%, 91%, and 88%, respectively. Risk factors in this experience for adverse coronary events included coronary patterns with a retropulmonary course of the main or left circumflex coronary artery, coronary patterns with coronary arteries coursing between the great arteries, all variations of intramural coronary arteries and commissural origin of coronary ostia.[101] Haas and his colleagues from the German Heart Center of Munich identified among 46 patients undergoing follow-up angiography 5 patients with coronary occlusion or stenosis.[221] Daebritz and her colleagues also showed that certain coronary artery patterns were determinants of late mortality including those with a single coronary ostium.[175] In the very extensive experience of the Marie Lannelongue Hospital, among the 278 patients undergoing post-switch coronary arteriography, 8% had coronary lesions.[215] It is interesting to see how the method of coronary artery transfer can impact on late outcome. Bonhoeffer and his colleagues reported a very high incidence of coronary artery obstruction following single-orifice reimplantation of both coronary artery ostia.[233] The incidence of obstruction (11 of 35 patients) using this technique led to its rapid abandonment.[233]

As one surveys the literature, it has been difficult to ascertain why some patients underwent coronary arteriography (i.e. elective investigation, difficult coronary pattern to transfer, symptoms of or evidence for myocardial ischemia, left ventricular dysfunction, worrisome rhythm disturbances, or near sudden-death events, etc.). If important residual coronary artery pathology can be clinically silent, what is the most sensitive methodology in isolation or in combination to define these abnormalities? The reality is that important coronary lesions result from coronary transfer and contribute to early and late morbidity and mortality. In response to these clinical findings there is ever increasing literature documenting coronary artery revascularization procedures. Again, Losay and his colleagues found that coronary revascularization was required in only 5 patients (0.46%), and this incidence is similar to that reported by Haas *et al.* (0.36%) and Daebritz *et al.* (0.34%).[175,215,221] Revascularization has usually been surgical with plasty of the coronary artery, grafting using the internal mammary artery, or the left subclavian artery,[175,215,221,234–236] but there have been some reports of coronary angioplasty to restore vessel patency.[237,238] It is unlikely that coronary insufficiency after the arterial switch operation reflects lack of growth,[239–241] but rather difficulty in achieving coronary transfer.[233]

In the face of certain coronary artery pathology amongst some survivors of the arterial switch, there has been an increased interest in the evaluation of myocardial ischemia using a variety of methodologies.[242–255] We have already commented on the findings of Millane *et al.* using dipyridamole sestamibi single-photon emission tomography (PET) to evaluate late survivors of the Mustard repair.[231] Myocardial perfusion defects have been demonstrated using thallium-201 and technetium-99 sestamibi in patients who have undergone the arterial switch. PET has been shown in the adult to have a greater sensitivity and specificity than other forms of myocardial perfusion imaging, allowing simultaneous ascertainment of coronary flow reserve.[252,254] Rickers and coworkers have used positron emission tomography to determine myocardial viability in infants and children with suspected infarction after the arterial switch.[249] They found that fluoro-18-deoxyglucose PET demonstrated viable myocardium in akinetic or hypokinetic regions corresponding to a coronary artery stenosis or occlusion.[249] This was used as an indication for revascularization in these particular children. Yates and his colleagues have also used PET scanning to evaluate myocardial perfusion following the neonatal arterial switch operation.[250] They showed an excellent correlation between the results of PET scanning and patterns of coronary artery pathology.[250] Coronary blood flow reserve has been evaluated in a number of studies of patients who have undergone the arterial switch procedure.[244,245,249,250,253] Magnetic resonance imaging (MRI) also provides multiple approaches for determining myocardial perfusion and viability.[253A] Although the coronary arteries can be imaged with MR, its utilization even in adults is still limited.[253B] Although the methodologies vary and the exact values also differ, most studies indicate that coronary flow reserve is reduced when compared to normal patients, and in the study of Hauser *et al.*, the reduction is significant.[245,253,254] It is of interest that in the same study, coronary flow reserve was normal in the small patient population who had been evaluated after the Ross procedure.[245] The reason for this difference between arterial switch and Ross patients can possibly be explained at least in part by the observations of Bellhouse *et al*.[256] Implantation of the coronary orifice in the arterial switch patient is often located above the aortic sinuses, whereas in the Ross patient they are implanted to lie within the sinues.[245] Bellhouse *et al*. observed that the sinotubular ridge is an invariable and well-marked anatomic feature of the normal aortic outflow tract and that the coronary ostia always lie within the sinuses.[256] If the ostia lie outside the sinues on the aortic wall, the normal function of the aortic sinus will be lost, resulting in a serious reduction in coronary flow reserve.[256] There are many other issues impacting on coronary flow reserve including endothelial function and coronary vasoreactivity. Oskarsson and colleagues have shown using an intracoronary Doppler guidewire technique that coronary flow reserve and coronary vasoreactivity to nitroglycerine is normal in children with transposition treated by the arterial switch operation.[256A] In this regard, Kondo *et al.* and others have shown that cardiac sympathetic nerves were denervated early after and reinnervated late after the arterial switch procedure.[257,258] The impact of this finding on coronary artery function has yet to be clarified. One other interesting finding that could result in myocardial ischemia was reported by Yatsunami and colleagues.[48,259] Using computer-assisted densitometry to measure the diameters of the right, left main trunk, anterior descending, and circumflex coronary arteries, they found that the left coronary arteries were smaller than those measured in a control population. They wonder whether this finding could contribute to myocardial ischemia in those patients without obvious coronary artery stenosis or occlusion after the arterial switch operation.[259] Others have also measured the caliber of the coronary arteries in transposition.[67] With the arterial switch experiences now approaching 30 years, and as increasing numbers of these patients reach adulthood, undoubtedly adverse coronary events are likely to increase. The observations of Losay and colleagues from the Marie Lannelongue Hospital are particularly germane in this regard.[241A] They have found that adverse coronary events are not rare after the arterial switch operation, usually occurring early and contributing to mortality. They urge selective coronary arteriography at 5, 10, and 15 years after the arterial switch, stating that non-invasive exploration are not sensitive enough to detect significant coronary artery stenosis. Tzifa and Tulloh have re-

cently provided an overview of coronary arterial complications before and after the arterial switch.[259A]

Left ventricular dysfunction

Left ventricular dysfunction in the patient with transposition of the great arteries is multifactorial and myocardial ischemia is just one of many factors impacting on the contractility of the left ventricle. There has been a substantial literature devoted to the evaluation of ventricular performance after the arterial switch operation, both after a primary switch and after the rapid two-stage switch.[38,39,64,66,75,95,100–102,160,165–167,173–175,182,183,210,212,215,240,241A,242,247,248,251,260] These evaluations have been performed using a variety of methodologies, and a wide variety of indices of contractility including assessment of wall-motion abnormalities have been performed. It is gratifying to note that from the earliest reports addressing ventricular function after the arterial switch and in the absence of serious complications, left ventricular function is characterized as normal or nearly normal. Clearly there are some patients with impaired contractility, abnormal ejection and shortening fractions and wall motion abnormalities. Myocardial ischemia is but one contributing factor, but others including myocardial protection, length of ischemic time during surgery, preoperative status, etc., all potentially impact on myocardial performance. Losay and his colleagues state that left ventricular function was normal in 96.4% of their very large patient volume,[215] echoing the findings of Haas and others.[221] These comments thus far all refer to patients undergoing primary arterial switch repair. There is some concern about the myocardial performance in those patients who have undergone the rapid two-stage repair. In the rapid two-stage group, the echocardiographic indices of left ventricular function (fractional shortening and velocity of fiber shortening) and contractility (stress-velocity and stress-shortening relations) were found to be mildly, but significantly reduced when compared to normal subjects or to those who underwent a primary arterial switch operation.[39,182,183] Patients who underwent serial examinations after a primary arterial switch operation showed an increase in left ventricular mass and dimension *Z*-score out of proportion to somatic growth, while all other variables including indices of function and contractility showed no change with time.[182,183] In the patients after a rapid two-stage arterial switch operation, there was a significant fall in wall thickness *Z*-score and rise in dimension *Z*-score with a consequent rise in end-systolic stress *Z*-score over time. However, similar to the one-stage group, including indices of function and contractility showed no change with time. It is unclear how these findings in the two-stage arterial repair patients will translate into clinical findings. Ventricular function is often abnormal after atrial repair of transposition (see Chapter 25A), and as well exercise performance is also significantly reduced after the Mustard or Senning atrial repairs for transposition.[261–269] Most studies indicate that cardiorespiratory exercise function is at, or slightly below, the lower limit of normal in patients after the arterial switch.[270–272]

Aortic regurgitation

It is not surprising that aortic regurgitation is commonly appreciated after the arterial switch operation considering the findings of Kovalchin and colleagues noted earlier.[99] Even when documented as trivial-to-mild from color flow Doppler assessment, not infrequently it is not appreciated by auscultation. Clinical evidence has been marshalled elsewhere that the pulmonary valve seems to work well in the systemic circulation, and it is unlikely that some degenerative process is responsible for the aortic incompetence.[197,198] More likely it is due to some eccentricity of the native pulmonary valve, perhaps further distorted by previous pulmonary artery banding or coronary artery transfer. There seems to be an increased incidence of aortic incompetence in those patients with an important discrepancy in size between the native aortic and pulmonary roots.[175,210,212,215,216,221,240] Aortic incompetence has been identified in from 20% to 40% of patients after the arterial switch procedure, but fortunately it is usually characterized as trivial to mild. Some patients have required aortic valve repair or even replacement years after the arterial switch operation.[273] Haas and his colleagues found that while only a minority of patients showed mild aortic insufficiency on echocardiography at the time of discharge, there was a significant increase of mild aortic insufficiency occurring in the three groups of patients: simple transposition, transposition with ventricular septal defect, and those with the Taussig–Bing or other forms of double-outlet right ventricle.[221] They also documented a progressive increase in aortic regurgitation in each group after 6 years. Three patients eventually required aortic valve replacement. Losay and his colleagues from the Marie Lannelongue Hospital in France have had an extensive experience with the arterial switch operation and this group, headed by Professor Claude Planches have contributed substantially to the clinical literature about this and other forms of congenital heart disease.[215] They recently commented on the outcome of the arterial switch procedure performed in 1200 patients between 1982 and 1999.[215] While reintervention for aortic regurgitation was uncommon in their experience (only 1.3% among the survivors), aortic regurgitation occurred during the entire period of follow-up, with a freedom from aortic regurgitation of 99.8% at 3 months, 99.1%, 97.6%, and 96.2% at 5, 10, and 15 years, respectively. Yamaguchi and his colleagues have reported that aortic regurgitation is more common in the two-stage repair than in those undergoing primary repair, again suggesting that the banding may have contributed to some thickening and nodularity of the left ventricular (pulmonary) valve.[274] This should not come as any surprise as pulmonary valve thickening is a well-described complication of longstanding pulmonary artery banding in hearts with normal segmental anatomy and connections.[275,276] There have been some studies to suggest that pulmonary artery banding in the short term does not compromise pulmonary valve function considered for a Damus–Kaye–Stansel operation.[277,278] Finally, in at least 1 patient a switch back maneuver was used to treat severe neoaortic valve incompetence after the arterial switch operation.[279] This child aged 3 years and 4 months demonstrated progressive dilatation of her aortic root and aortic regurgitation in follow-up after her primary arterial switch operation performed at 2 days of age. The pulmonary autograft was used to replace the severely regurgitant neoaortic valve, and the pulmonary outflow tract was reconstructed with a pulmonary homograft.[279] Yoshizumi and colleagues document their approach to the neoaortic valve for replacement after the arterial switch procedure.[279A] They mention that of 158 patients who had undergone the arterial switch operation, 3 patients required aortic valve replacement.

Hutter and his colleagues have studied the fate of the aortic root after the arterial switch procedure.[280] They showed that rapid dilatation of the new aorta occurs in the first year after the arterial switch, followed by growth towards normalization

of the valve and sinus size.[280] They also found that aortic dilatation by itself rarely contributed to the aortic regurgitation. Murakami and coworkers have found that the neoaorta demonstrates impaired distensibility after the arterial switch procedure,[281] a finding also noted by Sievers and his colleagues who documented both dilatation and decreased distensibility of the neoaortic sinus after the two-stage arterial switch operation.[121] Murakami speculates that the lack of normal aortic distensibility after the arterial switch procedure has several possible etiologies including: (1) manipulation related to the transfer of the coronary arteries may influence such changes; (2) although the histology of the aortic and pulmonary roots are similar at birth, the muscle fiber composition is different (it is conceivable that the increased vascular afterload of the systemic circulation may make the neoaortic sinus dilate and less distensible); (3) it is likely that the arterial switch surgery impairs blood flow to the neoaortic vasa vasorum, which may lead to medial necrosis, thus inducing the dilatation and altering the distensibility. Chronically decreased aortic distensibility is also known to cause deterioration of coronary perfusion, another concern in these patients.[282]

In these patients pre-existing left ventricular outflow tract obstruction in those patients undergoing the arterial switch operation predicts a high incidence of postoperative neoaortic regurgitation.[282A]

Atrioventricular valve dysfunction

Any number of mitral valve anomalies have been described in the patient with transposition, but in the overwhelming majority of patients functional integrity is preserved.[283–286] Mitral regurgitation has been observed as a consequence of chronic myocardial ischemia or acute infarction. It has also been observed in those patients with transposition of the great arteries and left ventricular outflow tract obstruction secondary to malattachments of the mitral valve following arterial switch surgery and attempted relief of the left ventricular outflow tract obstruction.[97,98] Finally, mitral regurgitation, sometimes severe, has been seen after repair of transposition of the great arteries, ventricular septal defect and straddling of the mitral valve.[287]

Tricuspid regurgitation is seen more frequently than mitral regurgitation in patients with complete transposition, and as discussed in the previous chapter the etiologies are multifactorial.[19,288–293] Again, tricuspid regurgitation may reflect traumatic damage to the valve at the time of septostomy; distortion of the valve at the time of ventricular septal defect closure; following repair of a ventricular septal defect and associated straddling of the tricuspid valve; following resection of the infundibular septum with tricuspid chordal attachments (usually more of a concern for the Rastelli or REV operation); as a consequence of right ventricular ischemia/infarction; or as a consequence of the failing right ventricle, this latter finding more common after atrial repair of transposition[19,288–293] (see also Chapter 25A).

Cardiac rhythm disturbances

Serious cardiac rhythm disturbances are quite uncommon after the arterial switch operation. Unlike the atrial repairs for transposition, the surgical substrate for sinus node dysfunction is not present, namely damage to the artery to the sinus node or the sinus node itself. Kramer and colleagues compared the prevalence of arrhythmias among patients with complete transposition after the arterial switch operation with patients who had undergone the Mustard repair in infancy.[294] Symptomatic brady/tachyarrhythmia syndrome never occurred in patients after the arterial switch, but they found a significant proportion of such symptomatic rhythm disturbances in the Mustard group. In addition, Holter monitoring did not detect bradyarrhythmias indicating sinus node dysfunction in a single patient after the arterial switch, but documented evidence of sinus node dysfunction in a substantial number of the post-Mustard patients.[294] Backer and his colleagues have also compared results of the Mustard procedure vs. the arterial switch.[295] The incidence of arrhythmias in the early postoperative Mustard patients was 39%, and only 11% in the switch group. The incidence of late arrhythmias in the Mustard group was 57% in the Mustard group and 3% in the arterial switch group.[295] One study with relatively small patient numbers addressing early rhythm disturbances after the arterial switch compared to those undergoing a Mustard repair showed little difference between the two groups.[296]

Rhodes and his colleagues reported in 1995 on the 364 survivors of the 390 arterial switch operations that in those patients not having a permanent pacemaker, sinus rhythm was present in 96% on the surface electrocardiogram and 99% during 24-h Holter monitor studies (1 month to 8.5 years, mean 2.1 years after the operation).[297] Intracardiac electrophysiologic studies (n = 158) demonstrated normal corrected sinus node recovery times and AH intervals in 97% of patients. Atrial ectopy was present in 152 of 172 (81%) patients, with the majority (64%) of patients having only occasional premature beats without repetitive forms. Ventricular ectopy was a frequent finding during 24-h monitoring. At hospital discharge 70% had ventricular ectopy; these values fell to 57% (in patients with intact ventricular septum) and 30% (in patients with a coexisting ventricular septal defect) at follow-up. In the early postoperative period, there were 25 episodes of supraventricular tachycardia (14 of which required therapy), 6 episodes of junctional ectopic tachycardia, and 9 episodes of ventricular tachycardia. The incidence of supraventricular tachycardia had fallen to 5% at follow-up, with no atrial flutter or fibrillation noted. Three patients had ventricular tachycardia on follow-up Holter studies. Losay and his colleagues reported on the long-term outcome of 1095 survivors of the 1200 patients who underwent the arterial switch between 1982 and 1999.[215] Sinus rhythm was present at last follow-up in 98.1%, with only 6 patients having episodes of supraventricular tachycardia. Fifteen patients had complete heart block, with 13 requiring pacemakers. Serious ventricular arrhythmias are uncommon, occurring primarily in those with an ischemic or otherwise compromised myocardium. From all of these clinical observations in the first two decades after routine neonatal arterial switch and nearly three decades after Jatenes' benchmark accomplishment, most patients following the arterial switch procedure have preserved sinus node function, ranging from 94% to 98% for variable lengths of follow-up.[100,173,175,215,221]

Pulmonary vascular obstructive disease

Pulmonary vascular obstruction has been studied in patients with transposition for the past 40 years,[298–306] and has been identified in some patients with an intact ventricular septum after an apparently successful form of atrial repair.[307–309] It is not surprising that pulmonary vascular obstruction is appreciated more frequently in those with transposition and large ventricular septal defect or patent arterial duct.[298–305] Despite pulmonary artery banding early in infancy some patients still develop

pulmonary vascular disease after atrial repair, and in some patients high pulmonary vascular resistance prohibits an atrial repair.[304,306] Similar observations have been made about patients with transposition in the era of arterial repair. Late-onset pulmonary vascular obstruction has been identified even in some patients who underwent neonatal arterial repair.[310–312] Haas and his colleagues mentioned that only one patient developed severe pulmonary vascular obstruction after the arterial switch procedure in 285 patients, but did not provide specific information about this child.[221] Brown and his colleagues mention pulmonary hypertension as the second most common cause of early postoperative death following left ventricular failure.[173] Daebritz and her colleagues state that in their experience of 312 arterial repairs the most common cause of late death was pulmonary vascular disease, being identified in 3 patients with simple transposition and an intact ventricular septum undergoing neonatal arterial repair.[175] This raised the possibility that the etiology of the pulmonary vascular disease was primary.[175] Only 5 patients in the large experience of the Marie Lannelongue Hospital developed pulmonary vascular disease leading to a late death after the arterial switch.[215] In 2 patients with an intact ventricular septum who developed this complication, the arterial switch operation was performed in the first month of life. One of the other 3 patients, all with a ventricular septal defect, was repaired late at 9 months of age. Enlarged systemic-to-pulmonary arteries or so-called bronchial arteries are often documented in patients with complete transposition, and some have suggested that these contribute to pulmonary vascular disease.[313–316]

General somatic and neurodevelopmental outcome

The general health status and neurodevelopmental outcome of children following the arterial switch procedure has received appropriate attention.[317–321] Compared to normal, Hovels-Gurich *et al.* found that growth was adequate, but weight and head circumference were slightly reduced.[317] After the median sternotomy, 23.4% had an abnormal thoracic configuration, with 16.9% showing some asymmetry and 6.5% a funnel chest deformity. Dunbar-Masterson and her colleagues found that children at age 8 years who underwent a neonatal arterial switch operation have an overall physical and psychosocial health status similar to that of the general population.[318] Lower IQ and academic achievement were associated with worse psychosocial health status whereas worse physical health status was associated with longer hospital course after the initial surgery.[318] These findings published from the Children's Hospital in Boston confirm Newburger *et al.*'s findings of two decades ago that age at repair is inversely associated with WPPSI intelligence-quotient scores, the visual-association subtest score, and the auditory-association subtest score.[322] Hovels-Gurich *et al.* also reported in 1997 that neurologic impairment was more frequent after neonatal arterial switch (9.1%) than in the normal population.[320] Intelligence was not different in these patients compared with normal children ($P = 0.11$), but motor function, vocabulary, and acquired abilities were poorer. Reduced intelligence was found in 9.1%, fine motor dysfunction in 22.1%, and gross motor dysfunction in 23.4% of the children. Intelligence was weakly but significantly inversely related to the duration of bypass (Spearman correlation coefficient –0.25, $P = 0.03$) and tended to be inversely related to the duration of circulatory arrest (–0.21, $P = 0.07$), but not to core cooling time on bypass or degree of hypothermia. Gross motor function, vocabulary, and acquired abilities were not significantly related to any of the perioperative parameters considered. No correlation was found between the test results and the variables perinatal asphyxia, perioperative and postoperative cardiocirculatory insufficiency, resuscitation events, and plexal or intraventricular cerebral hemorrhage. They concluded that the neonatal arterial switch operation with combined circulatory arrest and low-flow bypass in our experience was associated with neurologic as well as fine and gross motor impairment but appeared to be well tolerated concerning cognitive functions as based on formal intelligence testing.[320] The same group extended their observations about neurodevelomental outcome related to cerebral risk factors in patients who had undergone the neonatal arterial repair.[320] They found that neonatal arterial switch operation with combined circulatory arrest and low flow bypass is associated with neurological impairment, but not with reduced development as assessed by formal testing of motor, cognitive, language, and behavioral functions. Perioperative serum level of the neuron-specific enolase was not a valid marker for later developmental impairment.[321]

Hovels-Gurich and coworkers have also provided some information on the long-term neurodevelopmental outcomes in school-aged children after the neonatal arterial switch operation.[321A] Within a longitudinal study, 60 unselected children operated on as neonates with combined deep hypothermic circulatory arrest and low-flow cardiopulmonary bypass were re-evaluated at the age of 7.9 to 14.3 years (mean ± SD 10.5 ± 1.6 years). Neurologic and speech impairments were more frequent (27% and 40%, respectively) than in the general population. Intelligence and socioeconomic status were not different ($P = 0.29$ and $P = 0.11$), whereas motor function, acquired abilities, and language were reduced in those who had undergone a neonatal arterial switch operation ($P = 0.04$ for each). Overall rate of developmental impairment in one or more domains was 55%, compared with 26% at age 5.4 years. Multivariable analysis showed that severe preoperative acidosis and hypoxia predicted reduced motor function (mean deficit 52.7 points, $P < 0.001$), whereas longer bypass duration predicted both neurologic (odds ratio per 10 min of bypass duration 1.8, $P = 0.04$) and speech (odds ratio per 10 min of bypass duration 1.9, $P = 0.02$) dysfunction, and perioperative and postoperative cardiocirculatory insufficiency predicted neurologic (odds ratio 6.5, $P = 0.04$) and motor (mean deficit 6.8 points, $P = 0.03$) dysfunction. They concluded that the neonatal arterial switch operation with combined circulatory arrest and low-flow bypass was associated increasingly with age, with reduced neurodevelopmental outcome but not with cognitive dysfunction. In their experience, the risk of long-term neurodevelopmental impairment after neonatal corrective cardiac surgery is related to deleterious effects of the global perioperative management and to special adverse effects of prolonged bypass duration. Severe preoperative acidosis and hypoxia and postoperative hemodynamic instability must be considered as important additional risk factors. These observations are consistent with the more recent publications of Forbess and Mahle and their respective colleagues.[321B,321C]

Miscellaneous complications

A wide spectrum of other complications have been documented following the arterial switch operation. Esophageal

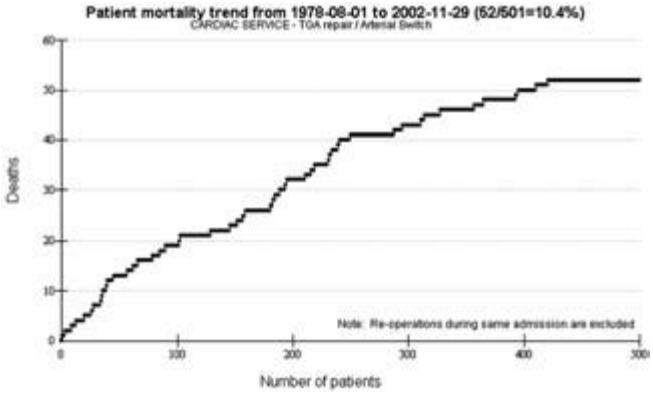


Fig. 25B-11 Toronto Hospital for Sick Children experience with the arterial switch procedure. The cumulative mortality of 10.4% for our entire switch experience of 501 patients operated from August 1, 1978 to November 29, 2002.

and tracheobronchial compression syndromes have been observed.[323,324] Others have documented small left pulmonary veins after the arterial switch procedure,[325] likely reflecting as suggested by Vogel, his colleagues and others the maldistribution of pulmonary blood flow related to the orientation of the pulmonary outflow tract.[326,327] Preferential flow to the right pulmonary artery has been observed after an early neonatal arterial switch repair.[328] In one patient reported by Fletcher *et al.*, despite a low right ventricular pressure, selective left pulmonary arteriography suggested the appearance of pulmonary vascular disease with sluggish flow. In the second patient reported from the same group, anatomic left lower pulmonary vein stenosis contributed to the preferential flow to the right lung.[328] This was treated with a Palmaz endovascular stent. This child died at about 20 months of age, 4 months after stent implantation, and at post-mortem grade IV pulmonary vascular changes were seen in the left lung.[328] Tracheobronchial compression is an uncommon complication of the arterial switch operation, attributed in some cases to compression of the left mainstem bronchus between the neoaorta and descending aorta.[328A] Chiu and colleagues suggest that spiral reconstruction of the great arteries at the time of the coronary transfer may obviate this complication.[204A,B]

Finally mechanical hemolysis has been documented in a patient with pulmonary artery stenosis following the arterial switch procedure.[329]

The arterial switch to treat the failing right ventricle after atrial repair of transposition

The failing right ventricle with or without tricuspid regurgitation contributes to late morbidity and mortality after the atrial switch options for the patient with simple and complex transposition (see Chapter 25A). Subsequent to Mee's initial report in 1986 of a two-stage repair consisting of pulmonary artery banding and subsequent switch for severe right ventricular failure after Mustard or Senning operation,[330] there has been considerable experience with this operation.[292,331–338] These patients are frequently quite fragile and do not tolerate a tight pulmonary artery band. They may require one or more operations to gradually tighten the band in order to retrain or prepare the left ventricle for the arterial switch operation. It is uncertain as to what is the upper age for this approach, and whether the older patient would be better served by cardiac transplantation. Some patients will tolerate pulmonary artery banding and in some an adequate left ventricular mass will not be achieved.[331–337]

The arterial switch operation as palliation

In several situations, the arterial switch operation has been used to palliate. One situation discussed in the previous chapter (Chapter 25A) was the arterial switch as palliation for transposition of the great arteries, ventricular septal defect and pulmonary vascular obstruction.[338,339] This operation has also been used to palliate the patient with complex transposition anatomy precluding a complete biventricular repair and disadvantageous intracardiac streaming.[340] The arterial switch option has been used to treat subaortic stenosis in the univentricular heart with discordant ventriculoarterial connections[341–343] (see also Chapter 36). Finally some years ago, we performed an arterial switch operation combined with a right atrioventricular valved conduit (Fontan-modification) to palliate several older patients with complex forms of tricuspid atresia.[344] One should not forget that some patients require atrial fenestration at the time of the arterial repair, especially those with peculiar confounding anomalies.[345] If the fenestration does not spontaneously close and if there is a late substantial left-to-right shunt, intervention may be required.

Other issues affecting outcome

We have reviewed elsewhere some of those factors contributing to an enhanced outcome for patients with congenital heart disease.[346] It is important to define the outcome of the entire cohort of patients presenting to any institution, not just those undergoing surgery.[346–350] This is perhaps less of an issue for patients considered for arterial repair than in those patients on a single-ventricle palliation tract. We have seen how over time identification of specific anatomic and procedural risk factors for anatomical repair of transposition (among a wide range of cardiac conditions) can be neutralized, enhancing the outcomes for these patients (Figs. 25B-11 to 25B-14). While certainly some centers with only small or modest patient volumes can achieve excellent surgical results, there is an increasing preponderance

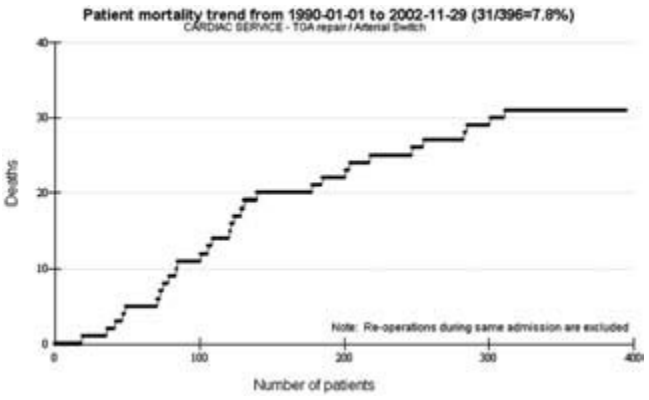


Fig. 25B-12 Toronto Hospital for Sick Children experience with the arterial switch procedure. The cumulative mortality of 7.8% for the switch operation in 396 patients operated from January 1, 1990 to November 29, 2002.

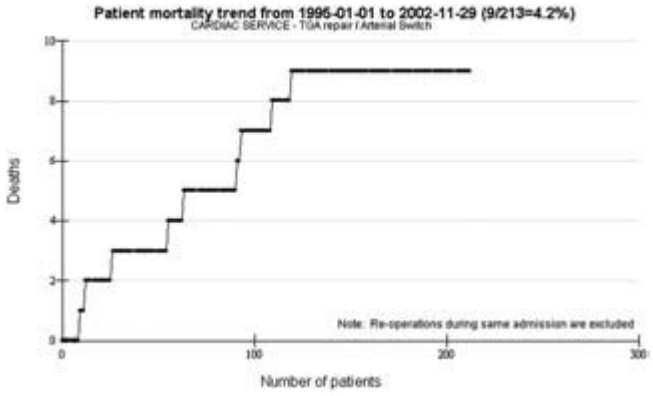


Fig. 25B-13 Toronto Hospital for Sick Children experience with the arterial switch procedure. The cumulative mortality of 4.2% in 213 patients operated between January 1, 1995 and November 29, 2002. Figures 25B-11 to 25B-13 demonstrate the continued improvement in the arterial switch operation at the Toronto Hospital for Sick Children. During the past 2 years, the early mortality is < 2%.

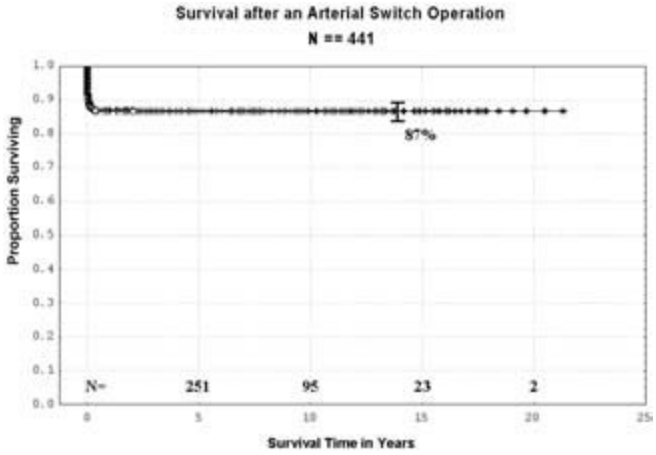


Fig. 25B-15 Kaplan–Meier curve depicting survival of the Toronto Hospital for Sick Children's experience with the arterial switch operation from 1978 to 2002.

of evidence that in-hospital mortality is inversely correlated with volume. There are now considerable data supporting an inverse relationship between outcomes of coronary artery surgery and volumes in the adult.[351] Subsequent to the initial report from Jenkins and her colleagues in 1995 addressing in-hospital mortality for surgical repair of congenital heart defects by hospital caseload,[352] these observations have been confirmed by others, both from North America and from Europe.[353–355] We and others have suggested that the type of institution where the patient care is conducted may also impact on patient outcomes.[346,353] The inference is that perhaps a better outcome would be anticipated in those institutions with a wide range of pediatric cardiac subspecialists and the entire gamut of ventricular support technologies. De Leval of the Great Ormond Street Hospital for Sick Children has in a very thoughtful way brought to our attention how human factors contribute to outcomes of pediatric cardiac surgery.[356,357] His initial observations were based on his own experience with a cluster of surgical failures of the neonatal arterial switch operations.[356] He found after an exhaustive analysis of the cluster of his failures there was an indication of suboptimal performance that was neutralized by retraining.[356] In his more recent publication, utilizing a multicenter study he and his colleagues again studied the role of human factors on the surgical outcomes of 243 arterial switch operations performed by 21 surgeons.[357] This study again highlighted the role of human factors in negative surgical outcomes, thus providing other areas to enhance outcomes, hopefully "fulfilling expectations" of patients, their families, and their caregivers.[358] Indeed, as de Leval indicated, there are lessons from the arterial switch operation.[359]

Thus as one surveys the somewhat more than a quarter of a century since the first successful arterial switch operation, what has been achieved and what lies ahead?

- The arterial switch operation can be performed with early mortality rates of 2% or less in patients with uncomplicated coronary artery anatomy.
- Mortality rates may be somewhat higher with a single coronary artery or the coronary artery with an intramural course.

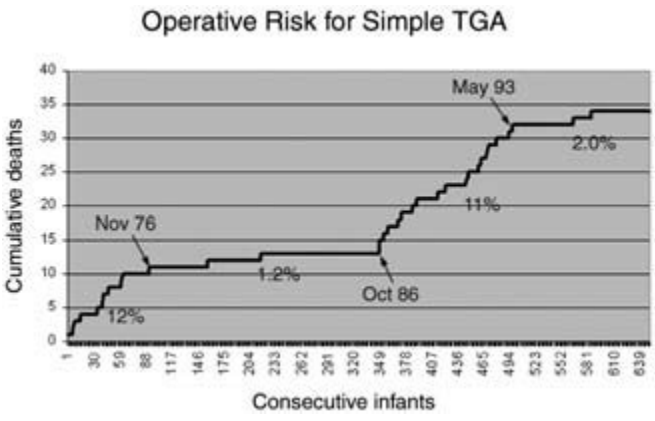


Fig. 25B-14 Graph depicting cumulative mortality for transposition of the great arteries and intact ventricular septum, at the Toronto Hospital for Sick Children. These data capture the Mustard experience as well as the arterial switch experience. The current mortality is < 2%.

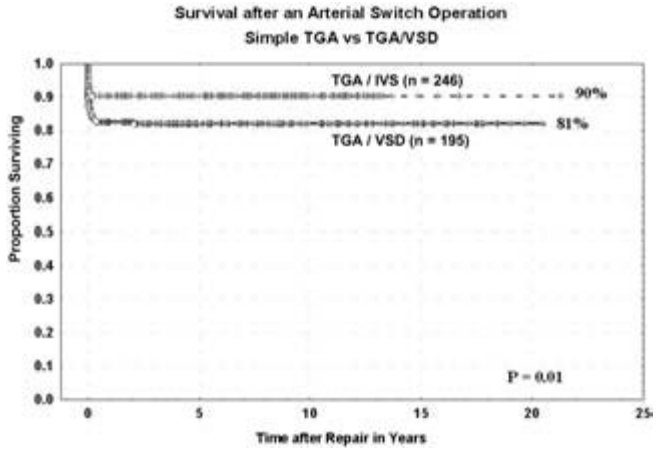


Fig. 25B-16 Kaplan–Meier curve depicting survival of the Toronto Hospital for Sick Children's experience with the arterial switch operation from 1978 to 2002 comparing patients with an intact ventricular septum to those with an associated ventricular septal defect.

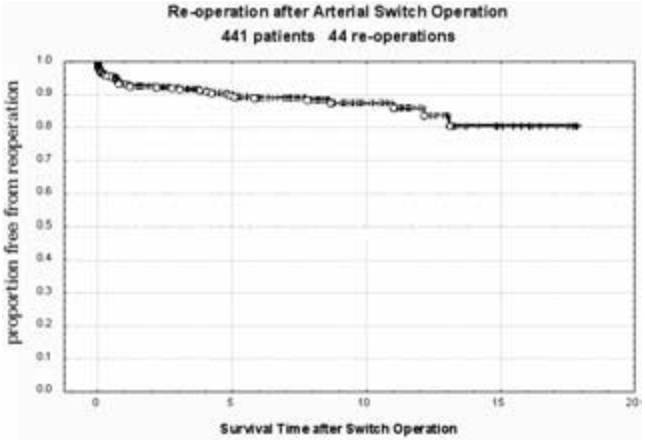


Fig. 25B-17 Kaplan–Meier curve depicting freedom from reoperation/reintervention following the arterial switch operation from 1978 to 2002 at the Toronto Hospital for Sick Children.

- Long-term survival is excellent following the arterial switch operation (Fig. 25B-15). The Toronto Hospital for Sick Children finds a different survival for those with transposition and an intact ventricular septum compared to those with a ventricular septal defect (Fig. 25B-16). Most of this difference can be attributed to a difference in early surgical mortality.
- Pulmonary outflow tract obstruction is the most common reason for reoperation or reintervention, but this complication has declined considerably in recent years. Post-switch supraaortic obstruction has been and continues to be uncommon (Fig. 25B-17).
- Can further technical modifications be introduced to further reduce the incidence of postoperative pulmonary outflow tract obstruction (i.e. such as spiral great artery reconstruction, etc.), and to insure late patency of the coronary artery anastomoses?
- Important aortic regurgitation is a well-documented complication, but uncommon. A trivial degree of aortic regurgitation is frequent as assessed by Doppler.
- Sick sinus syndrome is uncommon as are important supraventricular arrhythmias.
- Important ventricular dysrhythmias usually reflect myocardial ischemia and thus coronary artery pathology.
- Sudden death events are usually ischemic in origin and when such catastrophic events occur they take place usually in the first postoperative year.
- Left ventricular dysfunction usually reflects coronary artery pathology. Numerous methodologies have been used to identify residual coronary artery pathology. At this time selective coronary arteriography may be the most sensitive arbiter of post-switch coronary artery anatomy. Another factor contributing to left ventricular dysfunction is inadequate myocardial protection.
- Late adverse coronary artery events resulting in sudden death or near sudden death episodes are well documented. These events may be more common in those patients with uncommon coronary artery patterns. With many neonatal arterial switch patients now entering adulthood and the age of arteriosclerotic cardiovascular disease, late coronary artery problems may become more prevalent.
- The role of the Damus–Kaye–Stansel procedure has been obviated by techniques to transfer virtually all coronary artery patterns.
- It is important to define neurodevelopmental outcomes as an important consequence of neonatal surgery and to develop strategies to minimize cerebral damage.
- Arterial switch survivors require life-long cardiovascular surveillance.

In conclusion, it took just 25 years from Mustard's ingenious procedure in 1963, which revolutionized the care of patients with transposition, and only a decade after the renaissance of the Senning procedure, for atrial repairs to be virtually abandoned for most patients with simple and complex transposition.[360] In response to Fleming's question "Why switch?"[361] or to Stark's "Which operation?"[144] the answer at this time at the end of the old millennium and beginning of the new millennium seems clear[362] and as Losay states " the arterial switch technique keeps its promise."[215]

All references can be found at the end of the book. See pp. 747–57 for Chapter 25B.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

25C

Robert M. Freedom, Shi-Joon Yoo, and W.G. Williams

The Rastelli and Other Procedures for Complex Transposition of the Great Arteries

In the previous two chapters the indications for and outcome of atrial repair or arterial switch repair for transposition of the great arteries with or without ventricular septal defect have been presented in detail. This chapter will address the treatment challenges and outcomes of patients with complex transposition of the great arteries. This chapter will address the Rastelli operation (Fig. 25C-1, upper panel)[1–4] and the "reparation a l'etage ventriculaire" or the REV procedure of Lecompte (Fig. 25C-1, lower panel),[5–7] both used for patients with transposition of the great arteries, ventricular septal defect and pulmonary stenosis. The staging maneuvers, results of the Fontan procedure and its complications for complex forms of transposition best treated by univentricular palliation will be discussed in Chapters 35, 36, and 37. Giancarlo Rastelli (1934–70) contributed so very much to congenital heart disease, and his name is appropriately linked with his classification of the atrioventricular septal defect (see Chapter 5), as well as with the ventricular repair of complex transposition with left ventricular outflow tract obstruction, work done at the Mayo Clinic.[7A] Sadly he died prematurely at age 36 years from complications of Hodgkin's disease, none the less leaving a lasting legacy of academic and clinical accomplishment. As written by his colleagues and friends, Drs Umberto and Antonella Squarcia, "Dr Rastelli was both scientist and humanist – an exceptional physician with a natural curiosity who displayed enthusiasm, sensitivity, compassion, intelligence, courage, and respect in dealing with personal, collegial, and patient relationships. His classification and the procedure that was named after him have given the gift of life to numerous children all over the world."[7A] Such kind and thoughtful words can be applied to many, both living or dead, who contributed so much to the care of patients with congenital malformations of the heart.

Morphology

Posterior malalignment or displacement of the infundibular septum produces in the patient with complete transposition of the great arteries (concordant atrioventricular connection and a discordant ventriculoarterial connection) a ventricular septal defect beneath the infundibular septum and subpulmonary obstruction (Fig. 25C-2).[8–18] This displacement of the infundibular septum wedges the left ventricular outflow tract between the posteriorly displaced infundibular septum medially and the mitral valve–left-sided ventriculoinfundibular fold laterally. The caudal and posterior deviation of the infundibular septum results in a ventricular septal defect cradled between the anterior and posterior limbs of the trabecular septum. Other mechanisms producing left ventricular outflow tract obstruction include tissue tags, aneurysm of membranous septum, straddling and abnormally disposed atrioventricular valve tissue; pulmonary valvular stenosis, etc. (Figs 25C-3, 25C-4). Silberbach and his colleagues have made a comparison of the types of pulmonary stenosis with the state of the ventricular septum in complete transposition of the great arteries.[9] They inspected the pulmonary valve and left ventricular outflow tract in 126 hearts with transposition of the great arteries and intact ventricular septum and 88 hearts with transposition of the great arteries and ventricular septal defect. In this autopsy study, pulmonary stenosis, valvular, subvalvular, or in combination was found to be three times more frequent in the presence of a ventricular septal defect than in those with an intact ventricular septum. Furthermore, left ventricular outflow tract obstruction was more common in those hearts when the ventricular septal defect involved the infundibular septum when compared to those hearts where the defect was perimembranous. As one might anticipate, the mechanisms responsible for the left ventricular outflow tract obstruction were different when compared to the type of ventricular septal defect. It is rather common to see patients with multiple levels of left ventricular outflow tract obstruction, reflecting multiple etiologies. Thus posterior malalignment of the infundibular septum together with a conspicuous left-sided ventriculo-infundibular fold, pulmonary valvar stenosis, and fibromuscular obstruction may in combination contribute to a diffuse and tunnel form of obstruction. These may be further complicated or aggravated by malattachments of the mitral valve to the infundibular septum or to the crest of the ventricular septal defect further narrowing the left ventricular outflow tract.[14,19,20]

Intrinsic to any patient with complete transposition of the great arteries, but particularly in those with an intact ventricular septum is dynamic subpulmonary stenosis reflecting the usually higher right ventricular pressure, often associated with abnormal systolic anterior motion of the mitral valve (Fig. 25C-3A,B).[21,22] Dynamic subpulmonary stenosis can be seen in the immediate newborn period, but becomes more obvious after the first few weeks of life with maturation of the pulmonary vascular bed and reduction of left ventricular pressure. Longstanding dynamic subpulmonary stenosis produces a fibrous ridge analogous to that observed in the patient with classic subaortic stenosis.[23–25] Thus in the evolution of a dynamic process, the dynamic subpulmonary obstruction may be complicated by fixed elements as well. Some years ago we reported our institution's experience with left ventricular outflow tract obstruction in 46 patients with complete transposition of the

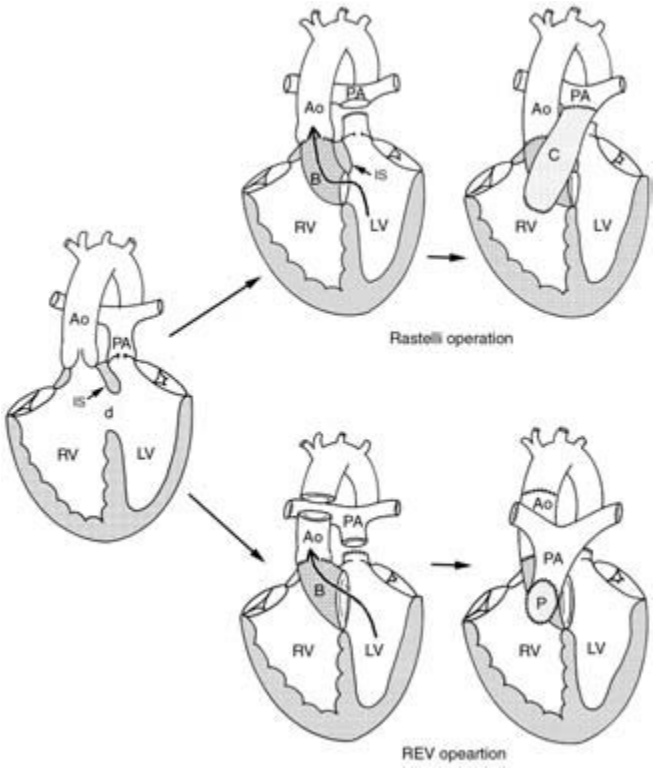


Fig. 25C-1 Rastelli and "réparation à l'etage ventriculaire" (REV) operations. Both procedures are for complete transposition of the great arteries, ventricular septal defect (d) and left ventricular outflow tract obstruction. In Rastelli operation, the left ventricle (LV) is tunneled to the aorta (Ao) by closing the ventricular septal defect (d) with a baffle (B). The pulmonary artery (PA) is divided, the proximal end closed and the distal end connected to a conduit (C) interposed between the right ventricle (RV) and distal main pulmonary artery. In REV operation, the infundibular septum (IS) is excised and the ventricular septal defect closed to the right of the aorta, and the pulmonary artery divided and oversewn proximally. A conduit is interposed between the right ventricle and pulmonary artery as in Rastelli operation, or alternatively, the distal pulmonary artery is mobilized sufficiently to allow a direct tissue connection with the ventricle, augmented anteriorly with a patch (P) as shown in the drawings. When the pulmonary artery cannot be pulled down to the right ventriculotomy site directly, the ascending aorta can be disconnected temporarily to mobilize the pulmonary artery anteriorly. In Rastelli operation, the tunnel of the left ventricular outflow tract makes acute turns (arrow in the middle diagram). In REV operation, the tunnel makes gentle curves (arrow in the middle diagram).

great arteries and essentially intact ventricular septum undergoing Mustard's operation.[24] The majority of these patients were found to have fibrous-fibromuscular obstruction, but about 20% were found to have abnormal mitral valve insertion; protrusion of the tricuspid valve through a restrictive ventricular septal defect into the left ventricular outflow tract; or other abnormalities of the atrioventricular valves (Fig. 25C-3). In only three patients was there a significant abnormality of the pulmonary valve requiring a commissurotomy, in two in isolation and in one, with associated fibromuscular left ventricular outflow tract obstruction. Chiu and colleagues have assessed those features of an intact ventricular septum susceptible to subpulmonary obstruction in transposition of the great arteries.[25] They found that in those patients with a bulging interventricular septum the aorta lay more anterior to the pulmonary trunk and these patients were more prone to develop a fibrous ridge on the left ventricular septal surface, consistent with left ven-

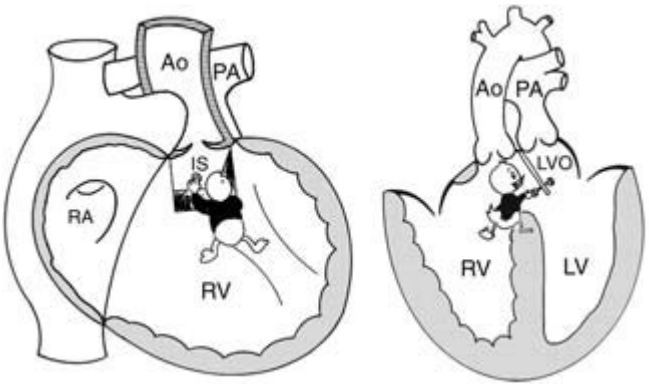


Fig. 25C-2 Mechanism of subpulmonary obstruction in association with posterior malalignment of the infundibular septum. The infundibular septum (IS, trap door) is pushed backward resulting in a posterior malalignment type of ventricular septal defect and narrowing of the subpulmonary outflow tract (LVO). Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

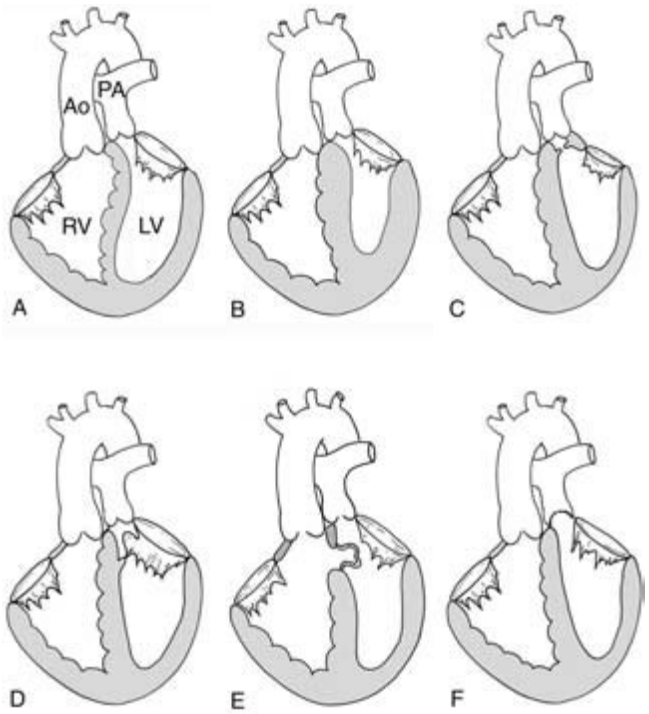


Fig. 25C-3 Left ventricular outflow tract obstruction in complete transposition with intact ventricular septum. **A**. Septal bulge with dynamic narrowing. **B**. Septal hypertrophy with dynamic narrowing. **C**. Fibrous or fibromuscular ridge with or without persistent left ventriculoinfundibular fold. **D**. Abnormal tension apparatus of and accessory tissue from the mitral valve. **E**. Protrusion of so-called membranous septal aneurysm with closing or closed perimembranous ventricular septal defect. **F**. Pulmonary valve stenosis. Ao, aorta; LV left ventricle; PA, pulmonary artery; RV, right ventricle.

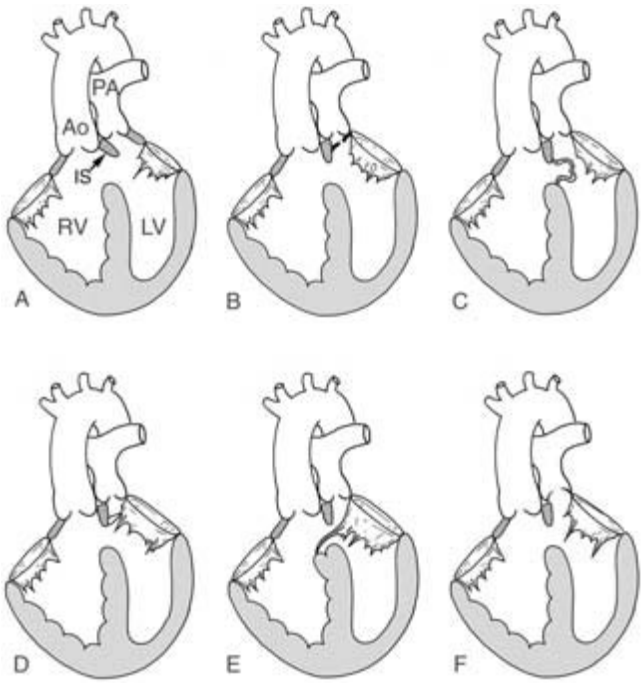


Fig. 25C-4 Left ventricular outflow tract obstruction in complete transposition with ventricular septal defect. **A**. Posterior deviation of infundibular septum (IS) with or without persistent left ventriculoinfundibular fold. **B**. Fibrous ridge below the pulmonary valve. **C**. Protrusion of so-called membranous septal aneurysm with closing or closed perimembranous ventricular septal defect. **D**. Insertion of the mitral valve tension apparatus to the infundibular septum or ventricular septal crest. **E**. Straddling mitral valve. **F**. Pulmonary valve stenosis. Ao, aorta; LV left ventricle; PA, pulmonary artery; RV, right ventricle.

tricular outflow tract obstruction. Their morphologic findings also indicated that patients with transposition of the great arteries and a left anterior aorta were more likely to develop a septal bulge and left ventricular outflow tract obstruction. The so-called dynamic form of left ventricular outflow tract obstruction may become particularly severe and this may "prepare" the left ventricle for the arterial switch procedure when conducted past the first month of life when there is increased risk associated with this procedure.

In those patients with transposition of the great arteries and posterior displacement of the infundibular septum, the ventricular septal defect is frequently, but not invariably large.[14,16,17] The size and indeed position of the ventricular septal defect is strategic to biventricular and anatomic repair of transposition of the great arteries, ventricular septal defect and pulmonary outflow tract obstruction. The infundibular septum in these hearts both separates the arterial outlets and as well is a component of the interventricular septum. Malattachments of chordal apparatus, especially but not exclusively from the tricuspid valve, may "crowd" the ventricular septal defect and may make tunneling the left ventricle to the aorta difficult.[26,27] Such attachments may make resection of the infundibular septum hazardous as well.

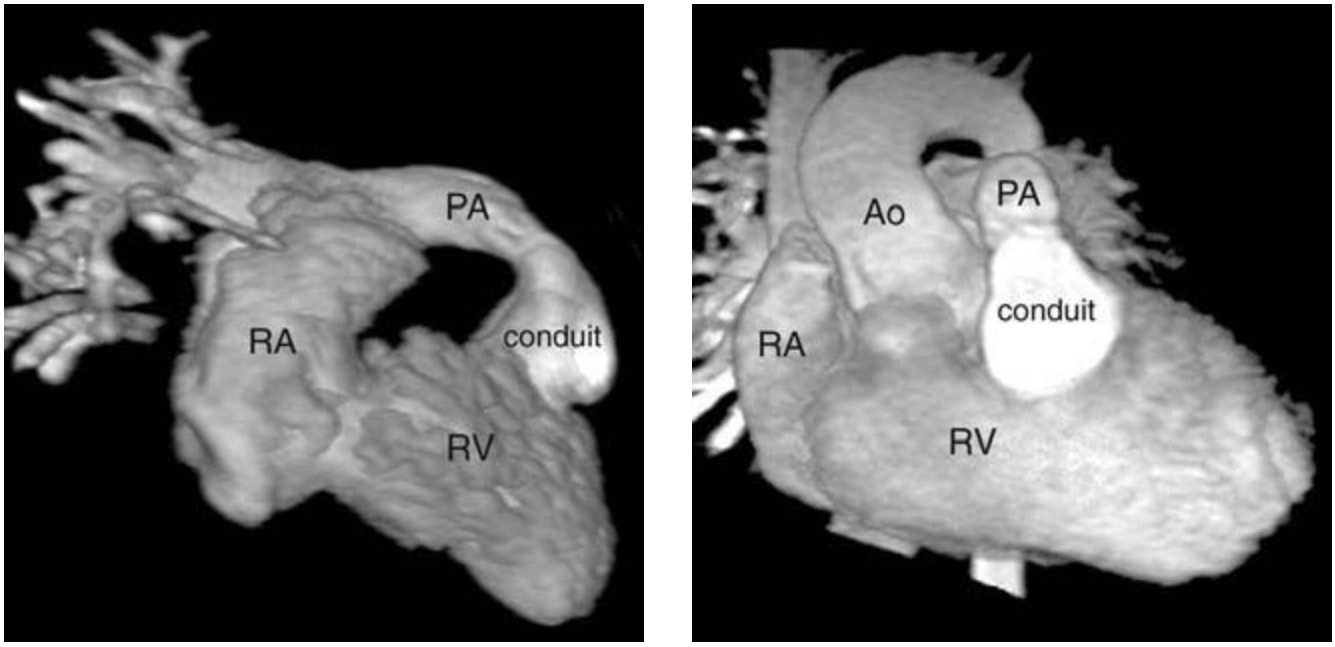
Patients with transposition of the great arteries, ventricular septal defect, and pulmonary stenosis share in common many anatomic features with patients with double outlet right (see Chapter 28) or left ventricle, or patients with so-called double discordance (see Chapter 26A). Because the assignment of specific ventriculoarterial connection may at times be difficult, some prefer to consider these hearts under the "umbrella" designation of hearts with abnormal ventriculoarterial connection, ventricular septal defect and pulmonary stenosis.[28–32] This overarching nomenclature is independent of the spatial relationship between the great arteries.[33,34] The basic goals and challenges of surgical intervention are the same for hearts with trans-position of the great arteries, ventricular septal defect, and pulmonary stenosis or double outlet right or left ventricle: connecting the morphologically left ventricle to the aorta without causing subaortic stenosis; completely separating the ventricles, and providing unobstructed continuity between the right ventricle and pulmonary arteries.[35] How these goals are accomplished and the outcomes of the innovative procedures are the topics of this chapter.

Outcome analysis

In a previous chapter (Chapter 25A) the fetal recognition of transposition and outcome of such pregnancies have been discussed. We have shown in an earlier study that about 4.1% of neonates with transposition who are potential candidates for the arterial switch operation die before operative intervention.[36] We cannot provide similar data for patients with complex transposition.

The patient with complex transposition of the great arteries, ventricular septal defect and left ventricular outflow tract obstruction has benefited from a variety of closed and open heart procedures. For many years these patients were palliated with some form of systemic-to-pulmonary artery shunt to augment pulmonary blood flow and later in childhood from a classic cavopulmonary shunt (see Chapter 35). Many required some form of atrial septectomy to enhance mixing at atrial level and this often took the form of a Blalock-Hanlon atrial septectomy. After 1966, when diagnosed as neonates, many underwent a Rashkind balloon septostomy (see Chapter 25A). The earliest attempts at repair began in the mid 1960s with the performance of a Mustard form of atrial repair, ventricular septal defect closure, and attempted resection and enlargement of the left ventricular outlet to the pulmonary artery.[2,37] The results of this approach were disappointing because the morphology of the left ventricular outflow tract did not lend itself to resection and remodeling.[2,37] This procedure was largely abandoned after the publication of Rastelli and his colleagues in 1969.[1–3] This innovative operation now bearing Rastelli's name tunneled the left ventricle through the ventricular septal defect to the aorta, closing the ventricular septal defect to the aorta (Figs 25C-1 lower panel, 25C-5). A conduit was interposed between the right ventricle and the distal pulmonary artery at the level of the confluence, with the main pulmonary trunk ligated or usually divided.[1–4] Because this procedure involved the use of a conduit, it was initially reserved for the older child.[1–4] In this regard the first patient repaired by Rastelli and his colleagues was a 14 $^1/_2$ year-old-boy who had been previously palliated with bilateral Blalock–Taussig shunts.[2] Sadly, as stated earlier, Gian Rastelli died so prematurely within a few years of this contribution from Hodgkin's disease.

The early results of the Rastelli procedure carried out at the Mayo Clinic were presented by Marcelletti and his colleagues in 1976.[38] Fifty-nine patients had corrective operation of the Rastelli type for transposition of the great arteries between 1968



A B

Fig. 25C-5 Rastelli operation. Contrast-enhanced MR angiograms (A and B) show the result of Rastelli operation. The conduit is mildly aneurysmal and there is mild stenosis in the distal conduit. Ao, aorta; LV left ventricle; PA, pulmonary artery; RV, right ventricle.

and 1975. In 12 patients (35%), the ventricular septal defect was enlarged by excising a portion of the septum. During the first 30 days after the operation, 11 patients (19%) died. The risk of repair in infancy in this era was greatly increased. There were 5 late deaths, and reoperation was required in 11 patients. Sixty-eight per cent of the survivors were in New York Heart Association (NYHA) class I and 29% were in class II. Some late complications related to deteriorations of the earlier aortic homograft conduit may be avoided by use of a Dacron conduit with a porcine valve, as suggested by short-term favorable results in 25 recent cases. The operative mortality decreased to 8% of the last 25 operations. These results led this group to conclude that the Rastelli operation is the procedure of choice for repair of transposition of the great arteries when associated with ventricular septal and pulmonary stenosis.[38]

Moulton and his colleagues also reported the early experience of the Great Ormond Street Hospital for Sick Children's experience with the Rastelli repair.[39] Forty-one children with transposition of the great arteries, ventricular septal defect, and left ventricular outflow tract obstruction underwent a Rastelli operation between 1971 and 1978. A variety of grafts from the right ventricle to pulmonary artery were used. The conduits were positioned to the left of the aorta whenever possible. The intraventricular tunnel from the left ventricle to the aorta was constructed from Dacron velour. There were 4 early and 7 late deaths. The last 13 consecutive patients all survived the operation. Early deaths were related to unfavourable anatomy, conduit compression, and sepsis. Residual ventricular septal defects and postoperative infection were the main factors contributing to the late deaths.

An important variation on the theme of Rastelli was published by LeCompte and his colleagues in 1982.[5,7] This operation was called "reparation a l'etage ventriculaire" or the REV procedure (Fig. 25C-1, lower panel). This operation departs from the classic Rastelli operation in that the infundibular septum is totally resected providing a short and direct tunnel from the left ventricle to the aorta, thus avoiding the potential for subaortic stenosis. The pulmonary artery is directly connected to the right ventricle without the use of a conduit.[5,7,40] Borromee, Lecompte and their colleagues provided in 1988 their early experience with the REV procedure in 50 patients who underwent anatomic repair of anomalies of ventriculoarterial connection associated with ventricular septal defect and pulmonary outflow tract obstruction.[32] The age at operation ranged from 4 months to 13 years (mean 3.5 years). Twenty-six patients had a classic type of transposition of the great arteries; all other patients had various types of anomalies of ventriculoarterial connection in which it was impossible, after the intraventricular connection of the left ventricle to the aorta, to use the natural pulmonary orifice for the pulmonary outflow tract reconstruction. There were 9 hospital deaths (18%) and 1 late death. Twenty-six of 29 patients whose follow-up time exceeded 1 year had an excellent clinical result. No stenosis of the aortic outflow tract was found. Four patients had significant pressure gradients in the pulmonary outflow tract.

Vouhe and his colleagues reported the outcomes of 62 patients who underwent complete repair for transposition of the great arteries, ventricular septal defect, and pulmonary outflow tract obstruction from 1980 to 1990.[41] Twenty-two patients (35%) (mean 8.1 ± 7.2 years) underwent the Rastelli operation: The ventricular septal defect was enlarged anteriorly in 8 patients, and right ventricular–pulmonary artery continuity was established with an extracardiac valved (9/22) or nonvalved (13/22) conduit. Forty patients (65%) (mean age 3.3 ± 3.2 years) underwent the Lecompte modifications. The infundibular septum was extensively excised when present (30/40), anterior translocation of the pulmonary bifurcation was performed in 32 patients, and right ventricular–pulmonary artery continuity was

established by direct anastomosis without a prosthetic conduit. There were 7 early deaths [11%; 70% confidence limits (CL), 7% to 17%]: 2 after the Rastelli procedure (9%; 70% CL, 3% to 20%) and five after the Lecompte operation (12.5%; 70% CL, 7% to 20%). Four patients were lost to follow-up, yielding a 93% complete follow-up (mean follow-up 55 months). There were 2 late deaths (1 in each group). Actuarial probability of survival (± SE) at 5 years was 83% ± 9% after the Rastelli operation and 84% ± 6% after the Lecompte procedure. All long-term survivors (except 1 in the Rastelli group) were in functional class I. Five patients in the Rastelli group underwent late reoperation for obstruction of the extracardiac conduit (28%; 70% CL, 16% to 42%). Three late reoperations (10%; 70% CL, 4% to 19%) were required after the Lecompte operation (1 for residual ventricular septal defect and 2 for residual pulmonary outflow tract obstruction). At most recent examination, residual pulmonary outflow tract obstruction was present in 7 patients of the Rastelli group (39%; 70% CL, 26% to 53%) and in 6 patients of the Lecompte group (19%; 70% CL, 12% to 29%). The combined likelihood of reoperation for pulmonary outflow tract obstruction and residual pulmonary outflow tract obstruction was significantly higher in the Rastelli group (67% vs. 26%; $P = 0.005$).

One of the issues that complicates intraventricular rerouting or tunneling the left ventricle to the aorta is attachment of tension apparatus from the tricuspid valve to the infundibular septum.[26] Some have considered this finding a contraindication to the Rastelli operation.[5,42,43] Niinami and his colleagues have addressed the management of so-called tricuspid malinsertion in the Rastelli operation by the use of the conal flap method.[44] In this method, the part of the infundibular septum bearing the tricuspid chordal attachments is mobilized by two incisions, one anterior and vertical and the other subaortic (Fig. 25C-6). This is then pulled backward as a pedicled flap. The intraventricular conduit is then sutured around the defect, thus simultaneously enlarging the ventricular septal defect.[44] In the study of Niinami, the outcomes of two groups of patients was assessed: both groups underwent a Rastelli operation, but one group with tricuspid chordal attachments to the infundibular septum underwent the conal flap method as well. There was virtually no difference in outcome, with minimal or no early mortality in each group. Postoperative echocardiograms revealed a slightly higher incidence of tricuspid regurgitation in the conal flap method when compared to the conventional group. Yet postoperative hemodynamic investigation showed similar right atrial mean pressures, right ventricular end diastolic pressure and volume (% of predicted normal) and right ventricular ejection fraction.[44] It is also of interest that during follow-up, the tricuspid regurgitation tended to improve, likely coincident with normalization of right ventricular pressures.[44] Another advantage of the conal flap method is that this procedure also enlarges the ventricular septal defect as in this series, 57% of the conventionally treated patients required enlargement of the ventricular septal defect.

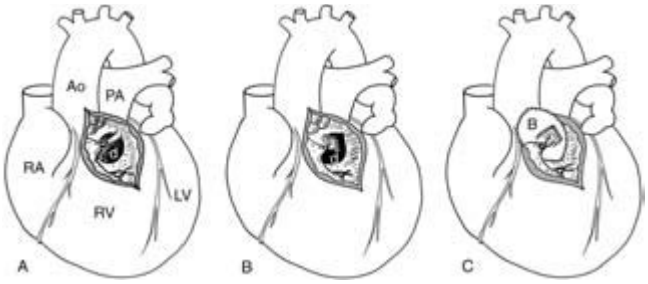


Fig. 25C-6 Niinami procedure. **A**. The interior of the right ventricular outflow tract showing tricuspid malinsertion to the infundibular septum across the ventricular septal defect (d). **B**. The part of the infundibular septum having chordal insertion of the tricuspid valve is mobilized and pulled backward as a pedicled flap. **C**. The intraventricular baffle (B) is then sutured around the defect and the pedicled flap is fixed to the baffle. Ao, aorta; LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

Kim and his colleagues reported the outcome of 19 patients treated by the Lecompte procedure for complete transposition of the great arteries associated with a ventricular septal defect and pulmonary stenosis operated on from December 1988 to February 1993.[45] The mean age at operation was 3.1 ± 0.8 years (mean ± SE). This technique consisted of resecting the outlet septum, constructing a tunnel that connected the left ventricle to the aorta, closing the proximal pulmonary arterial stump, pulling the distal pulmonary artery down to the right ventriculotomy site directly, and covering anteriorly with the fixed autologous pericardium. The early operative mortality was 5.3%. The mean follow-up was 24.2 ± 3 months, with no late death. One reoperation was performed because of residual right ventricular outflow tract obstruction. All survivors were studied by echocardiography at intervals of 6 months to 1 year. In all survivors (except for 1 child who underwent reoperation), the estimated pressure gradient between the right ventricle and the pulmonary artery, the structure of the left ventricular outflow tract, left ventricular function, and right ventricular contractility were all satisfactory.

Kim and his colleagues extended this series in 2001 by reporting the outcomes of 45 patients who underwent the Lecompte procedure during the past 11 years to achieve direct right ventricle to pulmonary artery continuity.[46] Mean age at operation was 2.4 ± 1.7 years (range 3.5 months to 6.9 years). The diagnoses involved anomalies of the ventriculoarterial connection with ventricular septal defect and pulmonary outflow tract obstruction, including transposition of the great arteries, double-outlet right ventricle, and double-outlet left ventricle. The early surgical mortality was 4.4% (2 of 45 patients) and late mortality was 4.7% (2 of 43). The mean follow-up was 4.9 ± 3.1 years. Fourteen patients (34.1% of survivors, $n = 41$) had pulmonary stenosis (pressure gradient > 30 mmHg), the main reason for which was a calcified monocusp valve ($n = 10$, 71.4%). Eight of 45 patients (17.8%) underwent reoperation: 2 for residual ventricular septal defect, 1 for recurrent septic vegetation, and 5 for pulmonary stenosis. The cumulative survival rates were 91.1% ± 4.2% at 10 years. The actuarial probabilities of freedom from reoperation for pulmonary stenosis were 93.8% ± 4.3% and 71.4% ± 11.8% at 5 and 10 years, respectively. The most important observation was that right ventricular outflow tract obstruction caused by degeneration of the monocusp valve was an ongoing problem.[46]

Pretre and his colleagues presented their retrospective analysis of 42 patients (median age at operation, 1.4 years) operated on between 1986 and 1999 for various forms of great artery malposition, ventricular septal defect, and pulmonary stenosis.[47] Relevant associated findings included the insertion of a tricuspid papillary muscle on the infundibular septum (nine patients),

absence of conal septum (6 patients), hypoplasia of a side pulmonary artery (4 patients), and hypoplasia of the right ventricle (1 patient). A preliminary systemic-to-pulmonary shunt was performed in 28 patients and a cavopulmonary anastomosis in 1 patient. At operation, the infundibular septum (whenever present) was resected (36 patients), the pulmonary bifurcation was usually translocated over the ascending aorta (37 patients), and the main pulmonary artery was enlarged with a patch of pericardium. A monocusp valve was fashioned within the patch in 40 patients. Follow-up information was complete in 32 patients and ranged from 0.4 to 14 years (mean, 5.4 ± 3.2 years). The survival rate at 5 years was 92 ± 5%. Three patients died postoperatively (mortality, 7%) but none thus far during follow-up. The freedom from reoperation was 86 ± 8 and 51 ± 22% at 5 and 10 years, respectively. Six patients were reoperated, all for pulmonary stenosis. Calcification of the monocusp patch was present in all. Pulmonary stenosis developed in three further patients: one underwent percutaneous dilatation and two are awaiting surgery (Fig. 25C-7).

In the past 2 years, comprehensive experiences with the Rastelli procedure have been published from the Mayo Clinic[48] and from the Children's Hospital in Boston.[49] Dearani and his colleagues from the Mayo Clinic reported on part of their 33-year experience with 231 patients operated on from June 26, 1968 to January 1, 2000.[48] This report focused on the late results of 160 early survivors who had been operated on from 1968 to 1990. The 160 patients ranged in age from 1 year to 44 years (median age at repair was 8 years, mean 9.7 years). One hundred and twenty-two patients had undergone 189 palliative operations. From 1968 to 1977, the mortality was 24.4% and this decreased to 4.8% from 1988 to 1997. Overall survival excluding early mortality was 82% at 5 years, 74% at 10 years, 69% at 15 years, and 59% at 20 years. The mean follow-up of the 160 hospital survivors was 11.9 ± 6.9 years. There were 53 late deaths of which 38 were considered cardiac in origin. Sudden death and arrhythmia accounted for 17 of these; congestive heart failure in 12; pulmonary hypertension in 5; endocarditis in 3, and myocardial infarction in 1. Freedom from reoperation for conduit failure was 78% at 5 years, 43% at 10 years, 29% at 15 years, and 27% at 20 years. Eighty-five patients required 107 conduit replacements. Sixty-six patients had one conduit replacement, 16 had two conduit replacements, and 3 patients required three conduit replacements. Subaortic stenosis was uncommon in this experience, with only 1% requiring reoperation. The mechanisms likely responsible for this complication are related to the size of the ventricular septal defect and failure of growth of the tunnel from the left ventricle to the aorta.[14,27,50,51] Others have reported the limited experience of the one-lung Rastelli operation.[49A,49B]

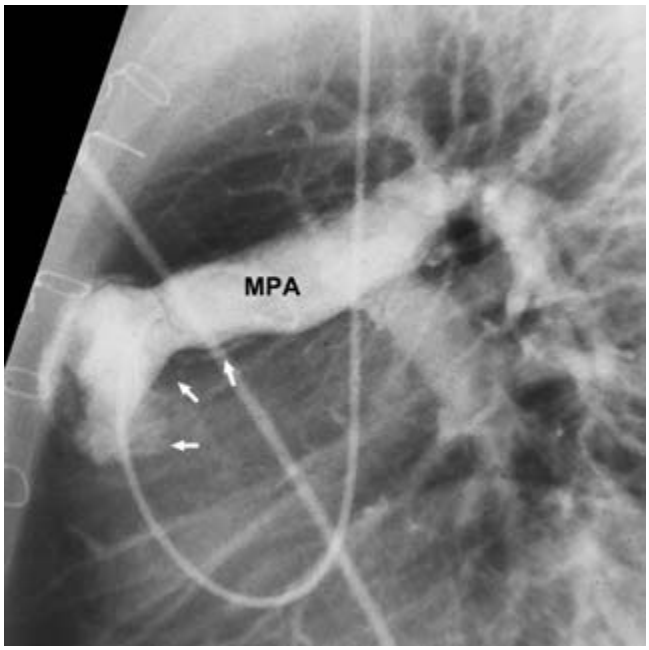


Fig. 25C-7 Pulmonary outflow tract obstruction after Rastelli operation. Conduit shows calcification and stenosis of its proximal part (arrows) and is fixed to the sternum.

Kreutzer and his colleagues from the Boston Children's Hospital presented in 2000 their review of 101 patients who underwent Rastelli's operation for complex transposition from March 1973 to April 1998.[49] Pulmonary stenosis was present in 73 patients and pulmonary atresia in 18; 10 patients had no left ventricular outflow tract obstruction. The median age and weight at the time of repair were 3.1 years and 12.8 kg, respectively. The majority of these patients had undergone some form of prior palliation, usually some form of systemic-to-pulmonary artery shunt and/or some form of atrial septectomy, either surgical or balloon-mediated. The ventricular septal defect was enlarged superoanteriorly in 47 patients, and only 2 patients had resection of the infundibular septum. A variety of conduit-types and procedures were used to provide continuity between the right ventricle and pulmonary artery. There were 7 early deaths which occurred in the early part of the experience, but no surgical deaths happened in the last 7 years of the study. When the deaths were stratified by age at repair, 3 of 24 patients < 1 year died; 4 of 69 patients aged 1–11 years died, and there were no deaths in the 8 patients ≥ 12 years. The causes of early death was related to residual left ventricular outflow tract obstruction in 3 patients, coronary insufficiency in 2, sudden atrioventricular block refractory to pacemaker therapy in 1, and pulmonary hypertension in 1. Survival at 1 month, 5 years, 10 years, 15 years, and 20 years was 93%, 82%, 80%, 68%, and 52%, respectively. At a median follow-up of 8.5 years (range 0.4–22.0 years) there were 17 late deaths and one heart transplant (Fig. 25C-8). The causes of late death were sudden death in 5, left ventricular dysfunction in 7, conduit pseudointima rupture in 1, myocarditis in 1, and 2 each, unknown or at reoperation. Freedom from death or reintervention (either surgical or catheter) was 53%, 24%, and 21% at 5, 10, and 15 years of follow-up, respectively. It is interesting to compare the need for reintervention on the left ventricular outflow tract in this paper compared to that from the Mayo Clinic.[48] Kreutzer and his colleagues found that 11 patients required surgical revision of the left ventricular outflow tract with no early deaths, considerably higher than the Mayo Clinic experience.[49] Reintervention, either surgical or catheter-based, on the right ventricular outflow tract was similar between the two groups. The Boston group reported freedom from reintervention for right-sided obstruction was 56%, 25%, and 21% at 5, 10, and 15 years, respectively.[49] Acknowledging a high incidence of postoperative complications, this group still advocates application of the Rastelli repair even to young infants, hoping to avoid the complications of and attrition from palliation.[49] The enlargement of the VSD in an anterosuperior direction by the

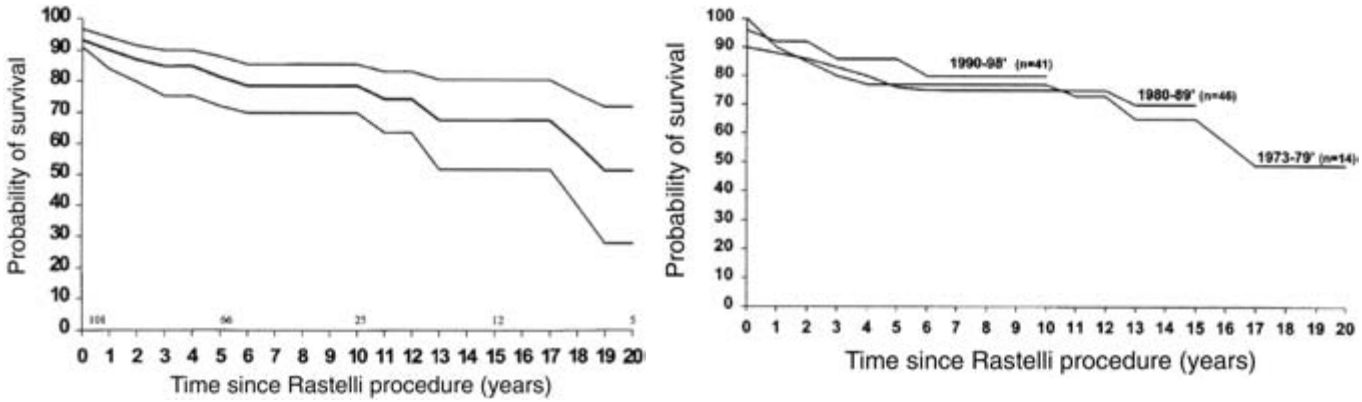


Fig. 25C-8 A. Overall survival of 101 patients at the Children's Hospital, Boston after the Rastelli operation, with 95% CL. B. Survival for three study periods. (Reprinted from Kreutzer *et al*.[49] Copyright (2000) Mosby Inc., with permission from Elsevier Inc.)

Boston group departs from the approach of Lecompte who enlarges the VSD by resecting the infundibular septum.[5–7] The Pediatric Cardiac Care Consortium has published its experience with the Rastelli operation.[52] This consortium identified between 1984 and 1994 1542 patients with transposition of the great arteries. The Rastelli operation was performed in 84 children ranging from 1.3 to 20.3 years with an average age of 7 years. The surgical mortality in this group was 8 of 84 (9.5%). No follow-up data were provided.[52] We have also reviewed our Rastelli experience which begins in 1974. Our total experience includes 80 patients, with thus far 10 early deaths (12.5%) and 13 late deaths (Figs 25C-9, 25C-10). Seventy-one patients had undergone prior palliation at a median age of 0.6 years. The median age at repair was 5.4 years, ranging from 0.2 to 36.8 years. The median follow-up is 9.4 years and 50% of the patients are now adults. The survival curve and freedom from reoperation for these patients are depicted in Figs 25C-9 and 25C-10. Thirty patients have required 43 reoperations at a median of 6.4 years after the initial operation. The majority of operations were necessitated by conduit change, with some late reoperations related to relieving subaortic stenosis. It is likely that the "REV" modification of Lecompte will reduce the requirement for reoperation/reintervention.[5,59]

Metras and Kreitmann have published a modification of the Rastelli-REV procedures.[53,54] Rather than a direct connection between the right ventricle and the pulmonary artery, they use an aortic autograft taken from the patient's ascending aorta to facilitate this connection. Sometimes a monocusp valve is positioned to provide temporary "pulmonary" valve competency. The authors favor this approach because the classic REV procedure with its direct connection between the right ventricle and the pulmonary artery places tension on the pulmonary connection, resulting in, as we have summarized, a frequent requirement for reintervention. The aortic autograft provides the potential for growth, and hopefully should obviate some of the need for reintervention. The drawback, of course, is the long-term effect of free pulmonary regurgitation on right ventricular function.

An interesting problem was reported by Deanfield and his colleagues.[55] A patient with transposition of the great arteries, ventricular septal defect, and obstruction of the left ventricular

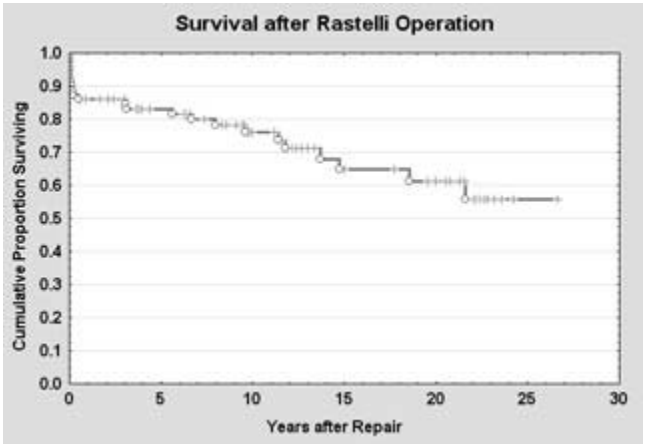


Fig. 25C-9 Kaplan–Meier actuarial survival curve of Rastelli patients from the Toronto Hospital for Sick Children and Toronto Hospital.

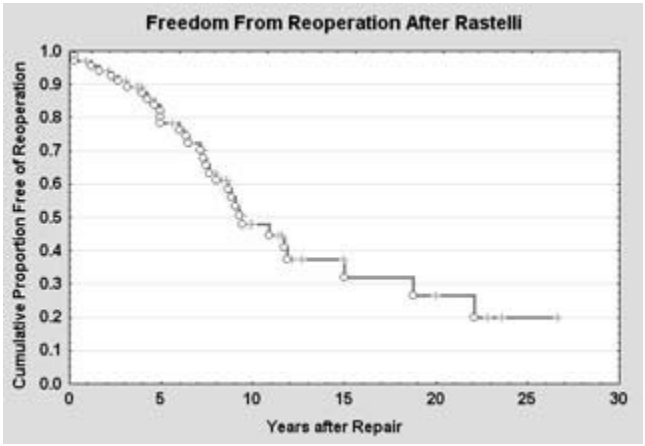


Fig. 25C-10 Kaplan–Meier actuarial survival curve depicting freedom from reoperation of Toronto patients.

outflow tract underwent a Rastelli repair. Unfortunately stenosis of the tricuspid valve was not recognised before or during operation; this severely compromised the postoperative hemodynamic function and necessitated reoperation. Insertion of a second homograft from the right atrium to the right ventricle bypassed the stenosis and resulted in a complete recovery with maintenance of a biventricular circulation. One would wonder in retrospect whether unloading the right ventricle with a bidirectional cavopulmonary shunt could have achieved the same result.

It should not be surprising that left ventricular failure has been observed in some patients after the Rastelli operation. Before the Rastelli operation, the patients usually are hypoxemic and the majority have been palliated with some form of systemic-to-pulmonary artery shunt that volume loads the left ventricle.[56,57] Graham and his colleagues have studied left ventricular wall stress in a small cohort of 11 patients after the Rastelli operation.[55] Left ventricular wall stress and contractile function were determined by echocardiographic methods in 11 patients.[55] They were studied 0.7–13.8 years (mean ± SEM = 5.6 ± 1.2 years) after undergoing the Rastelli operation for transposition of the great arteries associated with ventricular septal defect and left ventricular outflow tract obstruction. The age at operation ranged from 4.6 to 11.3 years (mean ± SEM = 7.4 ± 0.7 years). Data were compared with data of 24 normal subjects of similar age and heart rate. Left ventricular end-diastolic dimension and end-diastolic volume were significantly higher than normal, averaging 134% ± 8% of normal dimension ($P < 0.004$) and 106 ± 13 mL/m^2 vs. a normal volume of 60 ± 3 mL/m^2 ($P < 0.007$). In addition left ventricular wall mass was 215 ± 40 g/m^2 vs. a normal value of 72 + 6 g/m^2 ($P < 0.004$). Both meridional and circumferential end-systolic and peak systolic stress values were not significantly different between normal subjects and Rastelli patients. Estimates of ventricular pump function including shortening fraction, rate-corrected velocity of circumferential fiber shortening, and ejection fraction were all depressed when compared with normal values. Velocity of fiber shortening, evaluated as a function of end-systolic stress, demonstrated abnormal contractile function in eight of 11 (73%) patients. These data indicate that left ventricular function is usually abnormal and residual left ventricular dilation and wall hypertrophy remain despite successful application of the Rastelli operation.

Other applications of the Rastelli operation

The Rastelli operation has been combined with atrial repair of the Senning or Mustard types for the anatomical correction of atrioventricular discordance (see Chapter 26A).[58] Most patients who undergo this challenging operation have either double discordance or atrioventricular discordance with double outlet from the morphologically right ventricle.

In summary, both the Rastelli operation and the "REV" modification of Lecompte provide reasonable palliation for patients with transposition of the great arteries, ventricular septal defect and pulmonary stenosis as well as for other forms of hearts with abnormal ventriculoarterial connections. The long-term problems are likely related to:

- reintervention/conduit change
- pulmonary outflow tract obstruction and/or regurgitation (Fig. 25C-7)
- right ventricular dysfunction
- left ventricular dysfunction
- subaortic stenosis
- form and function of the atrioventricular valves
- cardiac rhythm disturbances
- sudden death.

Thus in the 35 years since the first Rastelli operations were carried out at the Mayo Clinic:

- This surgical technique conferred an anatomic repair for the patient with transposition of the great arteries, ventricular septal defect and pulmonary outflow tract obstruction.
- Early surgical mortality in recent years is < 5%. [48,49]
- Until recently, the patient with transposition of the great arteries, ventricular septal defect and pulmonary outflow tract obstruction has been repaired in stages: initial palliation and later repair.
- Repair frequently required the use of a right ventricle-to-pulmonary artery conduit, and thus the requirement for reoperation.
- There is now interest in primary repair even in infancy.[49]
- Early changes in ventricular geometry and ventricular septal defect size after the Rastelli operation contribute to the potential for late systemic outflow tract obstruction.[51] Thus some centers tend to routinely enlarge the ventricular septal defect.
- The introduction of the "REV" operation of Lecompte obviates the potential for subaortic stenosis and the translocation of the pulmonary artery to the right ventricle mitigates the requirement for right ventricle-to-pulmonary artery conduit. This operation with its resection of the infundibular septum also confers a geometrically shorter and more direct advantageous left ventricular outflow tract.
- The translocation of the pulmonary trunk to the right ventricle will lead to pulmonary regurgitation.

The late survival of the classic Rastelli operation is concerning.[48,49] Whether earlier repair will have an advantageous effect on late outcome is to be determined. It is unclear at this time whether the classic Rastelli or "REV" operation of Lecompte is or should be the operation of choice.[59] If the VSD is now routinely enlarged in the Rastelli operation,[49] then one must weigh the effects of conduit replacement vs. chronic pulmonary insufficiency on the long-term outcomes of these patients. Finally, Yamagishi and colleagues have reported in one patient an innovative approach to repair of complete transposition of the great arteries, ventricular septal defect and pulmonary stenosis.[60] This so-called half-turned truncal switch operation has the potential advantage of ensuring straight and nonobstructive aortic and pulmonary ventricular outflow tracts by using a half-turned truncal block that includes both semilunar valves. Only time will tell whether this approach gains greater popularity.

All references can be found at the end of the book. See pp. 757–9 for Chapter 25C.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

26A

Robert M. Freedom, Shi-Joon Yoo, and WG Williams

Conditions with Double Discordance (Congenitally Corrected Transposition of the Great Arteries)

It has been more than 115 years since Von Rokitansky first described two cases in which transposition of the great arteries was functionally corrected by the position of the interventricular septum.[1] Monckeberg and later Uher described the anterior atrioventricular node, a very important finding for surgical intervention in this condition.[2,3] That more than 60 years ago hearts exhibiting congenitally corrected transposition were considered novel is illustrated by the review of Harris and Farber, who in their compilation of 1939 could collect only 17 cases, whereas Anderson and Schiebler and their colleagues were able to increase the number to somewhat more than 100.[4–6] Data from the Hospital for Sick Children in Toronto published by Bjarke and Kidd in 1976 summarized more than 100 patients, and the institution's database has now been extended even further.[7]

Congenitally corrected transposition of the great arteries is an uncommon congenital cardiac anomaly characterized by double discordance: a discordant atrioventricular and ventriculoarterial connection (Fig. 26A-1).[8–11] While double discordance occurs in isolation, far more commonly the situation is complicated by associated ventricular septal defect, pulmonary outflow tract obstruction, and anatomic disturbances causing regurgitation of the systemic, morphologically tricuspid valve.[8–26] Furthermore because of the unusual disposition of the specialized conduction tissue, these patients are prone to congenital and acquired complete heart block.[27–31] And, it is the systemic morphologically right ventricle that supports the systemic circulation. As Richard van Praagh said more than two decades ago and Warnes more recently, one should hardly consider this condition "corrected!" [32,33]

Incidence and extracardiac malformations

Using data from the Hospital for Sick Children in Toronto, Bjarke and Kidd identified amongst 10 535 patients with congenital heart disease, 101 with corrected transposition of the great arteries, thus giving a prevalence of 0.95%, but these data included patients with a univentricular atrioventricular connection.[7,34] Excluding these patients would reduce the prevalence to 0.57%, similar to the 0.43% found by Beuren.[35] The New England Regional Infant Cardiac Program identified only 16 infants with corrected transposition of the great arteries.[36] This number provided a prevalence of 0.02/1000 live births. The Baltimore–Washington Infant Study identified 47 patients with corrected transposition of the great arteries from 4390 infants surveyed from 1981 to 1989.[37] Data recently provided by Fyler addressing patients seen at the Boston Children's Hospital revealed that over a 15-year period to 1987, 89 patients with corrected transposition of the great arteries were seen, or 0.6% of those with congenital heart disease.[38] The recently completed prospective Bohemia Survival Study identified 22 children born with double discordance among 815 569 children born between 1980 and 1990.[39] This provided a prevalence of 0.03 per 1000 live births, and these accounted for 0.4% of all congenital heart malformations encountered in this study.[39]

Morphological considerations

The heart position and its apex may be normal (levocardia), in the midline (mesocardia), but in about 20% of patients with congenitally corrected transposition of the great arteries, the cardiac apex is predominately right-sided, that is, dextrocardia. The atrial situs is solitus in *c*. 92–95% of patients; an inverse atrial situs was recorded in 5–8%. Some patients with congenitally corrected transposition of the great arteries will have a so-called twisted atrioventricular connection. Most of the morphological considerations germane to the patient with double discordance are relevant to the patient with atrioventricular discordance no matter what the ventriculoarterial connection: double-outlet ventricle; concordant ventriculoarterial connection; single outlet; or common arterial trunk.

While the ventricles in hearts with corrected transposition of the great arteries may be considered inverted, they are not in a mirror-image of a normal heart.[9–12] As pointed out by Losekoot and his colleagues, this is in large part a consequence of the fact that the arterial outflows are parallel to each other (Fig. 26A-1), remembering that in the normal heart the outflow tracts cross.[9–11] The internal organization of the morphologically right ventricle in hearts with solitus atria conforms to a left-hand pattern of internal organization. Rarely the pattern of internal ventricular organization will be non-harmonious with the type of atrioventricular connection.[40–46] Usually the aorta is anterior and to the left of the pulmonary trunk in the classic expression of congenitally corrected transposition of the great arteries, but this spatial relationship is not pathognomonic for this condition.[47–49]

The coronary arteries originate from the posterior facing sinuses of the aortic valve.[10–13,16–19,50–53] In patients with atrial situs solitus and congenitally corrected transposition of the great arteries, the coronary arteries show a mirror-image distribution. The right-sided coronary artery has the epicardial distribution of a morphologically left coronary artery, with the main right-sided coronary artery bifurcating into circumflex and anterior descending branches, while the left-sided coronary

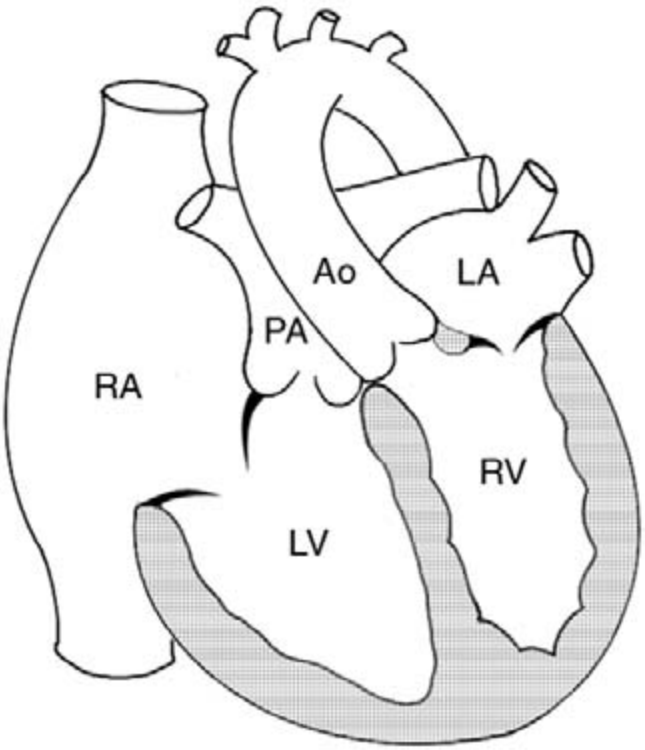


Fig. 26A-1 Illustration showing congenitally corrected transposition of the great arteries. Both atrioventricular and ventriculoarterial connections are discordant. Ao, aorta; LA, left atrium; LV left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

artery runs in the left atrioventricular groove, and gives rise to infundibular and right ventricular branches.[10–13,16–19,50–53]

The most commonly associated anomalies in patients with atrioventricular discordance include: (1) ventricular septal defect; (2) pulmonary outflow tract obstruction; (3) dysplasia and displacement of the left or systemic atrioventricular valve; (4) combinations of these associated lesions.[5–16,18–33]

Ventricular septal defect

A ventricular septal defect is the most common associated malformation in congenitally corrected transposition of the great arteries, having an incidence in clinical material of between 60% and 70%, and nearly 80% in autopsy material (Fig. 26A-2).[11] The most common ventricular septal defect is perimembranous and tends to be large. The ventricular septal defect is usually large, reflecting the malalignment between the atrial septum and ventricular septum characteristic of hearts exhibiting atrioventricular discordance, and the resulting left-to-right shunt important. The ventricular septal defect may be subarterial and roofed by the semilunar valves. This is uncommon in the Occidental, but not uncommon in the Oriental.[23] The ventricular septal defect can occupy any position.

Pulmonary outflow tract obstruction

Obstruction to the outflow tract of the morphologically left ventricle is identified in from 30–50% of patients with corrected transposition of the great arteries and atrial situs solitus (Fig. 26A-3).[8–21] Pulmonary outflow tract obstruction uncommonly occurs in isolation at valve or infundibular level but is more typically associated with a large ventricular septal defect (Fig. 26A-2). In about one-third of these patients with ventricular septal defect and pulmonary outflow tract obstruction, abnormalities of the morphologically tricuspid valve are seen as well. The left ventricular outflow tract obstruction is usually muscular, reflecting wedging of the subpulmonary outflow tract between the infundibular septum and the ventricular free-wall, with contributions from the right-sided ventriculoinfundibular fold as well. Fibrous tissue derived from the membranous septum may contribute to left ventricular outflow tract obstruction, and this may be wholly resectable (Fig. 26A-4). Tissue tags derived from tricuspid or mitral valve or from the pulmonary valve itself may obstruct flow into the pulmonary trunk. Blood cysts may also participate in subpulmonary obstruction. Single-outlet aorta with pulmonary atresia is well recognized with atrioventricular discordance.

The systemic, morphologically tricuspid valve

Abnormalities of the morphologically tricuspid valve are intrinsic to hearts exhibiting atrioventricular discordance.[5–22,25,26,50] While at the autopsy table, about 90% of hearts exhibit some abnormality of the morphologically tricuspid valve, considerably fewer demonstrate a functional disturbance during life. The most common and important underlying pathology is dysplasia of the valve, with or without displacement of the septal or posterior leaflets of the tricuspid valve (Fig. 26A-5).[25] Some hearts with congenitally corrected transposition of the great arteries will exhibit an unguarded tricuspid orifice, most with aortic

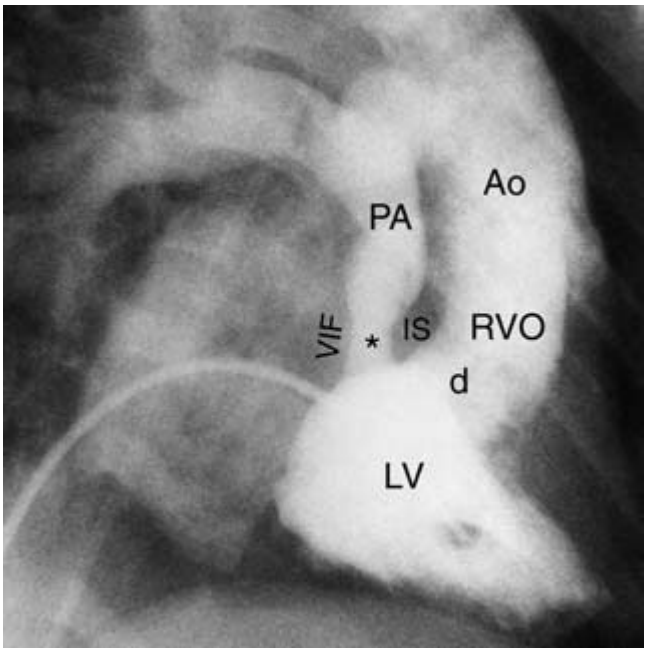


Fig. 26A-2 Congenitally corrected transposition of the great arteries with perimembranous ventricular septal defect (d). The subpulmonary outflow tract (asterisk) is encroached on between the infundibular septum (IS) and ventriculoinfundibular fold (VIF). Ao, aorta; LV, left ventricle; PA, pulmonary artery; RVO, right ventricular outflow tract.

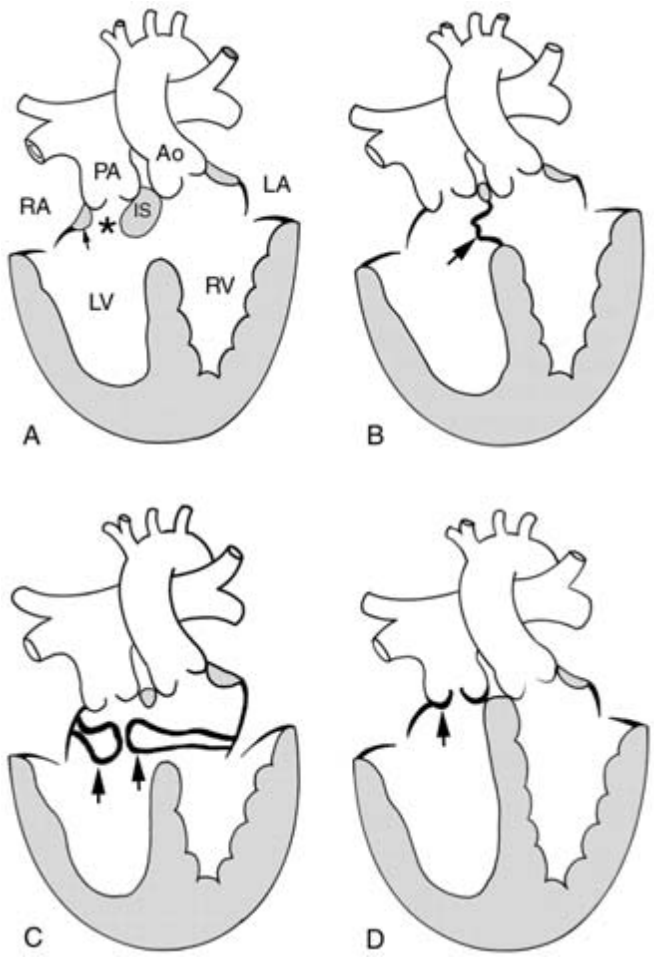
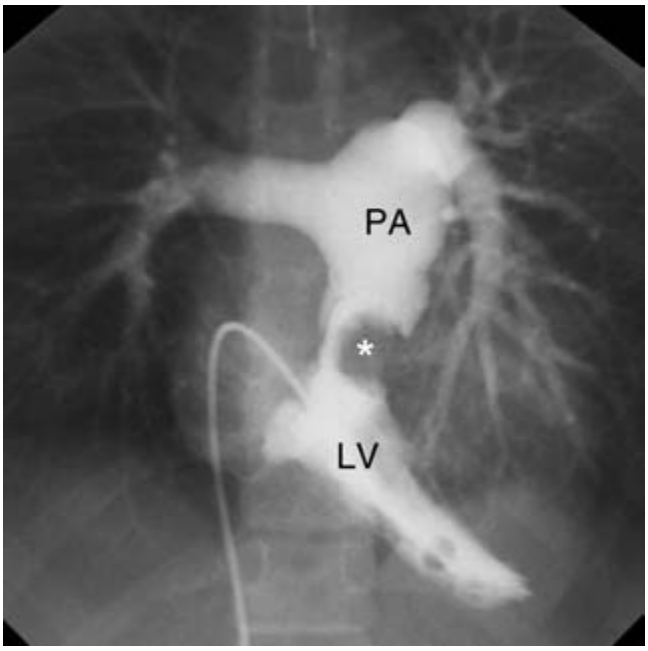


Fig. 26A-3 Various forms of pulmonary outflow tract obstruction in congenitally corrected transposition of the great arteries. **A**. Muscular tunnel obstruction (asterisk) due to its wedged position between the infundibular septum (IS) and left ventricular free wall. The right ventriculoinfundibular fold (arrow in part A) may also contribute to obstruction. **B**. Fibrous tissue (arrow) from the membranous septum. **C**. Tissue tags (arrows) from the atrioventricular valves. **D**. Pulmonary valve stenosis (arrow).

atresia as well, while in others the tricuspid valve may straddle and override a muscular inlet ventricular septal defect.[54–60] A stenotic, Ebstein-like tricuspid valve dividing the morphologically right ventricle has also been described.[61]

Other associated anomalies include a straddling and/or overriding left atrioventricular valve; superoinferior ventricles; coarctation of the aorta; interruption of the aortic arch; aortic or subaortic stenosis; hypoplasia of one ventricle (usually in association with a disturbed atrioventricular valve ipsilateral to the hypoplastic ventricle), and common arterial trunk. Functional or anatomic aortic atresia has been found in some patients with congenitally corrected transposition of the great arteries, and all such patients have had massive regurgitation of the systemic atrioventricular valve with a terribly disordered morphologically right ventricle, with marked thinning of its myocardium.[54–60] The systemic atrioventricular valve is very abnormal in these patients exhibiting features of dysplasia, displacement; and in some of the newborns the tricuspid annulus may be virtually unguarded. The systemic atrioventricular valve is more commonly abnormal than the morphologically mitral valve. Straddling of the mitral valve has been noted in patients with corrected transposition of the great arteries.[62] Clearly functional disturbances of the mitral valve are far less common than similar disturbances of the tricuspid valve. Yet in an autopsy study of 29 specimens of hearts with congenitally corrected transposition of the great arteries, 16 (55%) demonstrated abnormalities of the mitral valve.[62,63] The most common of these



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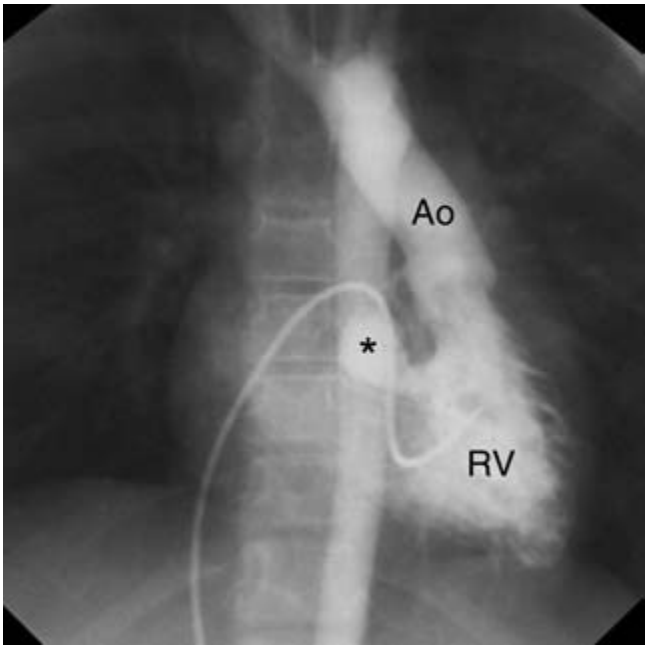
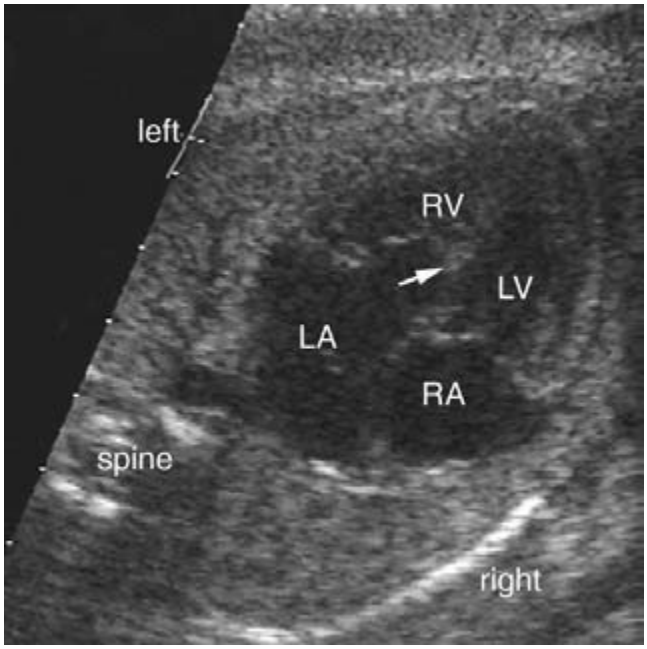


B

Fig. 26A-4 Left ventricular outflow tract obstruction in corrected transposition of the great arteries. Left (**A**) and right (**B**) ventriculograms show subpulmonary obstruction due to aneurysm (asterisk) of the membranous septum that bulges into the left ventricle (LV) on ventricular systole. Ao, aorta; PA, pulmonary artery; RV, right ventricle.



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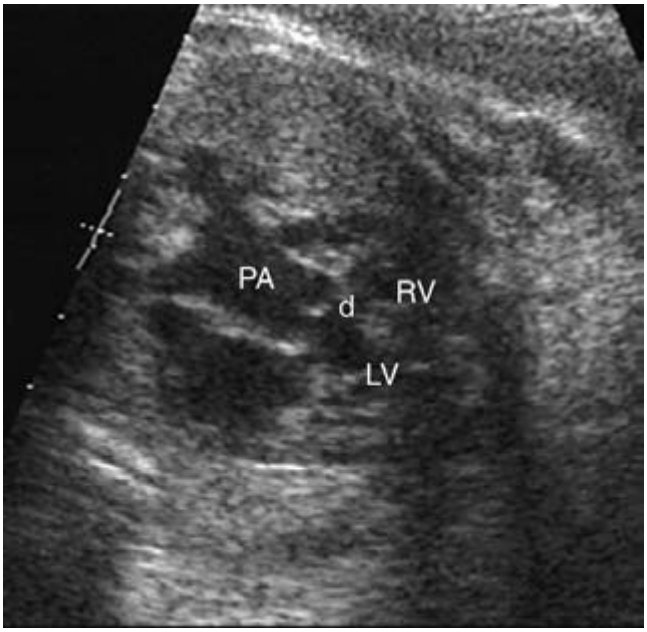

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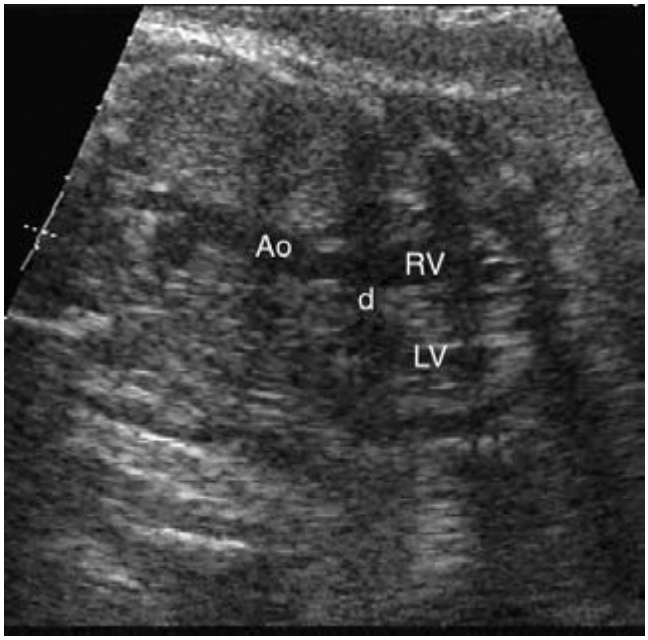

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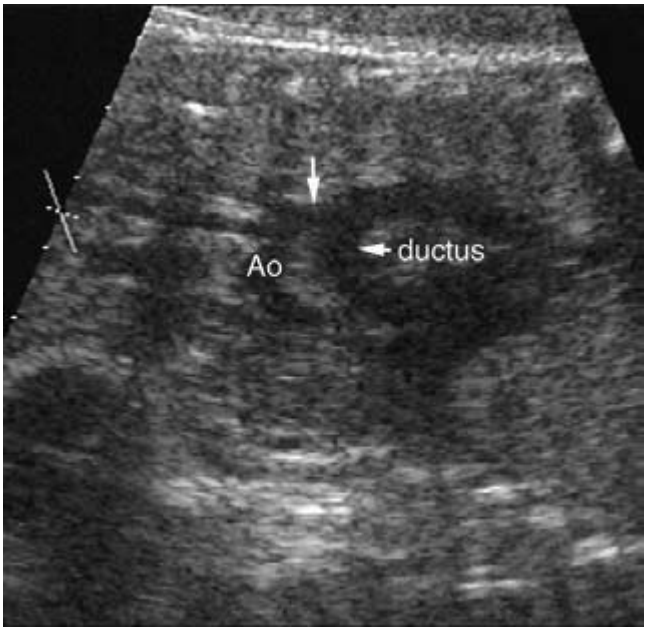

D

Fig. 26A-5 Ebstein's anomaly of the systemic tricuspid valve in a fetus with congenitally corrected transposition of the great arteries. **A**. Four-chamber view demonstrates dextrocardia with its cardiac apex pointing to the right anterior chest. The atrioventricular valve of the left-sided right ventricle (RV) shows apically displaced attachment (arrow) to the septum. **B** and **C**. Left and right ventricular outflow tract views show discordant ventriculoarterial connection and a perimembranous ventricular septal defect (d). **D**. The aortic arch view shows narrow aortic isthmus (arrow). Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium.

included abnormalities in cusp number and tension apparatus (each 21%), while less common findings included dysplasia, common atrioventricular orifice, stenosis, and cleft valve. In a rare case the mitral valve may be unguarded.[62A] Isolated aortic stenosis has also been observed in the patient with congenitally corrected transposition of the great arteries. Even in the adult with congenitally corrected transposition of the great arteries, patients will develop progressive systemic atrioventricular valve regurgitation unrelated to operation.

The specialized conduction tissue

Intrinsic to hearts exhibiting atrioventricular discordance is a particularly fragile specialized conduction system. It is the

unusual disposition of the conduction tissue that predisposes patients with atrioventricular discordance to spontaneous heart block. The sinus node is normally positioned in these hearts, but the atrioventricular conduction tissue is grossly abnormal. The abnormal disposition has been elegantly reviewed by Losekoot, Anderson, and others.[27–30] In brief, the basic anatomy dictates that the regular atrioventricular node, located at the apex of the triangle of Koch, cannot give origin to a penetrating atrioventricular conduction bundle. Thus an anomalous second atrioventricular node is present, located beneath the opening of the right atrial appendage at the lateral margin of the area between pulmonary valve and mitral valve continuity. As pointed out by Losekoot and Becker this anteriorly positioned node gives rise to the atrioventricular bundle which comes to lie immediately underneath the pulmonary valve leaflets.[11] The non-branching bundle has a superficial course underneath the right anterior facing leaflet of the pulmonary valve and descends for some distance before it branches. We have experienced the onset of complete heart block in the catheter laboratory before catheter manipulation.

Less common associations

Most series dealing with outcome of patients with atrioventricular discordance include those "close cousins" with other forms of ventriculoarterial arrangements. Atrioventricular discordance can occur with double-outlet of both great arteries from the morphologically right ventricle; double-outlet left ventricle; single-outlet aorta with pulmonary atresia or with normal ventriculoarterial connections. This latter condition has also been designated as isolated ventricular inversion or isolated atrioventricular discordance (see Chapter 26B). Other relatively uncommon conditions include a supravalvular stenosing ring of the left atrium; subaortic stenosis; and left ventricular hypoplasia with or without pulmonary atresia and intact ventricular septum; and hypoplasia of either the morphologically right or left ventricle.[12]

Outcome analysis

The long-term outcome of patients with double discordance is closely associated with the complexity of the associated anomalies, the form and function of the morphologically right ventricle and the competency of the morphologically tricuspid valve. A further issue for these patients is the potential for complete heart block. There is only scant information on the outcome of fetuses recognized to have double discordance. Allan states that the prognosis for the affected fetus tends to be poor because fetal detection is often predicated on the recognition of the associated malformations.[64] In her series, of the 19 cases diagnosed prenatally, the pregnancy was terminated in 7; there were 2 neonatal deaths and 8 were alive, most with clinically significant systemic atrioventricular valve regurgitation.[64]

Before 1987 and the report from Ilbawi and his colleagues,[65] patients with double discordance and associated conditions were treated with a variety of standard open and closed heart procedures. Early in the surgical history of this condition, those with a large ventricular septal defect underwent banding of the pulmonary trunk followed at a later date by debanding and patch closure of the ventricular septal defect.[12,13,16] Some by the late 1970s preferred one-stage repair of the ventricular septal defect.[16,20,22,23] Repair of the ventricular septal defect was frequently complicated by complete heart block until de Leval introduced the concept of ventricular septal defect closure from the morphologically right ventricular septal side.[30] Those with double discordance, ventricular septal defect and important pulmonary outflow tract obstruction would often be palliated in infancy with a systemic-to-pulmonary artery shunt, and later repair.[16,20,66–67] The repair included patch closure of the ventricular septal defect with a conduit interposed between the morphologically left ventricle and the pulmonary trunk.[16,20,66,67] The tricuspid valve would be repaired or replaced, but in the classic repairs just described, the tricuspid valve would be left in the systemic circulation. Those with important ventricular hypoplasia could be considered for single ventricle palliation, while those with concordant ventriculoarterial connections and two well-formed ventricles can be treated with an atrial inversion-type of repair (see Chapter 26B).

Data recently published on the Prospective Bohemia Survival Study indicated that of 22 children identified at birth with double discordance, 94.45% survived the first month.[39] An additional decline occurred between the first and sixth months of life to 82.27%, and at 3 years to 72.73% and remained at this level to the age of 15 years. Huhta and his colleagues reviewed the natural history of 107 patients with congenitally corrected transposition of the great arteries seen at the Mayo Clinic over a 30-year period (1951–81).[68] The only variable correlating with decreased survival was left atrioventricular valve insufficiency. These authors reported survival of 70% at 5 years and 64% at 10 years. Clearly this is a "biased" series because of the unique referral pattern of the Mayo Clinic. The mean age at Mayo Clinic diagnosis was 12.7 years, ranging from birth to 56 years.

Data on the natural history of the patient with congenitally corrected transposition of the great arteries have been provided by Lundstrom and colleagues from the United Kingdom.[69] They reviewed data on 111 patients with a biventricular heart managed over a 20-year period to 1988. The ages of survivors in their cohort ranged from 1 to 58 years, with a median of 20 years, and all but 10 had additional cardiac difficulties. Twenty-six patients had died by 1988. Sixteen patients were considered unlikely to require surgery because of absent or trivial associated cardiac lesions. Because of considerable heterogeneity in associated cardiac lesions, it became evident that patients who were very symptomatic from heart failure did not fare well. In addition, those young patients with severe tricuspid regurgitation and/or a failing morphologic right ventricle also did poorly. Data from Boston Children's Hospital suggest a more favorable outcome, but the data do not include as long a follow-up.[38] McGrath and colleagues have addressed death and other events after cardiac repair in 99 patients with discordant atrioventricular connections.[70] The 1-month, 1-year, and 10-year actuarial survival rates of these 99 surgical patients were 86%, 75%, and 68%, respectively. Voskuil and colleagues have also studied the post-surgical course of 73 Dutch patients from three institutions with double discordance.[71] Not surprisingly they found survival of patients with double discordance was significantly below normal, and in most patients right ventricular and tricuspid valve function deteriorated with age. Both of these complications developed more frequently after conventional intracardiac operations compared with patients undergoing palliative intervention or no surgery at all.

Prieto and her colleagues have studied systemic atrioventricular valve function in 40 patients with double discordance. Follow-up in these patients ranged from 7 to 36 years, with a

mean of 20 years.[72] Intracardiac repair was carried out in 21 patients and 19 were unoperated upon or had closed heart procedures. The only independently significant factor for death in their analysis was moderate to severe tricuspid regurgitation. For the entire cohort, 20-year survival without tricuspid regurgitation was 93%, but only 49% with tricuspid regurgitation. Twenty-year survival rates for operated patients with and without tricuspid regurgitation were 34% and 90%, respectively. Similarly, 20-year survival rates for unoperated patients with and without tricuspid regurgitation were 60% and 100%, respectively. This group concludes that tricuspid regurgitation represents the major risk for patients with double discordance, and that right ventricular dysfunction appeared to be a consequence of chronic tricuspid regurgitation. Many other studies are in agreement that right ventricular dysfunction and tricuspid regurgitation deteriorated more frequently following intracardiac operation than those either unoperated or treated with closed heart procedures.[66,67] In view of these observations on the importance of satisfactory tricuspid valve function in the outcome of these patients, we are challenged by Acar and associates to maintain tricuspid valve competence in double discordance.[73] As summarized by this group tricuspid valve function in double discordance with an abnormal tricuspid valve depends on the loading conditions of both ventricles and on the septal geometry.[73] Interventions that increase right ventricular volume or decrease left ventricular pressure induce and worsen tricuspid regurgitation. Furthermore in their experience, repair of the tricuspid valve always failed when the right ventricle was left in a systemic position and always succeeded when the right ventricle was incorporated into the pulmonary circulation.[73]

The unique disposition of the specialized conduction tissue sets the stage for the development of spontaneous heart block in any cohort of patients with congenitally corrected transposition of the great arteries. About 10% of patients may actually present in complete heart block. Data presented by Fyler based on the Boston Children's Hospital experience indicates that in a 20-year follow-up, 45% of the patients will have developed third-degree heart block.[38] This figure is somewhat higher than the figure of 30% suggested by Mullins.[13] Because acquired heart block frequently occurs in the setting of associated cardiac anomalies, the bradycardia is not well tolerated, and urgent pacemaker therapy is mandated. It has been suggested that spontaneous complete heart block in this population occurs at a rate of about 2% per year.[16,68–70]

One of the conundrums of this disorder is the question: Can the morphologic right ventricle function as the systemic right ventricle in the long term? This question has been addressed in several ways. First, some argue that the shape of the morphologically right ventricle; the configuration of the tricuspid valve; the disposition of the papillary muscles of the tricuspid valve; the fact that the right ventricle is a one-coronary artery ventricle whereas the left ventricle is a two-coronary artery ventricle, all these factors disadvantage the morphologically right ventricle as a systemic ventricle.[10] In addition, there are a number of reports of adults in the sixth, seventh, eighth, and ninth decades of life with congenitally corrected transposition of the great arteries who have come to medical attention for either cardiac or noncardiac reasons.[74–86] Such patients are used as evidence that, indeed, the right ventricle can function as the systemic right ventricle for many years. Benson and his colleagues and others provided evidence, based on radionuclide assessment of ventricular function, supporting preservation of right integrity.[87,87A,87B,87C] A similar conclusion based on different methodology was reached by Dimas and colleagues.[77] Yet data from Peterson *et al.*[88] suggest that the systemic ventricular ejection fraction does not increase from rest to exercise, indicative of an abnormal exercise response. The issue has not been completely resolved, although at rest systolic function of the systemic morphologic right ventricle may be reasonably well preserved. Relatively few data on morphologic right ventricular diastolic function are available. From clinical experience it is evident that patients with a systemic ventricle of right ventricular morphology are at some risk of contractile dysfunction. Hornung and colleagues have provided some evidence using sestamibi scanning that in patients with double discordance but without any additional associated cardiac anomalies have a high prevalence of reversible and fixed myocardial ischemia, and these defects were mostly associated with impaired wall motion and thickening.[89] In the patients studied the younger patient had a normal right ventricular ejection fraction, while it was somewhat reduced in the older patients. Dodge-Khatami and colleagues have compared systemic ventricular (morphologically left ventricle) function in healthy adult controls and patients with unoperated double discordance using MRI dobutamine stress testing.[89A] They found that compared with the left ventricle of the healthy controls, the systemic ventricles of patients with unoperated double discordance and patients with physiologically corrected double discordance had larger volumes, diminished ejection fraction, but an appropriate response to dobutamine stress. They also found that the values of unoperated patients with double discordance were closer to normal than those with double discordance who had undergone physiological repair.

But as one surveys the outcome of any substantial cohort of patients with double discordance, some will develop progressive systemic atrioventricular valve regurgitation after otherwise apparently successful surgery.[10,12,13,16,20,33,65,66,67,68–73] Others will demonstrate progressive deterioration in the form and function of the morphologically right ventricle, the systemic ventricle, a concern well known to the survivor of the Mustard or Senning repair for complete transposition of the great arteries (see Chapter 25A). In others progressive tricuspid valve incompetence and a failing systemic right ventricle will beg the question as to what is the main culprit: the failing ventricle leading to progressive tricuspid regurgitation, or progressive tricuspid regurgitation causing right ventricular failure, again a similar concern for the survivors of atrial repair for transposition. Indeed, these concerns about the outcome of the atrial switch patients stimulated the interest in the arterial switch protocol, a goal finally achieved by Adib Jatene of Sao Paulo, Brazil, in 1974, after the disappointing results of Mustard two decades earlier (see Chapter 25B). It was Ilbawi and his colleagues in the late 1980s who first reported a surgical maneuver that would allow the morphologically left ventricle to function as the systemic ventricle in the patient with double discordance.[65] In two patients with complex double discordance, ventricular septal defect, and pulmonary outflow tract stenosis/atresia, a venous switch operation was combined with a Rastelli-like operation in which the ventricular septal defect was tunneled to the left ventricle and aorta, and a conduit was interposed between the morphologically right ventricle and pulmonary artery. This allows the morphologically left ventricle to function as the systemic ventricle and places the morphologically right ventricle in the pulmonary circulation. By reducing the afterload on the morphologically

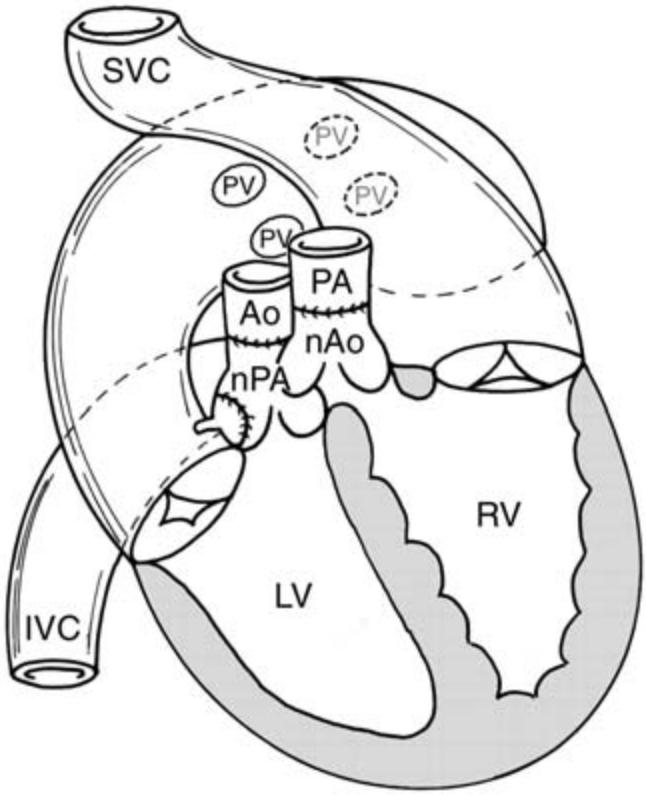

Fig. 26A-6 Double-switch operation of Imai *et al.* Mustard or Senning procedure is performed at the atrial level to divert the systemic venous flow to the morphologically right ventricle (RV) on the left side and the pulmonary venous flow to the morphologically left ventricle (LV) on the right side. Then, the arterial switch procedure is performed to establish concordant ventriculoarterial connection. Ao, aorta; IVC, inferior vena cava; nAo, native aorta; nPA, native pulmonary artery; PA, pulmonary artery; PV, pulmonary vein; SVC, superior vena cava.

right ventricle, this should improve the function of the tricuspid valve. Within a few years after the report from Ilbawi and his colleagues emanated the report of Imai and his colleagues of a combined atrial and arterial switch: a true double-switch for double discordance (Fig. 26A-6).[90] There is now a considerable surgical experience with the double-switch operation, both atrial switch and Rastelli and the true double-switch.[91–108] The theoretical benefits of these operations are apparent, but both forms of double-switch are accompanied by their own potential problems. Both types involve an atrial switch operation, and the mechanical and electrical complications of the atrial switch operation (Mustard or Senning) have been dealt with elsewhere (see Chapter 25A). The Rastelli approach frequently requires enlargement of the VSD and this is not without potential hazards to the patient.[106] This is not unusual considering the observations of Rychik and his colleagues.[106A] In the pure double switch, there are the long-term complications associated with coronary artery transfer, etc. None the less, the double-switch protocol has been quickly assimilated into our surgical algorithms, and there are clinical data suggesting excellent long-term outcomes from this approach.[96A,109,109A,109B]

Yeh and his colleagues from the Toronto Hospital for Sick Children have reported the outcome of repair in 127 patients with atrioventricular discordance from 1959 to 1997, extending the observations from our earlier experiences with this condition.[110] The ventriculoarterial connection was discordant in 87%, concordant in 6%, double-outlet right in 6%, and double-outlet left in 1%. At the initial presentation, the most common lesions in these 127 patients were ventricular septal defect in 86%, pulmonary outflow tract obstruction in 64%, important tricuspid regurgitation in 28%, and atrioventricular block in 12%. Nine patients underwent a double switch procedure and the remainder were managed conventionally. The operative mortality was 6% and did not vary by associated lesion. Twenty years after repair survival was only 48%. Within 20 years, 56% required reoperation, usually for tricuspid valve incompetence, pulmonary outflow tract obstruction, or both (Fig. 26A-7). Pacemakers were required in 50 patients, 4 before repair, 40 within 2 months of repair, and 6 remotely after repair. Tricuspid valve failure was an important cause of morbidity and mortality, both at initial repair and during subsequent follow-up. Forty-two of the 127 patients (34%) have required tricuspid valve repair or replacement to date. Twenty-seven of these required tricuspid valve replacement or repair at the initial operation. Of these 27, 4 have required a subsequent operation for tricuspid valve failure at a mean age of 10 years (median 14.2 years) after the initial repair. Of the 98 patients who did not require tricuspid valve surgery at the initial repair, 14 (14%) required subsequent tricuspid valve surgery by a mean age of 19.9 years (median 17.4 years). Fifty per cent of our patients with atrioventricular discordance required tricuspid valve surgery by 35 years of age, and tricuspid valve failure requiring surgery increased with age. Pulmonary conduit failure was also an important source of morbidity and mortality. Of the 66 patients who had a pulmonary conduit placed at the initial repair, within 12 years, 49% required conduit replacement. Twenty years after the initial

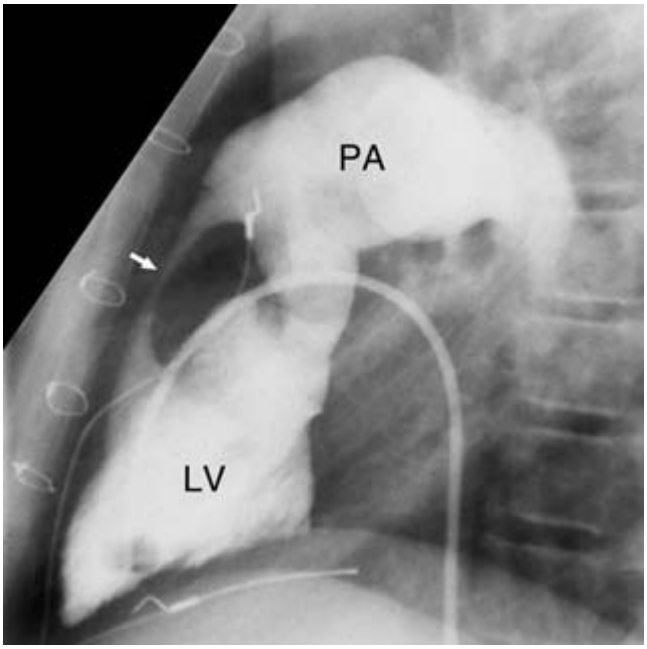

Fig 26A-7 Important stenosis (arrow) of the right ventricle-to-pulmonary artery homograft conduit in a patient with congenitally corrected transposition and severe left ventricular outflow tract obstruction. LV, left ventricle; PA, pulmonary artery.

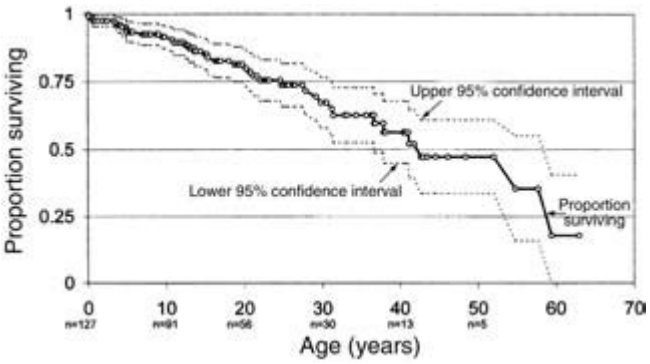

Fig. 26A-8 Kaplan–Meier survival curve of the Toronto Hospital for Sick Children's cohort of patients with atrioventricular discordance. (Reprinted from Yeh *et al.*,[110] Copyright (1999) Mosby Inc., with permission from Elsevier Inc.)

repair, 60% of the patients were free of pacemaker placement. In our early experience with the double-switch protocol, mortality was equivalent, but half the patients required a pacemaker for atrioventricular block, usually associated with the need to enlarge the ventricular septal defect. The overall survival from birth of our entire cohort of patients with double discordance is shown in Fig. 26A-8.

Graham and his colleagues in a multi-institutional study have addressed the long-term outcome of 182 adult patients 18 years of age or older from 19 institutions.[111] Two groups of patients were compared: group 1 with associated conditions and group 2, no associated lesions. No difference in ages was seen between the two groups, and for the entire 182 patients averaged 32 ± 13 years (range, 18–75 years). Clinical findings of congestive heart failure was common in both groups, but more common in those with associated lesions (51% vs. 34%). By age 45 years, 67% of patients in group 1 had congestive heart failure compared to only 25% of patients in group 2. Systemic right ventricular dysfunction was common in both groups, 70% and 55%, as was tricuspid regurgitation, 82% and 84%. Dysfunction of the morphologically left ventricle supporting the pulmonary circulation was identified in 25% of patients in group 1 and in only 7% in group 2. Aortic regurgitation was similar in both groups, 36% in group 1 and 25% in group 2. For clinical congestive heart failure and right ventricular dysfunction, the strongest risk factors included tricuspid valve surgery, important tricuspid regurgitation, history of any open heart surgery, and pacemaker therapy. Similar findings have been reported by Connelly and his colleagues from the Toronto Congenital Cardiac Center for Adults.[80]

How and why new operations are introduced is the subject of some interest.[109] This has been discussed in the context of the rapid evolution from the atrial switch to the arterial switch for complete transposition of the great vessels. Indeed, the answer today to the question "Why switch?" is obvious and the midterm results certainly justify the change in surgical protocol.[112] But is the change in protocols for double discordance justified, a reasonable question posed from colleagues at the Mayo Clinic.[113] They caution us that while the operative results and early follow-up have been optimistic, to this date no intermediate or long-term results have been published. To this end, the Mayo Clinic group offers their results and follow-up data for comparison. They reported in 2001 on 111 children operated on from July 1, 1971 to January 31, 1996. Complex associated anomalies included double-outlet right ventricle in 43 and situs abnormalities in 38. Patch or suture closure of a ventricular septal defect was required in 101 patients, a conduit from the morphologically left ventricle to the pulmonary artery in 65 patients, repair or replacement of the systemic atrioventricular valve in 22, and other miscellaneous procedures. The overall early mortality was 16%, but for the 29 patients operated on after 1986 early mortality was 3% (Figs 26A-9A,B). Follow-up for the 93 early survivors extended to 26.5 years (mean, 11.4 years). The overall survival was 77% ± 4% at 5 years and 67% ± 5% at 10 years. Late survival was adversely affected by prior operations, more severe preoperative functional class, and cardiac rhythm other than sinus. Reoperation was required for 39 patients (41%), most commonly for conduit replacement (n = 22) or surgery for the systemic atrioventricular valve (n = 13). Pacemakers were required before surgery in 3 patients, or at the

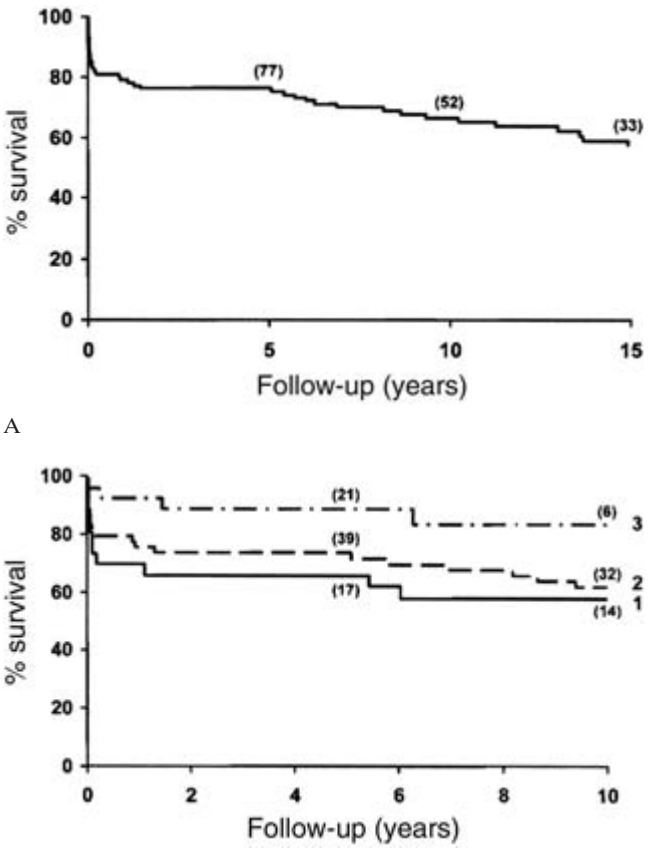

Fig. 26A-9 **A**. Kaplan–Meier survival curves for all 111 patients with congenitally corrected transposition of the great arteries undergoing operation at the Mayo Clinic from 1971 to 1996. The number of patients at risk at each 5-year interval is shown in parentheses. **B**. Kaplan–Meier survival curves for 111 patients stratified by time interval of operation. Group 1, 1971–76; group 2, 1977–86; group 3, 1987–96. The 5-year survivals for groups 1, 2, and 3 were 67% ± 9%, 74% ± 6%, and 90% ± 6%, respectively. (Reprinted from Biliciler-Denktas *et al.*,[113] Copyright (2001) Mosby Inc., with permission from Elsevier Inc.)

time of the operation, 10 patients. Within the first 30 days after surgery, 10 additional patients required pacemakers. Subsequent need for pacemakers in later follow-up was also common. Among the 68 patients alive at 30 days without a pacemaker, an additional 8 patients required pacemaker placement. At last follow-up, 19 (28%) of 67 survivors had pacemakers. As in the data from Toronto and elsewhere, progressive deterioration in right ventricular function and tricuspid valve function were common. Interestingly, patients with atrioventricular discordance and double-outlet right ventricle seemed to have lesser degrees of tricuspid valve regurgitation. The surgical mortality for the double-switch operation and early surgical follow-up data are encouraging. Indeed, in one series of 22 double-switch operations reported from the Cleveland Clinic in 2000, there was no early or late mortality.[102] In 1997, Reddy and his colleagues reported the early experience of the University of California in San Francisco group.[104] Of 11 patients undergoing a double-switch operation, they encountered one early and no late deaths. Stumper and Brawn reported in an editorial that their group from the Birmingham Children's Hospital had performed a double-switch operation in 32 patients with 1 early and 1 late death.[99] A somewhat earlier experience was reported by Yagihara and his colleagues in 1994.[95] Of 10 double-switch operations and a follow-up of only 4 years, they encountered 1 early and 2 late deaths. Imai and his colleagues from the Heart Institute of Japan, Tokyo Women's Medical Hospital have also had a substantial experience with the double-switch operation, reporting on 44 patients in 1997.[90,108] All but 4 patients survived the operation, with a hospital mortality of 9.1%, with a mean follow-up of 3.0 ± 2.2 years. Jahangiri and colleagues have made a case for anatomic correction in atrioventricular discordance by observing the effects of surgery on tricuspid valve function on 97 patients.[114] They observed that after pulmonary artery banding in 26 patients tricuspid valve function improved, while after the Blalock–Taussig shunt in 28, the severity of tricuspid regurgitation worsened. After physiological repair, there was no immediate improvement or worsening of tricuspid valve function, but later tricuspid valve repair/replacement was required in some patients. The operative mortality for the 70 patients undergoing physiological repair was 7%, while no operative mortality was encountered in the 19 patients undergoing anatomic repair. Ilbawi and his colleagues have recently extended their experience with anatomic repair of double discordance to 12 patients.[115] Two of these patients underwent Mustard and arterial repair, while the majority underwent Mustard and Rastelli-type operations. The mean age for the entire group was 9 ± 3.6 months. There was one death and only one patient required pacemaker therapy. The UK Birmingham Children's Hospital has recently published its experience with various forms of double switch operations in patients with atrioventricular discordance, addressing midterm results.[101A] Between November 1991 and June 2001, a total of 54 patients (median age 3.2 years, range 7 weeks–40 years) with either congenitally corrected transposition of the great arteries (n = 51) or atrioventricular discordance with double-outlet right ventricle (n = 3) underwent anatomic repair. This comprised a Senning procedure in all patients plus a classic arterial switch (double-switch group) in 29 cases (53.7%), plus a Rastelli procedure (Rastelli–Senning group) in 22 cases (40.7%), and plus intraventricular rerouting (Senning-tunnel group) in 3 cases (5.6%). Left ventricular training by pulmonary artery banding was performed before the double-switch operation in 9 of 29 cases (31%). The follow-up is complete (median 4.4 years). The early mortality was 5.6% (n = 3), with 2 late deaths. Kaplan–Meier survivals ± SEM) were 94.4% ± 3.1% at 1 year and 89.7% ± 4.4% at 9 years. Survivals at 7 years were 84.9% ± 7.1% in the double-switch group and 95.5% ± 4.4% in the Rastelli–Senning group (P = 0.32). Of the 49 survivors, 46 (94%) were in New York Heart Association functional class I. Six have acquired new left ventricular dilatation or impaired systolic ventricular function. Four patients in the double-switch group developed moderate aortic valve regurgitation, with 2 requiring valve replacement. Overall freedoms from reoperation at 1 and 9 years were 94.2% ± 3.3% and 77.5% ± 9.0%, with no significant difference between the groups (P = 0.60). Data published from Rutledge and her colleagues on the outcomes of 121 patients with double discordance also support consideration of the double-switch as an alternative to physiological repair.[115A] Replacement of the systemic tricuspid valve may be of benefit to some patients, while others will continue to demonstrate deterioration in right ventricular function.[116,117]

Beauchesne and colleagues have recently reported the outcome of the unoperated adult patients with congenitally corrected transposition of the great arteries.[118] They identified 44 patients aged from 20 to 79 years (mean 44 years) who had not had prior surgery, and in 29 the correct diagnosis was made ≥ 18 years ago. These patients were followed up to 144 months. Fourteen patients did not undergo surgery and 13 were alive at the last follow-up with 1 sudden death. Thirty patients required surgical intervention, and again at last follow-up, 29 were alive and 1 died from a noncardiovascular cause. All 30 patients undergoing surgery required replacement of the systemic atrioventricular valve because of severe regurgitation. One patient underwent at age 32 years a double-switch (Mustard and Rastelli) as well as replacement of the systemic atrio-ventricular valve. While there were no early postoperative deaths, 2 patients required pacemaker implantation because of postoperative heart block, and 3 other patients required internal defibrillators. Four of the 30 operated patients eventually required orthotopic heart transplantation because of systemic ventricular failure.[118] The most common hemodynamic problem encountered in this cohort was significant systemic atrioventricular valve regurgitation in the setting of impaired function of the systemic morphologically right ventricle. One of the issues faced by the Mayo Clinic in treating these patients was that in 53% of the patients, the referral for surgery was inappropriately delayed.[118]

Connolly and her colleagues have addressed the issue of pregnancy among women with double discordance.[119] Twenty-two women had 60 pregnancies resulting in 50 live births (83%). There were 11 unsuccessful pregnancies. One patient had multiple pregnancy-related complications, and there were no pregnancy-related deaths. The mean birth weight of the infants was 3.2 ± 0.4 kg. None of the 50 live offspring has been diagnosed with congenital heart defects.[119]

In the follow-up of these patients whether unoperated or operated with conventional surgical techniques, they must be scrutinized for the following issues:[12]

- abnormal rhythm and complete heart block
- function of the systemic atrioventricular valve
- function of the systemic right ventricle
- function of morphologically left ventricle to pulmonary artery conduit
- pulmonary artery branch stenosis (after previous shunt or conduit surgery).

If the patient has undergone a classic double-switch operation with an atrial repair of the Mustard or Senning type and an arterial switch operation, then surveillance for the typical baffle obstructions and leaks, and rhythm disturbances of atrial inversion surgery, and the panorama of complications subsequent to the arterial switch procedure must be defined (see Chapters 25A and 25B). One would still focus attention on myocardial performance and atrioventricular valve function as well. The potential complications of an atrial switch operation and ventricular switch include many of the issues just summarized above, but as well the potential for systemic outflow tract obstruction, etc.[12] One should also remember that some patients with double discordance may be at risk for tracheal compression secondary to the elongated aorta.[120]

In summary, the entity known as congenitally corrected transposition of the great arteries has a long and interesting history:

- Patients with this entity should not be considered "corrected."
- Frequent coexisting anomalies include ventricular septal defect, pulmonary outflow tract obstruction, and an Ebstein-like malformation of the morphologically tricuspid valve.
- The unique disposition of the specialized conduction tissue predisposes these patients to spontaneous onset complete heart block or surgically induced complete heart block.
- The De Leval convention has reduced surgically induced heart block subsequent to VSD closure.[30]
- The morphologically right ventricle supports the systemic circulation.
- Late right ventricular dysfunction and tricuspid regurgitation occur in both operated and non-operated individuals with double discordance.
- The classic surgical operation confers a physiological repair as the morphologically right ventricle retains its function as the systemic ventricle.
- An anatomic repair is more complicated, but advantageous as the morphologically left ventricle becomes the systemic ventricle.
- Anatomic repair can be achieved by:
  atrial and arterial switch operations in those patients without important pulmonary valvular stenosis
  atrial and ventricular switch operations in patients with ventricular septal defect and pulmonary outflow tract stenosis/atresia
- Ventricular switch surgery may require VSD enlargement.
- Patients with congenitally corrected transposition of the great arteries, unoperated, operated with either a physiological or anatomic repair require life-long cardiac surveillance.

All references can be found at the end of the book. See pp. 759–63 for Chapter 26A.

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26B

Robert M. Freedom and Shi-Joon Yoo

Isolated Atrioventricular Discordance

Isolated atrioventricular discordance is an uncommon cardiac malformation usually producing cyanosis in the neonate and first well described by Van Praagh and Van Praagh in 1966, although earlier descriptions of this entity had been recorded.[1,2] The initial documentation of this rare disorder by Ratner and his colleagues was noteworthy as well for the association with dextrocardia. This unusual anomaly has been designated both isolated ventricular inversion and isolated atrioventricular discordance. The latter designation focuses on the fundamental nature of the disorder: a discordant atrioventricular connection, but a concordant ventriculoarterial connection or normal arterial connections (Fig. 26B-1). In patients with normal atrial arrangements or solitus atria, the morphologically right atrium receiving the superior and inferior caval veins and coronary sinus connects through a mitral valve with the morphological left ventricle. This left ventricle supports a concordantly connected aorta, usually with mitral–aortic fibrous continuity. The left atrium receiving the pulmonary veins connects with the morphological right ventricle through a tricuspid valve with its normal septal attachments, and the right ventricle supports the pulmonary artery. The pulmonary valve and the tricuspid valve are not in fibrous continuity. Thus this uncommon congenital cardiac anomaly produces "transposition" physiology, two circulations in parallel rather than in series, but importantly without the fundamental anatomy of transposition of the great arteries.[1–13] The designation of isolated atrioventricular discordance focuses on the nature of the connections and thus these patients should elicit the same concerns as the patient with so-called double-discordance or congenitally corrected transposition of the great arteries.

An extensive literature has described the basic morphologic substrate of isolated atrioventricular discordance.[1,2–30] This condition has been found primarily in patients with atrial situs solitus, but is well described in those with mirror-image atrial arrangements. The patient reported by Geva and his associates described as having atrioventricular alignment discordance with situs concordance had the uncommon finding of a right-hand pattern of internal organization of the morphologically right ventricle despite atrioventricular discordance.[17] This "discordancy" between atrioventricular connection and type of ventricular looping underscores the necessity of defining both the type of connection and the type of internal organization of the ventricle.[18–20] A similar patient has been reported by Sklansky and colleagues who commented on the superoinferior nature of the ventricular relationship, a tricuspid valve that was anterior and to the right of the pulmonary valve and the associated left juxtaposition of the right atrial appendage.[28]

Some reports have defined isolated atrioventricular discordance in patients when the atria are not clearly anatomically lateralized.[10,27,30] In such patients, it is likely that the atrial arrangement are that of left isomerism, but with lateralized or appropriate systemic and pulmonary venous connections. Being "segmentally correct" this type of patient does not fulfill the criteria for isolated atrioventricular discordance, although some would disagree with the concept of isomerism of the atrial appendages.[22] Isolated atrioventricular discordance makes no inference about the conal or infundibular anatomy. With concordant ventriculoarterial connections, the infundibular anatomy is often normal, although we have described patients with bilateral muscular infundibulum in this condition. In patients with isolated atrioventricular discordance in isolation, the clinical presentation is that of a newborn with transposition physiology and inadequate mixing at atrial level. By definition this would exclude patients with a double-inlet left ventricle, a left-sided rudimentary right ventricle (l-loop type double inlet left ventricle) and concordant ventriculoarterial connections.[23,24]

Those features in common with corrected transposition of the great arteries include (see also Chapter 30):

- a discordant atrioventricular connection
- an abnormal specialized atrioventricular conduction tissue with the potential for spontaneous onset complete heart block
- an abnormal morphologically tricuspid valve with dysplasia and displacement and functional regurgitation
- a ventricular septal defect, usually perimembranous outlet
- the potential for pulmonary outflow tract obstruction.

Associated cardiac malformations

The most common associated anomalies include a perimembranous outlet ventricular septal defect; atrioventricular septal defect;[7,27] pulmonary outflow tract obstruction; varying degrees of hypoplasia of the morphologically right ventricle; and regurgitation of the morphologically tricuspid valve.[26] In some patients the degree of right ventricular hypoplasia is so severe as to preclude a biventricular repair. Less frequently there is obstruction to the systemic outflow tract, with the subaortic area wedged between the right-sided ventriculoinfundibular fold and the infundibular septum. Regurgitation of the morphologically tricuspid valve may be very severe.[26]

Medical management

For the baby with isolated atrioventricular discordance without a large ventricular septal defect, the immediate management is

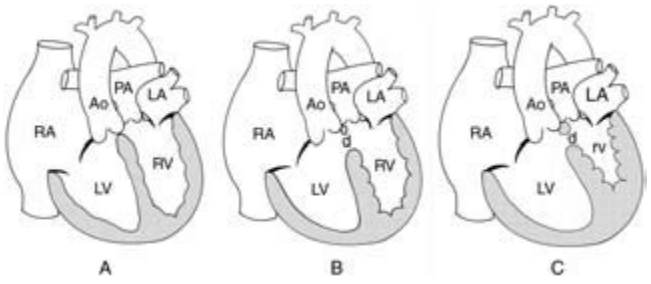

Fig. 26B-1 Isolated atrioventricular discordance. There is discordant atrioventricular connection but concordant ventriculoarterial connection, producing "complete transposition physiology." The ventricular septum may be intact (**A**) or associated with a ventricular septal defect (d) (**B** and **C**). The right ventricle is often hypoplastic, precluding biventricular repair. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV or rv, right ventricle.

to alleviate the hypoxemia reflecting inadequate atrial mixing. Thus the use of prostanoid therapy followed by an atrial balloon septostomy are the first lines of therapy.[26]

Surgical management

Some patients with isolated atrioventricular discordance with either normal atrial arrangements or inversus will be candidates for an atrial inversion procedure of either the Mustard or Senning type (see Chapter 25A).[10,14–16,26] These patients have the potential for nearly all of the mechanical complications of an atrial repair, including baffle leaks, superior or inferior caval vein obstruction; pulmonary venous obstruction; and sinus node dysfunction reflecting damage to the sinus node or its artery (see Chapter 29). Unlike patients with complete transposition, the morphologically left ventricle supports the aorta and the systemic circulation, and thus it is likely these patients will be spared late systemic ventricular dysfunction. In the baby with associated ventricular septal defect and important pulmonary outflow tract obstruction, a systemic-to-pulmonary artery anastomosis may be required, but if palliation can be deferred 4–6 weeks, then palliation with a bidirectional cavopulmonary connection could be considered (see Chapter 39). This maneuver makes the Mustard procedure technically easier because only the inferior caval vein needs to be baffled to the tricuspid valve and morphologically right ventricle.

One can thus define several surgical algorithms for the patient with isolated atrioventricular discordance:

1 Isolated atrioventricular discordance with two well-formed ventricles:
   Mustard or Senning and closure of ventricular septal defect if present (see Chapter 25A).
2 Isolated atrioventricular discordance and mild-to-moderate hypoplasia of morphologically right ventricle:
   Mustard or Senning and cavopulmonary shunt ($1^1/_2$ ventricle repair).
3 Isolated atrioventricular discordance, VSD, and severe pulmonary outflow tract obstruction:
   Mustard or Senning, ventricular septal defect closure;
   right ventricular outflow tract reconstruction/reconstitution.
4 Isolated atrioventricular discordance and severe hypoplasia of morphologically right ventricle or other anomaly precluding a biventricular repair:
   Stage to Fontan (see Chapters 35–37).

Outcomes

For patients with atrioventricular discordance and a biventricular heart, Yeh and his colleagues from Toronto have reviewed the outcome of the various forms of repair (see Chapter 30). The Kaplan–Meier curves for the patient with complete transposition with or without VSD are depicted in Chapter 29. The outcome and complications of the Fontan operation can be found in Chapters 36 and 37.

All references can be found at the end of the book. See pp. 763–4 for Chapter 26B.

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Robert M. Freedom

Anatomically Corrected Malposition of the Great Arteries

This "peculiar" terminology does not readily nor fully describe nor convey information about a group of hearts embraced by this designation. Furthermore hearts exhibiting anatomically corrected malposition of the great arteries cannot be repaired by one "general" surgical technique, as for instance tetralogy of Fallot, a malformation sharing in common a large malalignment ventricular septal defect, right ventricular outflow tract obstruction, etc. Van Praagh stated in an editorial in 1976 that: "Anatomically Corrected Malposition of the Great Arteries is hardly a household word, even among pediatric cardiology buffs."[1] There is a century-long history to this disorder, but Harris and Farber in 1939 described a *theoretically* abnormal relationship between ventricles and great arteries as anatomically corrected *transposition* of the great arteries.[2] This designation infers that each of the abnormally located great arteries originates above the anatomically correct or appropriate ventricle but with the aorta anterior to the pulmonary artery (Fig. 27-1). The benchmark anatomical descriptions of these entities by Van Praagh and Van Praagh in 1967 were still designated as "transposition," but because the great arteries are not really transposed, the nomenclature was revised to malposition in 1971.[3] The unusual relationship between the great arteries and the ventricles and the great arteries requires understanding of normal and abnormal infundibular development in the context of often complex forms of congenital heart malformations.[1,3–12]

The normal heart is characterized by a well-expanded subpulmonary infundibulum, and thus there is separation between tricuspid and pulmonary valves. The subaortic infundibulum is normally quite attenuated, thus bringing into close approximation the anterior leaflet of the mitral valve and the aortic valve. The disparity between the normally well-developed subpulmonary infundibulum and the attenuation of the subaortic infundibulum accounts in part for the more superior and leftward position of the pulmonary valve relative to the aortic valve in the normal heart.[3–8,13–19] In patients with so-called anatomically corrected malposition of the great arteries in its classical form, there is inversion of infundibular anatomy, or nearly so (Fig. 27-1).[20] That is, there is a well-defined or expanded subaortic infundibulum preventing aortic–mitral fibrous continuity, and the subpulmonary infundibulum is significantly attenuated, bringing the tricuspid valve closer to the pulmonary valve. In the patient with atrial situs solitus, concordant atrioventricular and ventriculoarterial connections and anatomically corrected malposition of the great arteries, the aorta is frequently levopositioned, but importantly without ventricular inversion or atrioventricular discordance.[1,3–12] If anatomically corrected malposition of the great arteries indicates a type of abnormal infundibular development (or maldevelopment), then it is possible that anatomically corrected malposition may be identified in patients with a wide range of segmental arrangements.[21,22] Anatomically corrected malposition of the great arteries has been frequently associated with left juxtaposition of the right atrial appendage. It can be seen also in the patient with isolated atrioventricular discordance (Fig. 26B-1).

Hearts with the fixed forms of subaortic stenosis often demonstrate aortic valve–mitral valve fibrous discontinuity.[15,16] Indeed, the degree of aortic–mitral separation in such patients may be very impressive, with the mechanism of aortic–mitral separation related to persistence of the left-sided ventriculoinfundibular fold. But in these patients the subpulmonary infundibulum is usually very well expanded, and the aortic valve is still usually posteroinferior to the pulmonary valve. Thus patients with the usual so-called short-segment or fixed forms of left ventricular outflow tract obstruction are not considered examples of anatomically corrected malposition of the great arteries.

Associated cardiac malformations

The commonly associated malformations are listed in Table 27-1.

In most clinical series, pulmonary outflow tract obstruction is perhaps more common than systemic outflow tract obstruction. Yet in patients with anatomically corrected malposition the subaortic infundibulum may be the substrate for subaortic stenosis. The ventricular septal defect frequently is of the infundibular-malalignment type with perimembranous-inlet extension. Dextrocardia is not uncommon as are abnormalities of the tricuspid valve. Because anatomically corrected malposition is infundibular maldevelopment, the spectrum of associated cardiac malformations is diverse.

Outcome analysis

There is no single medical or surgical algorithm that can be readily applied to patients with the infundibular anatomy of anatomically corrected malposition of the great arteries. Some patients may be candidates for a biventricular repair, while in others single ventricle palliation will be the only option (Fig. 27-2).

The long and frequently narrow subaortic infundibulum predisposes patients to a complex form of left ventricular outflow

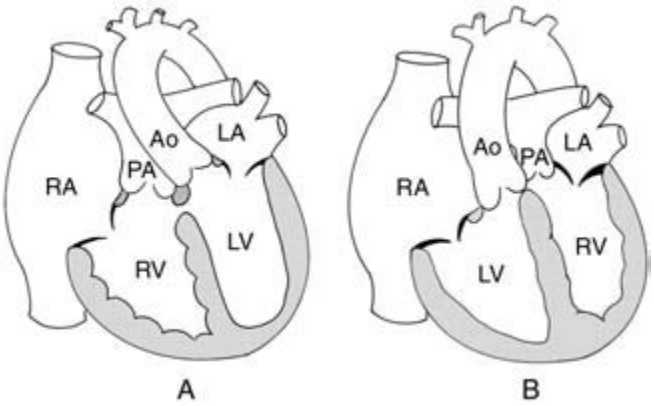

Fig. 27-1 Anatomically corrected malposition of the great arteries with concordant atrioventricular connection (**A**) and discordant atrioventricular connection (**B**). The left ventricle (LV) supports the aorta (Ao), but it is abnormally related with the pulmonary artery (PA) and there is subaortic infundibulum. LA, left atrium; RA, right atrium; RV, right ventricle.

Table 27-1 Anatomically corrected malposition of the great arteries

Fundamental nature of the disorder	1 Attenuated subpulmonary infundibulum and well-expanded subaortic infundibulum 2 Not transposition as pulmonary artery from right ventricle and aorta from left ventricle
Frequently associated anomalies	Ventricular septal defect Pulmonary outflow tract obstruction and/or left ventricular outflow tract obstruction Left juxtaposition of right atrial appendage Abnormalities of atrioventricular junction Levopositioned aorta without ventricular inversion

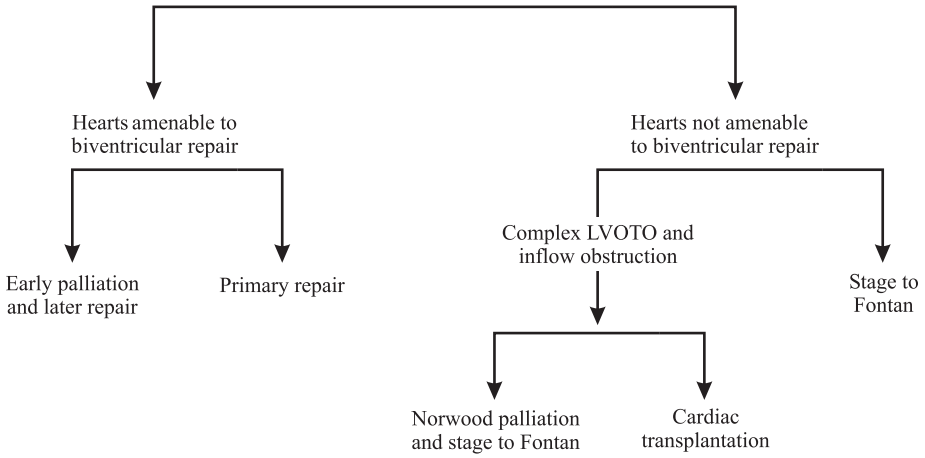

Fig. 27-2 Management of anatomically corrected position of the great arteries. LVOTO, left ventricular outflow tract obstruction.

tract obstruction, making a Norwood-type palliation likely in some neonates.[9,22–47]

Rittenhouse and his colleagues noted that the right ventricular outflow tract obstruction may be difficult to relieve with a transannular patch because the right coronary artery courses in front of the posteriorly-positioned pulmonary artery, thus necessitating a conduit repair.[30] The course of the right coronary artery had been noted by others, both in patients with anatomically corrected malposition and in double-outlet right ventricle with an l-malposed aorta[6,9,48,49] In late 2001, Morita and co-workers published a novel approach to repair the narrowed right ventricular outflow tract in three patients with anatomically corrected malposition of the great arteries in the setting of concordant atrioventricular and ventriculoarterial connections: atrioventricular groove patch plasty.[49] They took advantage of the fact that there is a leftward shift of the right coronary artery away from the right atrioventricular groove, and furthermore the atrioventricular conduction bundle has its normal posterior location.[49] These anatomic features permit a transannular subpulmonary incision of the right ventricular outflow tract between the course of the right coronary artery and tricuspid annulus. This novel approach was used successfully in 3 patients.[49]

All references can be found at the end of the book. See pp. 764–5 for Chapter 27.

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Double-Outlet Ventricle

Part I: Double-outlet right ventricle

Apparently one of the earliest descriptions of a heart with origin of both great arteries from the right ventricle was that of Mr Abernathy, a surgeon at St Bartholomew's Hospital in London who first described such a heart in 1793.[1] A century later in 1893, Birmingham described a similar entity.[2] Braun and his colleagues in 1952, described a case in which "both the aorta and stenotic pulmonary artery originate from the right ventricle," and they went on to state that the "right ventricle serves as a 'double-outlet ventricle,' " perhaps one of the earliest designations of this entity.[3] Some attribute to A. Calhoun Witham the earliest introduction or use of the specific term "double-outlet right ventricle" which he considered a partial transposition complex.[4] There has been considerable discussion over the years as to how best to define this entity known as double-outlet right ventricle. As stated earlier, once considered a form of partial transposition, subsequently there seemed to be emphasis on the presence of bilateral muscular infundibulums or conus as the criteria for this diagnosis.[5–9] However this was not specific because bilateral muscular infundibulums were observed in some patients with complex forms of transposition of the great arteries, particularly those with an associated ventricular septal defect and left ventricular outflow tract obstruction and that peculiar entity now known as anatomically corrected malposition of the great arteries, amongst others.[10–17] There is now some consensus that double-outlet right ventricle is but one form of abnormal ventriculoarterial connection (Fig. 28-1).[18] While this definition is independent of infundibular anatomy, certainly infundibular anatomy is important to the understanding of the totality of this malformation.[7–9,18] Most would agree with the definition that this particular ventriculoarterial connection is characterized by the origin of 50% or more of the circumference of each great artery above the morphologically right ventricle, although some are less precise.[19] When both great arteries originate above the morphologically right ventricle and the ventricular septum is intact, there is no difficulty (nor disagreement) in defining the ventriculoarterial connection as double-outlet right ventricle.[20–28] However, an intact ventricular septum is very rare in this situation, and in most patients one or both great arteries are closely related or indeed override the ventricular septal defect, making the assignment of arterial connection difficult and imprecise.[29–40] As Roberson and Silverman pointed out in their echocardiographic study, malalignment of the ventricular septum (a "hockey-stick" configuration) also complicates the assignment of the ventriculoarterial connection as does the reality that the infundibular septum when present in hearts with double-outlet right ventricle does not partition the ventricles, but rather separates the arterial outlets.[41]

Incidence

The New England Regional Infant Cardiac Program recorded only 35 patients with double-outlet right ventricle of the 2251 infants with congenital heart disease surveyed by this study,[42] providing a prevalence of 0.033 per 1000 live births. Data from the Baltimore–Washington Infant Study defined a somewhat higher prevalence for double-outlet right ventricle of 0.056 per 1000 live births.[43] The Alberta Heritage study showed a prevalence for double-outlet right ventricle of 0.145 per 1000 live births.[44] This is considerably higher than that defined for either the New England Regional Infant Cardiac Program or the Baltimore–Washington study. The reasons for this difference remain unclear, and do not seemingly reflect different methodologies of diagnosis. The prospective Bohemia Survival Study identified 69 children with double-outlet right ventricle from 815, 569 children born between 1980 and 1990, giving a prevalence of 0.08 per 1000 live births. These accounted for 1.37% of all heart malformations encountered during this study.[45] The Pediatric Cardiac Care Consortium found a prevalence for double-outlet right ventricle of 0.035 per 1000 live births.[46] As with any conotruncal anomaly, there is the potential association with a chromosome 22q11 deletion and the clinical manifestations associated with this chromosomal abnormality.[47–50] Double-outlet right ventricle has been seen in association with a number of abnormal chromosomal abnormalities, but there does not appear to be any specific type of genetic predisposition. Finally, the ventriculoarterial connection of double-outlet right ventricle is particularly frequent in hearts exhibiting right isomerism.[51,52]

Morphology

Lecompte and his colleagues have presented an elegant and most informative surgical synthesis of double-outlet right ventricle based on their own evolving surgical experiences.[34] They suggest that the concept of ventriculoarterial connection is not perfectly clear in the definition of double-outlet right ventricle, raising several questions. Does this designation suggest that one ventricle ejects blood into one artery? Or does the ventriculoarterial connection of double-outlet right ventricle refer to an anatomic relationship between the ventricular cavity and the great arteries, or to the vessel alignment with the interventricu-

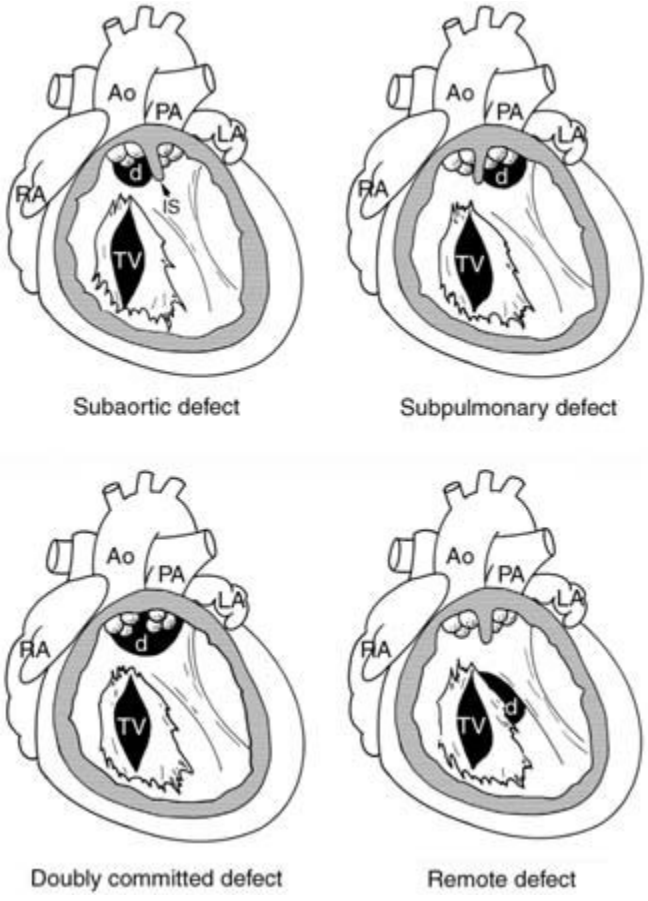

Fig. 28-1 Double-outlet right ventricle. The common denominator of double-outlet right ventricle is the origin of 50% or more of each great artery from the morphologically right ventricle. According to the proximity of the ventricular septal defect (d) to the great arterial valve, ventricular septal defects in double-outlet right ventricle can be classified into: subaortic defect; subpulmonary defect; doubly committed defect; remote or non-committed defect. Ao, aorta; IS, infundibular septum; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; TV, tricuspid valve.

lar septum, or to some amalgamation of these three concepts or visions of double-outlet right ventricle? Capuani and his colleagues have also recently presented an overview of the anatomic spectrum of abnormal ventriculoarterial connections and the surgical implications derived from these morphologic observations.[35] The emphasis of this paper is the location and insertion of the outlet or infundibular septum relative to the remainder of the muscular ventricular septum; appreciation of the extent of the of the inner curvature of the heart, the so-called ventriculoinfundibular fold; and the degree of formation of the posterior limb of the septal band. Observations about these structures are germane to the entire spectrum of conotruncal anomalies, some of which are characterized by abnormal transfer of the aorta from the left to the right ventricle. Whether one uses the definition of "double-outlet right ventricle" or "hearts with an abnormal ventriculoarterial connection" as the overarching definition, these designations do not provide any information about the situs, type of atrioventricular connection, internal organization of the morphologically right ventricle (i.e. right or left hand pattern), or the type of associated cardiac malformations. It is well known that among hearts with a double-outlet right ventricle, the situs may be normal, inverted, or not clearly lateralized (right or left isomerism).[18,38] The type of atrioventricular connection may be normal, discordant, absent right or left atrioventricular connection, or a double-inlet atrioventricular connection.[18,38,53–55] And the arterial roots may have a wide spectrum of spatial relationships, all despite the ventriculoarterial connection of double-outlet right ventricle.[37,56]

For many years, biventricular hearts with double-outlet right ventricle have been categorized by the position of the ventricular septal defect relative to the arterial outlets. This convention was first introduced by Lev and his colleagues in 1972 (Fig. 28-1).[36] Thus there are patients with double-outlet right ventricle with a subaortic ventricular septal defect; a subpulmonary ventricular septal defect, a ventricular septal defect committed to both arterial outlets (reflecting absence or significant attenuation of the infundibular septum), and finally a ventricular septal defect that is remote from either arterial outlet. These definitions are not strictly anatomic, but do convey physiologic/hemodynamic information. In the setting of biventricular hearts with double-outlet right ventricle, the most common associated malformations include either singly or in some combination ventricular septal defect, pulmonary stenosis, straddling and overriding atrioventricular valve, right ventricular outflow tract obstruction, and an obstructive anomaly of the aortic arch. Other associated anomalies include complete form of atrioventricular septal defect, juxtaposition of the atrial appendage, superoinferior ventricles, crossed atrioventricular connections, anomalies of systemic and pulmonary venous connections, ventricular hypoplasia, etc. The so-called Taussig–Bing form of double-outlet right ventricle has received considerable attention.[57–62] The ventricular septal defect is subpulmonary and bilateral muscular infundibulum prevents semilunar valve–atrioventricular valve fibrous continuity. In these patients the right ventricular outflow tract to the aorta is often narrowed; coarctation of the aorta is common; and straddling of the mitral valve is frequent as well.[63–83] The mitral valve may be cleft, not as in the atrioventricular septal defect, and may leak, promote outflow tract obstruction, compromise the ventricular septal defect and in some patients make a biventricular repair hazardous.[69] Beekman and colleagues have recently studied the morphological nature of the non-committed ventricular septal defect and associated anomalies in specimens with double-outlet right ventricle.[82] They categorize these ventricular septal defects as not directly committed, but opening into either the subaortic or subpulmonary outflow tract and those that are non-committed. In this latter group are the defects that are muscular inlet or atrioventricular septal defect without extension to the outlet.

Particular risk factors

For patients considered for a biventricular repair, anatomical concerns potentially complicating management include restrictive ventricular septal defects, multiple ventricular septal defects, straddling atrioventricular valves, cleft mitral valve with attachment of chordal apparatus to the infundibular septum, some degree of ventricular hypoplasia, and an obstructive anomaly of the aortic arch.[63–83] Complex coronary artery anatomy may be encountered in those patients undergoing the arterial switch operation,[74,84,85] but this factor has been over-

come with increasing experience with this operation (see Chapter 25B). An abnormal spatial relationship between the ventricles with a horizontal interventricular septum is frequent in patients with double-outlet right ventricle.[86,87,87A] There has been particular interest in the patient with double-outlet right ventricle and the complete form of atrioventricular septal defect, considered a remote form of ventricular septal defect.[88] Bharati and her colleagues in an autopsy study found in 507 specimens of complete atrioventricular septal defect only 34 with double-outlet right ventricle.[88A]

Outcome analysis

Because of the morphological heterogeneity of hearts with double-outlet right ventricle, an outcome analysis is difficult and complex. Some patients may clearly have a better outcome than others. As we have stated in earlier chapters, there is considerable experience with the fetal recognition of conotruncal abnormalities.[89–91] Hornberger and her colleagues reported on the outcome of 62 fetuses diagnosed with double-outlet right ventricle.[91] Termination of pregnancy took place in 34, two had a spontaneous intrauterine death, neonatal death occurred in 5 and 4 deaths occurred in infancy. The 17 survivors constitute 27.4% of the entire fetal cohort and 51% survival in the continuing pregnancies. Samanek and Voriskova reported on the outcome of the 69 children born with double-outlet right ventricle that were identified in the prospective Bohemia Survival Study.[45] More than 13% died in the first week after birth. In the first month of life the survival curve stabilized at 78.6% (95% CL, 68.3% to 88.2%). The decline did not stop until 3 years of age at an average survival rate of 47.8% (95% CL, 35.8% to 61.3%). Between 3 and 5 years, the curve decreased by only 2.9% and between the fifth and tenth years by 1.5%. The survival rate then remained at 43.4% (95% CL, 31.5% to 55.4%). It is quite surprising then to discover a woman at the age of 65 years with double-outlet right ventricle and unprotected pulmonary vascular bed.[92]

As with most forms of complex congenital heart disease, surgical therapy evolved from that of palliation to repair, with repair in earlier eras often preceded by some form of palliation.[93,94] Those patients with pulmonary hypertension and excessive pulmonary blood flow underwent pulmonary artery banding, while those with reduced pulmonary blood flow some form of shunting procedure to augment pulmonary blood flow. The patient with Taussig–Bing form of double-outlet right ventricle often required pulmonary artery banding and an atrial septectomy to facilitate mixing or after 1966 balloon atrial septostomy. Patients with double-outlet right ventricle and a subpulmonary ventricular septal defect, i.e. those with transposition physiology, benefited after 1963 from Mustard's form of atrial inversion surgery with closure of the ventricular septal defect (see Chapter 25A). Repair of double-outlet right ventricle with a subaortic ventricular septal defect was first achieved in 1957[95] and repair of double-outlet right ventricle with a subpulmonary ventricular septal defect in 1962.[96] Intraventricular rerouting was introduced by Kawashima *et al*. in 1971 for double-outlet right ventricle with a subpulmonary ventricular septal defect (Fig. 28-2).[97,98] It was in the late 1970s that repair of the double-outlet right ventricle with a remote ventricular septal defect was reported.[99] Stewart and his colleagues from the University of Alabama reported in 1979 the results of

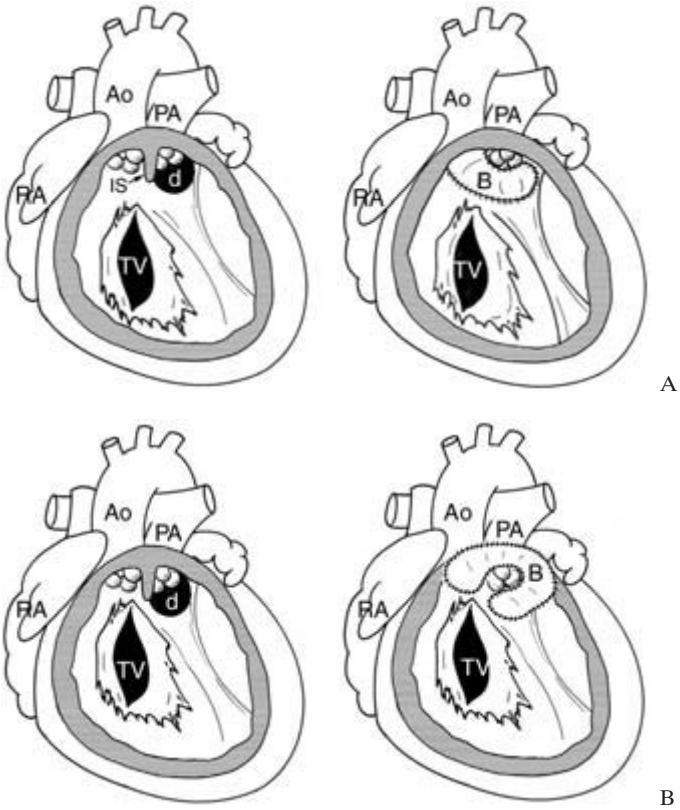

Fig. 28-2 Intraventricular rerouting in double-outlet right ventricle with subpulmonary ventricular septal defect. **A**. When the distance between the tricuspid valve (TV) and the pulmonary valve allows unobstructed intraventricular rerouting, the baffle (B) can be placed between the two valves with resection of the infundibular septum (IS). **B**. When the tricuspid and pulmonary valves are too close, the baffle should be placed around the anterosuperior margin of the pulmonary valve (Kawashima procedure). Ao, aorta; d, ventricular septal defect; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

repair from 1967 to 1978 of double-outlet right ventricle in 62 patients.[94] In this review, the overall surgical mortality was 34%. The risk was considerably lower for those with a subaortic ventricular septal defect and higher for those with a subpulmonary or remote defect. These repairs were carried out before the arterial switch operation was incorporated into the surgical algorithm.[94] Kirklin and his colleagues extended these observations by reporting in 1986 an 18 year experience with repair of double-outlet right ventricle in 127 patients.[100] The overall actuarial survival for the entire cohort was 38% at 12 years. In some subsets of patients it was much better, with an early survival at 2 weeks for repair of double-outlet right ventricle and subaortic ventricular septal defect of 99% and a 10 year survival of 97%. Results were also quite good for repair of double-outlet right ventricle and a doubly committed ventricular septal defect, but again the results in this era were poor for those patients with double-outlet right ventricle and either a subpulmonary or remote ventricular septal defect.[100] Indeed, in the current era most experiences suggest an excellent outcome and freedom from reintervention for patients with double-outlet right ventricle and subaortic ventricular septal defect ± pulmonary outflow tract obstruction.

With increasing surgical experience, it became possible to perform a biventricular repair in most patients with double-outlet right ventricle, including those with a remote ventricular septal defect and many with straddling atrioventricular valves. As pointed out by Uemura and others, the orientation of the ventricular septal defect needs to be precisely determined if the ventricular outflow tracts are to be properly reconstructed, thus avoiding obstruction across either the newly created subpulmonary and subaortic channels.[101] The subaortic pathway tends to be long and tortuous in those patients with a non-committed ventricular septal defect and also in those with a subpulmonary ventricular septal defect when a Kawashima intraventricular rerouting procedure is considered.[97,98] Attachment of chordal apparatus to the infundibular septum can also interfere with optimum construction of the intraventricular pathway to the aorta,[32–35,71–74,76,77,102] although various approaches to surgery of the infundibular septum have been employed to avoid this complication.[103–105] In the current era, two operative strategies have been employed for the correction of the double-outlet right ventricle with subpulmonary ventricular septal defect. These are the arterial switch operation often advocated when the great arteries are in an anteroposterior spatial relationship and for the patient with side-by-side great arteries, the Kawashima intraventricular repair (Fig. 28-2).[61,71–79,106,107] The approach of using the Mustard repair with closure of the ventricular septal defect has been abandoned largely because of the poor mid- and long-term outcome of these patients who experienced a substantial incidence of poor right ventricular function, congestive heart failure and sudden death (see Chapter 25A). We have stated earlier that the right ventricular origin of systemic outflow tract with obstruction seemed early on a risk factor for a biventricular repair.[71] The etiology of the systemic outflow tract obstruction was largely related to rightward and anterior displacement of the infundibular septum.[56,62–64,71–74,77–79] Some advocated a Damus–Kaye–Stansel approach to obviate this complication.[108–115] This necessitated closing the ventricular septal defect to the pulmonary orifice; dividing the main pulmonary trunk and connecting the proximal main pulmonary trunk to the ascending aorta; then a conduit was interposed between the morphologically right ventricle and the distal pulmonary trunk. The disadvantage to this procedure was that it required a conduit and the potential for thrombosis in the aortic root.[112] Some felt that this procedure could distort the semilunar valves, promoting valvular insufficiency.[116] We reported almost a decade ago our results with the Damus–Kaye–Stansel operation in 9 patients with the Taussig–Bing malformation.[115] Three patients did not survive the operation. The survivors have all required conduit replacement. Semilunar valve incompetence was common both before and after the operation, but most did not progress in severity. From our own experience and from that in the literature, this approach has largely been abandoned in favor of either the arterial switch option or intraventricular rerouting.[72–76,97,98,106]

There are some data indicating a strong association between side-by-side great arteries and unusual coronary artery patterns.[84,85] Uemura and his colleagues found that a single coronary artery was present in 27% of hearts with double-outlet right ventricle and side-by-side great arteries.[84] Similar findings had been published a few years earlier by Gordillo and colleague.[85] Mavroudis and his colleagues reported on a modest series of patients with the Taussig–Bing anomaly repaired by one of these two methods with excellent early and intermediate results for both methods.[106] Serraf and his colleagues from the Marie Lannelongue Hospital reported on 27 consecutive patients who underwent anatomic repair of the Taussig–Bing malformation between 1978 through 1990.[79] Seven patients underwent an intraventricular rerouting operation of the Kawashima type and 20 patients underwent an arterial switch repair with ventricular septal defect closure. The great vessel relationship was in a "d-transposition" relationship in 12 patients and side-by-side in 15. Seventeen patients had undergone a previous palliative operation. There were two early deaths, one in each group. The patient who died early after the intraventricular rerouting had severe left ventricular outflow tract obstruction which was attributed to non-resection of the infundibular septum. The other death which occurred in the arterial switch group was related to a right coronary ostial stenosis.[79] Reoperations were required in 7 patients, 2 in group 1, and 5 in group 2. There were two late deaths, one in each group. One patient died with severe left ventricular outflow tract obstruction and recurrent pulmonary infections and the other following a heart transplant required because of progressive myocardial ischemia. Actuarial survival and freedom from reoperation at 5 years were 73 ± 14.6% and 58 ± 13% (70% CL) respectively.[79] Lacour-Gayet and his colleagues extended these observations in 1997 with their publication addressing biventricular repair in 103 patients operated on between 1984 and 1996 with conotruncal anomalies with associated aortic arch obstruction.[78] Thirty-two of these patients had double-outlet right ventricle with subpulmonary ventricular septal defect. Twelve of these 32 patients underwent a two-stage repair with 4 early deaths, while 20 underwent a one-stage repair with 2 early deaths. Indeed, in the consideration of the entire cohort of 103 patients, the two-stage mortality was 27%, while the hospital mortality for a single-stage repair was 12%, and this fell even further to 9.4% in the last 3 years of the clinical experience.[72,78]

Masuda and colleagues reported on the results of the arterial switch operation performed in 27 patients with double-outlet right ventricle with subpulmonary ventricular septal defect between 1986 and 1997.[75] The great artery relationship was nearly anteroposterior in 15 and mostly side-by-side in 12. There was one operative and three late deaths. The predicted Kaplan–Meier survival at 9 years was 83 ± 8%. Freedom from reoperation was only 46 ± 20% at 9 years, with much of the need for reintervention occurring early in the clinical experience.[75] Takeuchi and colleagues in 2001 reported on the outcomes of 20 patients who underwent an arterial switch repair of double-outlet right ventricle with subpulmonary ventricular septal defect between 1992 and 1999.[73,74] Nine of the 20 patients had undergone some form of palliation before the arterial switch operation. Three patients had side-by-side great arteries, 10 had unusual coronary artery patterns, five had multiple ventricular septal defects, 5 had a hypoplastic aortic arch and 7 coarctation of the aorta.[74] Four patients died early after surgery. Their analysis indicated that side-by-side great vessel anatomy was identified as an independent risk factor by Cox multivariable regression analysis. Estimated one-year survival was considerably worse for those with side-by-side great arteries (72% [70% CL, 58% to 86%]) compared with patients with other great artery spatial relationships (70% CL, 90% to 100%) ($P = 0.05$, log-rank test). Two of the deaths were also directly related to

difficulties encountered with coronary artery transfer in infants with an unusual coronary artery pattern and side-by-side great arteries. One of these patterns was an inverted coronary pattern and the other was the left anterior descending coronary originating from the right coronary artery.[74]

An obstructive anomaly of the aortic arch is also well known to be commonly associated with the Taussig–Bing form of double-outlet right ventricle.[37,56,63–65,71–80] These include aortic arch hypoplasia, coarctation of the aorta, aortic arch atresia, or interruption. There is now considerable experience with biventricular repair of conotruncal anomalies associated with aortic arch obstruction.[78] Comas and his colleagues from the Royal Children's Hospital in Melbourne, Australia, showed that in their experience aortic arch obstruction does not influence or disadvantage the arterial switch repair option for the patient with the Taussig–Bing malformation.[80] Lacour-Gayet and his colleagues have had an extensive experience of biventricular repair in 103 patients with conotruncal anomalies associated with aortic arch obstruction.[78] Among these patients were 32 with double-outlet right ventricle and subpulmonary ventricular septal defect. The twelve year survival for this group was 72%. This compared to 100% survival for those with an arch obstruction in the setting of transposition of the great arteries and an intact ventricular septum and 80% survival for those with transposition and ventricular septal defect.[78] In the same review, the actuarial survival for those treated with one-stage repair was 83%, and 71% with a two-staged approach.

Kleinert and colleagues reviewed the anatomic features and surgical strategies in 193 children with double-outlet right ventricle and assessed the risk factors for early mortality.[117] These patients underwent surgery between 1978 and 1993. The authors divided this large cohort into two groups: noncomplex patients (group 1) had atrioventricular (AV) concordance, a single ventricular septal defect (VSD), balanced ventricles, no straddling AV valves, and no major pulmonary artery anomaly. Group 2 (complex) comprised all remaining patients. Independent risk factors analyzed included location of the main VSD, presence of additional VSDs, coarctation, ventricular outflow obstruction, ventricular hypoplasia, age at operation, operation before 1985, previous palliation, and type of definitive operation. Of 193 patients, 117 were in group 1 and 76 in group 2. In 148 patients, biventricular repair was undertaken, including 111 of 117 group 1 patients and 37 of 76 group 2 patients. Early mortality was higher among group 2 patients undergoing biventricular repair than among group 1 patients (8 of 37 versus 4 of 111, $P < 0.005$) and higher than group 2 patients undergoing a Fontan procedure (none of 29, $P < 0.01$). Aortic arch obstruction, operation before 1985, and multiple VSDs were significant risk factors for mortality. Age < 1 month ($P < 0.05$) and multiple VSDs ($P < 0.005$) were independent risk factors after definitive repair. Up-to-date follow-up is available on 144 surviving patients, with 127 (88%) in New York Heart Association class I and the remaining 17 in class II. Overall 10-year survival probability was 81%, whereas probability of survival, free from reoperation (after definitive surgery), was 65% at 10 years. This group found that biventricular repair was achieved in most patients with double-outlet right ventricle with low risk. However in this experience, a Fontan procedure was associated with a lower surgical mortality in those with complex double-outlet right ventricle.

The group from the Marie Lannelongue Hospital in Paris has had a very extensive experience with the repair of all forms of double-outlet right ventricle.[71,72,76–79,81] They have employed strategies to accomplish a biventricular repair whenever possible. Belli and colleagues from this institution reported in 1998 the outcomes in 154 consecutive patients who underwent biventricular repair for double-outlet right ventricle from 1985 through 1996.[76] The presence of bilateral infundibular structures was the major inclusion criterion (142 patients). According to the relationship of the ventricular septal defect (VSD) to the great arteries, there were 86 patients with a subaortic VSD (56%), 45 patients with a subpulmonary VSD (29%), 18 patients with a noncommitted VSD (12%), and 5 patients with a doubly committed VSD (3%). Sixty-five patients (42%) had undergone previous palliative procedures. At repair, the median age was 10 months, and the median weight was 6.5 kg. Two main types of repair were used: intraventricular baffle repair ($n = 115$) and arterial switch operation with VSD-to-pulmonary artery baffle ($n = 39$). There were 14 hospital deaths (9%; 70% confidence limit [CL], 7% to 12%). The only significant risk factor for early death was the presence of congenital mitral valve anomalies ($P = 0.02$). Twenty-eight patients (18%) required 39 repeat operations. The repeat operation rate was higher in patients with associated VSD enlargement at baffle construction ($n = 29$; 19%) ($P = 0.01$). There were 6 late deaths (4%; 70% CL, 2% to 7%). Patients presenting with pulmonary stenosis constituted a low-risk group for global death ($P = 0.008$). The median follow-up was 52 months. Ten-year actuarial survival and survival with freedom from repeat operation rates were 86% and 62% (70% CL, 83% to 89% and 54% to 70%), respectively. Jacobs in an editorial[118] to this paper concludes his comments with the same question posed by Delius and his colleagues: "Is a high-risk biventricular repair always preferable to conversion to a single ventricle repair?"[119] Some have clearly answered that question.[120,121]

The same group with Belli again as first author reported in 1999 the outcome of 23 patients with a double-outlet right ventricle and non-committed VSD who underwent biventricular repair between January 1987 and December 1997.[122] Nine (39%) had undergone previous palliation. The median age was 20 months at the time of the repair and the median weight was 8.5 kg. Two main types of repair were used: intraventricular baffle repair ($n = 21$) and arterial switch operation with VSD to pulmonary artery baffle ($n = 2$). At repair, 12 (52%) patients required concomitant VSD enlargement. In two other patients presenting with restrictive inlet VSD associated with tricuspid attachments, crossing the subaortic pathway biventricular repair was abandoned at operation. There were two hospital deaths (9%, 70% CL: 3–19%). Eight patients (35%, 70% CL: 23–48%) underwent nine reoperations, six for subaortic stenosis. No late death occurred. At last visit, all patients were asymptomatic and only two had cardiac medication. On the basis of this experience, this group concluded that biventricular repair of double-outlet right ventricle with non-committed VSD was possible in the vast majority of cases with comparable results to other subsets of double-outlet right ventricle. However, after repair the subaortic region is at risk for development of stenosis. A similar experience was reported by Lacour-Gayet and his colleagues reporting the approach of tunneling the left ventricle through the non-committed ventricular septal defect to the pulmonary infundibulum and then performing the arterial switch.[122A] This was accomplished successfully in 10 patients with one non-cardiac death. This approach required superior enlargement of the ventricular septal defect to prevent subaor-

tic stenosis. Barbero-Marcial and his colleagues have advocated the advantages of multiple patches in the repair of double-outlet right ventricle with non-committed VSD,[123] an approach he and his group have taken in 18 patients. There were two early and three late deaths. The authors conclude that the use of multiple patches for biventricular repair of double-outlet right ventricle with non-committed VSD simplifies the operation,[123] indeed making the operation a reality where a one-patch technique seemed impossible.[124] One of the more difficult groups of patients includes those with double-outlet right ventricle and a complete form of atrioventricular septal defect.[71,72,76,81,88,117,117A,117B,119–122,125–129] Some of these patients can be managed with a biventricular repair, but others have advocated univentricular palliation.[119–122] Uemura and his colleagues reported the outcome of eight patients with double-outlet right ventricle and doubly committed ventricular septal defect.[101] Pulmonary stenosis was present in two patients and interruption of the aortic arch in a third patient. All patients survived intraventricular rerouting. Wilkinson reported in 2002 the surgical results of 23 patients with double-outlet right ventricle and the complete form of atrioventricular septal defect treated between 1978 and 1993 at the Royal Children's Hospital in Melbourne.[5] Using a variety of reparative and palliative techniques there was one death among 18 patients. Tchervenkov has reviewed the surgical strategies employed to correct double-outlet right ventricle and the complete form of atrioventricular septal defect.[128A] He facilitated repair by enlarging the ventricular septal defect anteriorly, a maneuver termed ventricular septal defect translocation. This allowed closure of the ventricular septal defect to the aorta and a conduit was used to treat the associated pulmonary outflow tract obstruction.

Subaortic obstruction may be present before operation and develop as a complication of repair.[15] We have summarized elsewhere those mechanisms responsible for preoperative systemic outflow tract obstruction.[15] The ventricular septal defect may be restrictive in some patients, more commonly when the defect is subaortic, but a subpulmonary defect may also be obstructive. In the setting of the Taussig–Bing form of double-outlet right ventricle, the right ventricular infundibular aortic outflow tract may be intrinsically narrowed, wedged between the ventriculoinfundibular fold laterally and medially by the prominent infundibular septum.[15] Serraf and his colleagues have reported their experience with 30 patients with preoperative subaortic obstruction complicating double-outlet right ventricle operated between 1981 and 1992.[117A] Using a variety of surgical techniques to alleviate the systemic outflow tract obstruction, there were two early and one late deaths. Actuarial survival and freedom from reoperation were 86.6% and 87%, respectively. In some patients not considered preoperatively to have a restrictive ventricular septal defect, left ventricular volume unloading operations may lead to early changes both in ventricular geometry and ventricular septal defect size.[117B] Cognizant of these observations, one should usually consider enlargement of the ventricular septal defect when possible, acknowledging especially when the ventricular septal defect is "borderline" in size, its potential to become smaller.

Surgical algorithms for patients with double-outlet right ventricle are summarized in Table 28-1.

In a separate paper from the Marie Lannelongue Hospital, Piot and his colleagues report the echocardiographic appearances of subaortic obstruction following correction of double-outlet right ventricle in 8 children reoperated between January 1994 and June 1996.[130] The initial repair of the double-outlet right ventricle was performed before 3 months of age in 6 patients. Those patients with subaortic ventricular septal defects (4 cases) and those with non-committed ventricular septal defects (2 cases) had been treated by tunneling between the left ventricule and the aorta, and those with subpulmonary ventricular septal defects (2 cases) by tunneling between the left ventricle and pulmonary artery and then performing the arterial switch operation. Reoperation for subaortic obstruction was performed after 18 to 33 months. The instantaneous maximal gradient measured by Doppler echocardiography ranged from 60 to 145 mmHg. The causes of the postoperative subaortic obstruction were stenosis of the tunneling patch ($n = 2$), subaortic fibrous ring ($n = 3$), muscular septal hypertrophy ($n = 1$), anterolateral muscular hypertrophy ($n = 1$), relics of tricuspid tissue inserted on the infundibular septum ($n = 1$). Subaortic obstruction was diagnosed in the echocardiographic subcostal views in all cases; the nature of the obstruction was determined in 6 of the 8 cases. The mechanism of obstruction by stenosis of the tunneling patch was only detected in 1 of the 2 cases. In this regard, cross-sectional echocardiographic imaging has largely replaced cardiac catheterization with angiography, especially in those who have not had prior palliation.[131] Hemodynamic investigation may still be necessary in those patients presenting late with unprotected pulmonary blood flow, and angiography may complement the echocardiographic examination in those patients with multiple ventricular septal defects, concerns about ventricular hypoplasia, or where there are specific concerns about coronary artery anatomy.[56]

Table 28-1 Surgical algorithms for patients with double-outlet right ventricle

Associated anomaly	Surgical approach
Subaortic ventricular septal defect	Primary repair
Subaortic ventricular septal defect and pulmonary stenosis	Treat like tetralogy
Subpulmonary ventricular septal defect	Arterial switch, or Kawashima
Doubly committed	Repair
Remote	Intraventricular repair or Fontan

One of the more difficult anatomic features complicating the management of the patient with double-outlet right ventricle is straddling of the atrioventricular valve.[66–71] In the presence of major straddling of an atrioventricular valve, most abandon a biventricular repair, opting instead for univentricular palliation.[119–121] Yet clearly biventricular repair has theoretical advantages because it has the potential for establishing normal anatomy and physiology. Since 1984, Serraf and his colleagues again from the Marie Lannelongue Hospital operated on 34 patients with double-outlet right ventricle ($n = 15$) or transposition of the great arteries ($n = 19$) with isolated straddling tricuspid valve ($n = 17$), isolated straddling mitral valve ($n = 9$), both mitral and tricuspid straddling ($n = 2$), or abnormal insertion of tricuspid ($n = 7$) or mitral ($n = 2$) chordae in the left ventricular outlet, precluding an adequate tunnel construction.[71] Straddling was categorized according to the location of the papillary muscle insertion in the opposite ventricular chamber: type A, on the edge of the ventricular septal defect ($n = 14$); type B, on the opposite side of the ventricular septum away from the

edge of the defect ($n = 8$); type C, on the free wall of the opposite ventricular chamber ($n = 8$). Abnormal chordal insertions were classified according to the location of their attachments around the edges of the defect. Three types of chordal distribution were identified: on the aortic conus, on the pulmonary conus crossing the ventricular septal defect, or around the defect closing it like a curtain. All but three patients had two ventricles of adequate size. Sixteen patients underwent palliation. Median age at the definitive operation was 6.5 months (range 1 to 130 months). Thirty patients underwent a biventricular repair and four had a univentricular repair. Biventricular repair was achieved by an arterial switch operation in 18 patients and by tunnel construction from the left ventricle to the aorta in 12. In isolated straddling of types A and B, the ventricular septal defect was closed by adjusting the septal patch on the ventricular side above the straddled papillary muscle. In type C, the patch was sewn over the papillary muscle by applying it on the septum. In double straddling, the ventricular septum was incised between the two papillary muscles, and an ellipsoid patch was used to reconstruct the septal defect, directing each subvalvular apparatus into its own ventricular chamber. When the abnormal chordae in the left outflow tract inserted on the aortic or pulmonary conus, the conus was incised and tailored to make a flap, leaving an unobstructed left ventricular outflow tract. In two patients the subvalvular apparatus was resected and reattached to the patch. Curtain-like chordae were a contraindication to biventricular repair in double-outlet right ventricle but not in transposition. There were four early deaths and one late death, all occurring in the group having biventricular repair. Death was due to myocardial ischemia ($n = 1$), right ventricular hypoplasia ($n = 1$), pulmonary hypertension ($n = 1$), and residual subaortic stenosis ($n = 1$). Two patients had moderate to severe postoperative atrioventricular valve incompetence, caused by a cleft in the mitral valve in one patient. Three patients were reoperated on for subaortic stenosis ($n = 1$), pulmonary stenosis ($n = 1$), and mitral regurgitation ($n = 1$). Mean follow-up of 30.7 ± 19.4 months was achieved in the survivors. All but one patient (univentricular repair) were in New York Heart Association class I, without atrioventricular valve incompetence. Actuarial survival at 4 years was 85.3% ± 3%. They concluded that straddling or abnormal distribution of chordae tendineae of the atrioventricular valves does not preclude biventricular repair in double-outlet right ventricle or transposition of the great arteries provided that the ventricles are of adequate size. Curtain-like abnormal tricuspid chordae remain a contraindication to biventricular repair in double-outlet right ventricle. Fraisse and colleagues have discussed the management and outcome of patients with abnormal ventriculoarterial connections and a cleft mitral valve.[69] Firstly, from their review of the literature, they state that mitral valve anomalies are identified and may complicate arterial repair in from 2.8% to 5% of patients. Also they state that in autopsy studies, the incidence of mitral valve anomalies is considerably higher, approaching 30%. They identified 21 patients operated on with a cleft mitral valve, abnormal ventriculoarterial connections, and two well-developed ventricles. The majority of patients in this experience had transposition of the great arteries. Eight patients had ventricular outflow obstruction due to the mitral valve, and 2 had more than mild mitral regurgitation. One patient required initial mitral valve surgery. Eleven patients underwent biventricular repair, associated with mitral valve repair in two cases: arterial switch operation ($n = 4$), Senning operation ($n = 3$) associated with an arterial switch operation in one case, intraventricular repair ($n = 3$), and Rastelli-type extracardiac conduit repair ($n = 1$). Single-ventricle palliation was performed in 10 patients with major straddling of the mitral valve ($n = 5$), outflow tract obstruction ($n = 2$), and noncommitted or multiple VSDs ($n = 3$). There were three hospital deaths, two of which occurred after biventricular repair and one after an early reoperation after a bidirectional cavopulmonary anastomosis. Postoperatively after biventricular repair, 1 patient required permanent pacemaker implantation and 3 patients were reoperated on for subaortic stenosis ($n = 1$) and mitral regurgitation ($n = 2$), with one late death. By multivariate analysis, patients with a double-outlet right ventricle were at greater risk of death ($P = 0.04$). After a mean follow-up period of 60.7 months (± 68.6 months), 16 patients are in New York Heart Association (NYHA) class I. One patient with a moderate mitral regurgitation on Doppler study is in NYHA class II. On the basis of this experience they concluded that the surgical management of this group of patients remains controversial. A biventricular repair may not always be feasible, especially in cases of complex intracardiac anatomy associated with major straddling of the mitral valve. Single-ventricle palliation can be achieved in these patients, although it is unknown whether the long-term results are as good as those obtained with biventricular repair.[69]

Tchervenkov and his colleagues from the Montreal Children's Hospital reported in 1995 the outcomes in 24 consecutive neonates and infants with double-outlet right ventricle and atrioventricular concordance (median age, 4 months) who underwent anatomic biventricular repair beginning in May, 1989.[132] One patient (4%) had undergone prior pulmonary artery banding but was still repaired as a neonate at 22 days of age. Twelve patients had a subaortic ventricular septal defect (VSD), 5 patients a subpulmonary VSD, 3 patients doubly committed VSD, and 4 patients a noncommitted VSD. Sixty-nine of 72 associated lesions were repaired simultaneously. Four types of repairs were used: intraventricular rerouting in 16 patients, arterial switch operation with VSD closure into the pulmonary artery in 4 patients, Rastelli-type repair with extracardiac conduit in 3 patients, and the Damus–Kaye–Stansel repair with concomitant repair of aortic arch obstruction in 1 patient. Ventricular septal defect enlargement was necessary in 15 patients. Repair of subpulmonary stenosis and of subaortic stenosis was carried out in 13 and 4 patients, respectively. Three patients underwent simultaneous repair of aortic arch obstruction with no mortality. Two of the patients with noncommitted VSD had simultaneous repair of complete atrioventricular canal and repair of severe pulmonary venous obstruction. The perioperative mortality was 8% (2 patients), and there was one late death (4%). Two patients (9%) underwent early successful reoperations (5 and 8 weeks postoperatively). The two reoperations were for residual VSD (1 patient) and severe mitral regurgitation (1 patient). All 21 survivors are alive at a mean follow-up of 40 months (range, 7 months to 6 years). The estimated 5-year actuarial survival was 88%, with no deaths after 2 months postoperatively. Ninety-five per cent of long-term survivors had no restriction of physical activities because of cardiac status and are receiving no cardiac medications.

Aoki and his colleagues from the Children's Hospital in Boston reported in 1994 a 10 year institutional experience with the repair of 73 patients with double-outlet right ventricle.[133] Five types of repair were used during the study period: intra-

ventricular tunnel repair, arterial switch with ventricular septal defect-to-pulmonary artery baffle, Rastelli-type extracardiac conduit repair, Damus–Kaye–Stansel repair, and atrial inversion with ventricular septal defect-to-pulmonary artery baffle. Overall actuarial survival estimate at 8 years is 81%. The presence of multiple ventricular septal defects and patient weight lower than the median were nearly significant risk factors for early mortality ($P < 0.06$). Nineteen patients (26%) required 24 reoperations. Patients with subaortic ventricular septal defects were significantly reoperation free ($P < 0.05$). Patients with noncommitted ventricular septal defects were at significantly higher risk for reoperation during the study period ($P < 0.05$). The prevalence of late right or left ventricular outflow obstruction in the non-subaortic VSD groups was concerning. The median age at repair in this series was 0.76 years, and there was a nonsignificant trend ($P = 0.13$) for early mortality in patients younger than 1 year of age. These patients tended to have other serious cardiac anomalies associated with double-outlet right ventricle that necessitated early operation. Wilkinson documented the Royal Children Hospital's results with surgical treatment of double-outlet right ventricle with multiple ventricular septal defects.[5] Twenty-three patients were treated with a variety of surgical procedures with 5 deaths.

Brown and his colleagues reported their 20-year (1980–2000) experience with the surgical repair of 124 patients with double-outlet right ventricle.[133A] Four basic types of repair were used in these patients including an intraventricular tunnel repair; use of a valved or non-valved conduit, an arterial switch repair for those with a subpulmonary ventricular septal defect, and staging to the Fontan. For the entire series, there were 6 early deaths (4.8%), 4 late deaths (3.2%) and 2 heart transplants (1.6%). The overall 15-year survival for those with an uncomplicated form of double-outlet right ventricle and a subaortic ventricular septal defect was 95.8%; for those with a subpulmonary ventricular septal defect, 89.7%; and for those with a complex form of defect, 89.5%. Freedom from reoperation for these three groups at 15 years was 87%, 72%, and 100%, respectively. This group found that the ventricular septal defect, was restrictive on preoperative investigation in only 2 patients, but ventricular septal defect enlargement by resection of the infundibular septum was performed in an additional 14 patients to improve the baffle geometry or to reduce the potential for late transseptal obstruction.[133A] In follow-up, residual left ventricular outflow tract obstruction was identified in 3 patients, 2 considered mild and moderate in one. Wu and his colleagues reported the excellent outcomes in 9 patients of primary repair of double-outlet right ventricle with left-malposition of the great arteries using a modified Rastelli repair.[133B] All patients had a subaortic infundibulum and a levopositioned aorta. Eight of the 9 patients had either valvular or subvalvular stenosis. The ventricular septal defect was subpulmonary in 3 and noncommitted in 6. There were no operative deaths and no injury to the right coronary artery that typically crosses the stenotic pulmonary outflow tract in front of the pulmonary valve.[133B]

Preminger and her colleagues first called attention in 1994 to a peculiar type of "intramural" residual ventricular septal defects seen after repair of conotruncal anomalies.[134] These departed from the more common postoperative ventricular septal defect which usually resulted from additional defects, patch dehiscence, or incomplete closure and lie in the septal plane. However, after a right ventricular aorta is baffled to the left ventricle, the ventricular septal defect patch and RV free wall form part of the systemic outflow tract. This "neo-left ventricular" outflow tract thus provides a potential location for residual interventricular communications which are out of the septal plane. In a relatively short period of time from June 1990 to October 1992, they observed such defects in 8 patients, 5–26 years old, after repair of double-outlet right ventricle ($n = 6$), tetralogy of Fallot ($n = 1$), or truncus arteriosus ($n = 1$). In each, the ventricular septal defect patch was anchored to the right ventricular free wall near the aortic root. None the less, channels were observed around the edge of the patch, between the neo-systemic outflow tract and the right ventricle. All patients had right ventricular hypertension; in seven, the pulmonary-to-systemic flow ratio (Qp:Qs) was ≥ 2. These defects were difficult to close, either surgically or with transcatheter umbrella closure, and two patients died. Belli and his colleagues reported in 2000 their experience with the residual intramural ventricular septal defect which they define as resulting from the insertion of the patch within the trabeculated right ventricular free wall related to the ventriculoinfundibular fold (Fig. 28-3).[135] This creates a communication through the intertrabeculated spaces to the right ventricular cavity. They had difficulty in exposing and repairing this type of defect through a right ventricular approach, but found the defects easy to close through the aortic root.[135]

One of the recurrent postoperative themes is that of subaortic stenosis (Fig. 28-4).[136] This complication has been documented after most forms of correction of double-outlet right ventricle, and is often related to the tortuous tunnel between

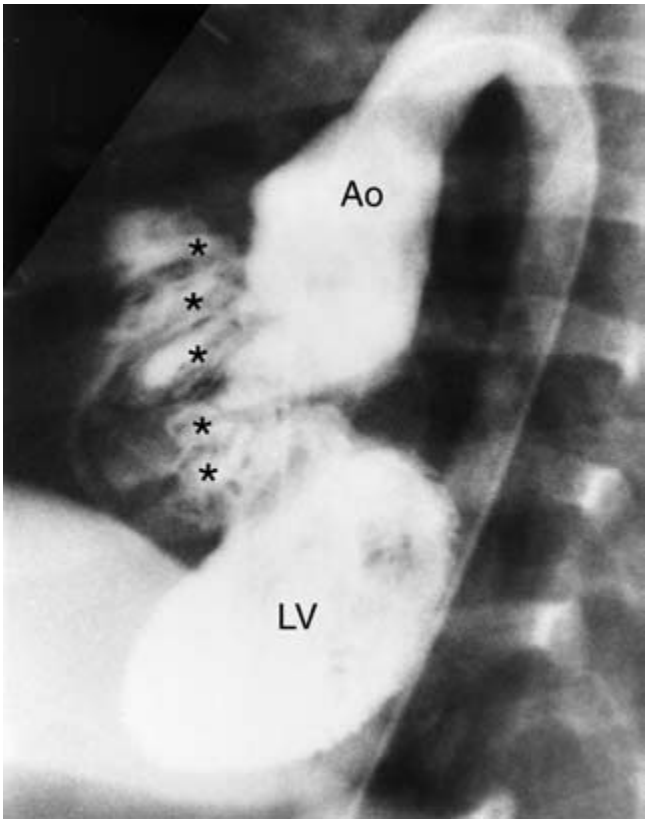

Fig. 28-3 Residual intramural interventricular defects. Postoperative left ventriculogram shows shunts through the residual defects flowing through the intertrabecular spaces in the right ventricle (asterisks). Ao, aorta; LV, left ventricle.

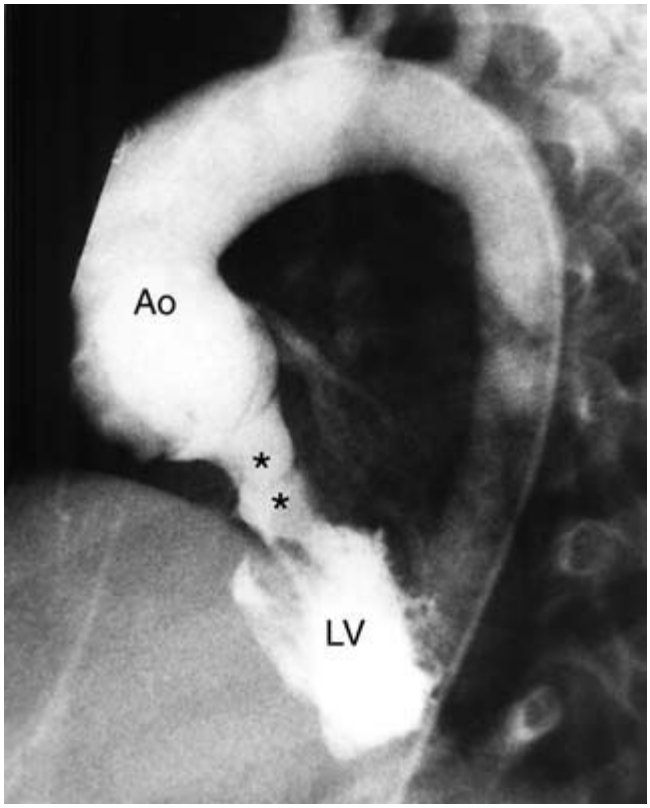

Fig. 28-4 Postoperative subaortic stenosis (asterisks) after repair of double-outlet right ventricle with a subaortic ventricular septal defect. Ao, aorta; LV, left ventricle.

the left ventricle and aorta.[71–74,76,79,81,98,106,117,122,123,124–130] Of 180 patients who underwent biventricular repair of double-outlet right ventricle at the Marie Lannelongue hospital in Paris, 9 (5%) required reoperation because of subaortic stenosis.[136] The median age at biventricular repair was 4 months. The subaortic stenosis was progressive, beginning with an immediate postoperative left ventricle to aortic gradient of 10 ± 10 mmHg and became 84 ± 27 mmHg over a mean interval of 45 ± 66 months. At reoperation the obstruction was caused by the protrusion of the inferior rim of the ventricular septal defect associated with subaortic hypertrophied muscle and fibromembranous tissue. The surgical technique to relieve the subaortic stenosis was an extended septoplasty. According to the authors,[136] an incision was made in the septal patch and was extended into the muscle towards the apex creating a large opening of the left ventricular outlet. A new patch was then positioned to streamline the left ventricular outflow tract. The extended septoplasty improved the left ventricular outflow tract obstruction and no patient died at reoperation.

Some patients including those with mitral atresia, major straddling of one or both atrioventricular valves, ventricular hypoplasia or double-outlet right ventricle with an intact ventricular septum may be candidates for single ventricle palliation.[119–121,137,138] Those patients with double-outlet right ventricle and an intact ventricular septum may have spectacular ventriculocoronary connections,[26] and may be at risk for adverse coronary artery events. The Fontan procedure, its varying staging maneuvers, and postoperative complications are considered in Chapters 35–37. For the outcomes of the atrial or arterial switch protocols which either have been or are applied primarily to the patient for double-outlet right ventricle with subpulmonary ventricular septal defect, please see Chapters 25A and 25B. In those patients undergoing intraventricular repairs, long-term issues are likely related to:

- residual intramural ventricular septal defects (Fig. 28-3)
- systemic outflow tract obstruction (Fig. 28-4)
- pulmonary outflow tract obstruction
- pulmonary regurgitation (for those undergoing "tetralogy-like" repair
- fate of the right ventricular–pulmonary artery conduit
- form and function of atrioventricular valves
- long-term problems related to pacemaker therapy
- damage to the right coronary artery.

In summary, what are the fundamental issues with hearts considered to have double-outlet right ventricle?

- The morphology is diverse, with abnormalities of situs, atrioventricular connection, size and position of the ventricular septal defect relative to the great arteries. The spatial relationships between the great arteries vary considerably as well.
- Particular confounding features include straddling and overriding atrioventricular valves, cleft mitral valve, systemic outflow tract obstruction, obstructive anomalies of the aortic arch, and multiple ventricular septal defects.
- Numerous surgical strategies have been employed to correct hearts with double-outlet right ventricle including atrial repair of the Mustard or Senning-type with closure of the ventricular septal defect; the Kawashima or Rastelli approach; arterial switch repair with closure of the ventricular septal defect; the Damus–Kaye–Stansel approach; multiple intraventricular patches.
- Some consider univentricular palliation in patients with complex forms of double-outlet right ventricle preferable to high risk biventricular repair.
- The Mustard–Senning approach with ventricular septal defect closure and Damus–Kaye–Stansel approaches are for-the-most-part obsolete and are no longer employed.
- The specific complication will depend in part on the surgical technique employed. Systemic outflow tract obstruction may occur at the VSD level as the left ventricle as tunneled to the aorta, or within the right ventricle itself.

Part II: Double-outlet left ventricle

Double-outlet left ventricle is a rare congenital cardiac anomaly characterized by origin of both great arteries, or more than 50% of each arterial root above the morphologically left ventricle.[1–7] Wilkinson suggests that double-outlet left ventricle accounts for only about 5% of all hearts with a double-outlet ventriculoarterial connection in the setting of a biventricular heart, corresponding then to an incidence of less than 1 in 200,000 births.[7]

In hearts where the interventricular septum is intact, the diagnosis can be readily established, without debate or discussion.[1,8,9] However when a ventricular septal defect is present, it is possible for one or both arterial orifices to override the ventricular septal defect, and then it may become more difficult to assign the ventriculoarterial connection. In the first case of double-outlet left ventricle well described by Paul and his colleagues and where the ventricular septum was intact, both the subaortic and subpulmonary infundibula or conuses were deficient.[1] Initially this feature was considered important in the

setting of double-outlet left ventricle. Some years later Van Praagh and colleagues studied infundibular development in 31 hearts with double-outlet left ventricle and a right-hand or D-ventricular loop, characterizing the infundibular anatomy as follows: a subpulmonary infundibulum was noted in 48%; a subaortic infundibulum in 26%; bilateral infundibuli were represented in 12%; and the infundibula were grossly deficient in 13%.[4] Thus the diagnosis of double-outlet left ventricle indicates an abnormality of ventriculoarterial connection, not an infundibular anomaly *per se*. Van Praagh and his colleagues considers three factors fundamental to the morphogenesis of double-outlet left ventricle.[3,4] In addition to the infundibular maldevelopment, hypoplasia of the morphologically right ventricle and malalignment of the conotruncus from the ventricle are seemingly important in the genesis of this disorder. Thus it is not surprising that disturbances of the right atrioventricular junction are defined in a considerable number of patients with this double outleft ventricle.[5] These abnormalities include tricuspid atresia, stenosis, straddling and override. Bharati and her colleagues have also called attention to the frequently observed abnormalities of the tricuspid valve and right ventricular underdevelopment in patients with double-outlet left ventricle.[5] Like the designation of double-outlet right ventricle, this diagnosis is independent of situs or atrioventricular connection.[3,6,7,10–12]

Manner and colleagues have identified double-outlet left ventricle in a chick embryo.[13] They found the anomaly leading to double-outlet left ventricle is a misalignment of the ventricular septum. The subarterial portion of the ventricular septum above the crista supraventricularis was not oriented in the normal oblique plane between the pulmonary and aortic valve, but is oriented in a frontal plane anterior to the origin of both great arteries. The consequences of this anomaly are the separation of the right-ventricular infundibulum from the origin of both great vessels (double-outlet left ventricle) and a lack of continuity between the malpositioned portion of the ventricular septum (posterior wall of the right-ventricular infundibulum) and a septum dividing the semilunar valve level. The infundibulum of the right ventricle is derived from the upstream portion of the embryonic conotruncus (conus) whereas the semilunar valves and great arteries are derived from its downstream protion (truncus arteriosus) and the aortic sac. Therefore, their findings suggest that the division of the conotruncus is performed by at least two different septa, one dividing the conus and another dividing the truncus arteriosus and aortic sac. The misalignment of the ventricular septum leading to this type of double-outlet left ventricle could result from a misalignment of the septal anlagen of the embryonic conus, the conus ridges. Interestingly, this malformation like other conotruncal malformations has also been identified in the dog.[14]

Associated malformations

The most exhaustive review of hearts with this condition has been carried out by Van Praagh and his colleagues in a report referred to earlier in this chapter.[3] They compiled 109 patients with this disorder, and subcategorized them into 8 anatomic types with two well-formed ventricles, and 7 anatomic types with only one well-developed ventricle. This analysis indicated that in those hearts with two well-formed ventricles, double-outlet left ventricle with a subaortic ventricular septal defect was the most common form, being identified in 62 of the 80 biventricular cases. They defined 4 subtypes of double-outlet left ventricle with a subaortic ventricular septal defect, with the most frequent of these, the so-called tetralogy-type. Less common are those forms resembling posterior transposition; transposition, ventricular septal defect with leftward aorta; and the form with aortic stenosis and coarctation. A subpulmonary ventricular septal defect was observed in 11 of the 80 biventricular hearts, and a doubly committed ventricular septal defect in 7. Other infrequent forms of double-outlet left ventricle with a biventricular heart include hearts exhibiting atrioventricular concordance with atrial situs inversus; atrioventricular discordance with situs solitus (the "corrected transposition" type); and atrioventricular discordance in situs inversus.[1–13,15–22] Tricuspid atresia is the most common anomaly of the atrioventricular junction in patients with a univentricular atrioventricular connection, occurring in 20 of 29 cases.[1,3,5,6,8,9,17,18] Ebstein's malformation of the tricuspid valve was observed in a few patients, and mitral atresia in one. Juxtaposition of the atrial appendages, abnormalities of systemic and pulmonary venous connections, and cor triatriatum have all been described in hearts with double-outlet left ventricle. Van Praagh and others have described double-outlet from the dominant left ventricle in patients with a univentricular atrioventricular connection.[2,3,20] Amongst those hearts with double-outlet left ventricle and an intact ventricular septum, the right ventricle is hypoplastic, and ventriculocoronary connections are present.[1,8,9]

Outcome analysis

There are too few such hearts to permit a meaningful outcomes analysis and there is little information about fetal recognition of this rare anomaly. While in the literature review carried out by Van Praagh and his colleagues more than a decade ago, 109 hearts with double-outlet left ventricle were identified,[3] this number has certainly increased. Yet no institution has had experience with a substantial number of these patients. Sakakibara. Pacifico, and Kerr and their respective colleagues reported the earliest experience with biventricular repair of a number of these patients.[23–25] The repair in this era usually consisted of closure of the ventricular septal defect, closure as well of the left ventricle-to-pulmonary artery pathway, and insertion of a right ventricle-to-pulmonary artery conduit. Some have been able to carry out a Fallot-type repair when the ventricular septal defect is subaortic and the spatial relationships between the great arteries are advantageous. There has been considerable discussion as to the optimum surgical approach in patients with double-outlet left ventricle.[26–28] For the most part, the particular surgical technique is dictated by the cardiac anatomy.[29–33] Although most biventricular repairs have utilized a conduit between right ventricle and pulmonary artery, some have successfully utilized the maneuver of pulmonary root translocation.[34–36] The downside of the conduit is the reality and necessity of conduit replacement. Pulmonary root translocation will leave the patient with pulmonary regurgitation and the long-term effects of this on the right ventricle have been discussed in Chapter 16. Imaging has evolved from angiocardiography to cross-sectional echocardiography and to magnetic resonance imaging.[37–45]

The thorough compilation of hearts with double-outlet left ventricle by Van Praagh reveals that at least 70% of such specimens are characterized by one developed ventricle, and are

thus candidates for univentricular palliation[3] (see Chapters 35–37). It is likely that some patients with only moderate tricuspid stenosis and right ventricular hypoplasia may be candidates for a one-and-a-half ventricle repair. In those patients with double-outlet left ventricle with an intact ventricular septum, ventriculocoronary artery communications may be conspicuous and may exact a toll of the left ventricle, analogous to some patients with pulmonary atresia and intact ventricular septum[1,8,9] (see also Chapter 30).

All references can be found at the end of the book. See pp. 765–70 for Chapter 28.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

29

Robert M. Freedom and Shi-Joon Yoo

Tricuspid Atresia

Tricuspid atresia is an uncommon form of congenital heart disease, clearly less frequent than transposition of the great arteries, tetralogy of Fallot, or common arterial trunk. Unquestionably described by Kreysig in 1817,[1–3] the clinical features of tricuspid atresia were first characterized by Bellet and Stewart in 1933[4] and Taussig and Brown in separate publications in 1936.[5,6] In the classic form of tricuspid atresia, the situs is normal, the tricuspid valve is absent, and there is an obligatory right-to-left shunt at atrial level (Fig 29-1). The main ventricle is of left ventricular morphology and there is a right-sided rudimentary right ventricle communicating with the dominant left ventricle through a ventricular septal defect. When first described, the left ventricle supported the aorta and the hypoplastic right ventricle, the main pulmonary trunk. Thus the ventriculoarterial connections were concordant, or normal.

Incidence

The New England Regional Infant Cardiac Program (NERICP) provided a diagnostic frequency for tricuspid atresia of 0.057/1000 live births, although this probably slightly overestimates the frequency because of inclusion of left-sided atrioventricular valve atresias in the setting of a univentricular heart, L-ventricular loop-type.[7] The Baltimore–Washington Infant Study showed a lower prevalence at live birth of 0.039/1000 live births,[8] and data from the Pediatric Cardiac Care Consortium, a prevalence of 0.044.[7] Data from Toronto indicate a frequency for tricuspid atresia of 1/9956 live births or 1.2% of congenital heart disease.[10] There is little information on spontaneous fetal loss of babies with tricuspid atresia. Familial instances of tricuspid atresia have been reported.[9,11] Seven per cent of babies with tricuspid atresia in the NERICP had birth weights < 2.0 kg and 13% were considered to have severe extracardiac anomalies.[7] A rare case of tricuspid atresia has been associated with 22q11 deletion, and there is one report of tricuspid atresia and Ebstein's anomaly of the tricuspid valve in siblings.[11A,11B]

Morphology

One's understanding of both the morphology of tricuspid atresia as well as the natural history of patients with this disorder has evolved considerably over the past quarter century, precipitated in large part by Fontan's operation.[12] A number of morphologic expressions produce the physiology of tricuspid atresia; that is an obligatory right-to-left shunt at atrial level.[13–26] The classic morphological expression of tricuspid atresia is an absent right atrioventricular connection, rather than an imperforate one (Fig. 29-1). Characteristic of an absent atrioventricular connection is the absence of continuity, potential or otherwise, between the right atrium above and right ventricle below because atrioventricular sulcus tissue separates the floor of the right atrium and right ventricle (Figs 29-1A, 29-2).[13–26] A dimple is often observed in the floor of the right atrium, suggesting from the atrial perspective a potential connection between the atrium and ventricle.[20,21,26] This dimple, however, does not have potential connection with the rudimentary right ventricle and the atrioventricular connection is thus absent.[13–18,20,21,26] Interestingly, Wenink has examined microscopically the rudimentary right ventricle of patients with so-called classic tricuspid atresia, and there is some suggestion that even in patients considered to have an absent right atrioventricular connection that remnants of tension apparatus are present.[24] Less commonly the tricuspid valve will be imperforate with tensor apparatus interposed between a membranous or muscular imperforate tricuspid valve and the right ventricle (Fig. 29-1B).[27–37] Rarely, the morphologic basis for tricuspid atresia is an imperforate and displaced tricuspid valve, the imperforate Ebstein's form of tricuspid atresia.[36,37] In the classical expression of tricuspid atresia, the mitral valve connects with the morphologically and dominant left ventricle. The rudimentary right ventricle is right-sided and anterior, conforming to a d-ventricular loop.

The most common classification of tricuspid atresia, that originally proposed in 1949 by Edwards and Burchell, addressed both the type of ventriculoarterial connection and the clinical status of the magnitude of pulmonary blood flow (i.e. normal or concordant ventriculoarterial connections or discordant ventriculoarterial connections).[38] This classification has subsequently been revised to take into consideration those patients with a common arterial trunk (truncus arteriosus) as well as those patients with a univentricular heart of left ventricular type, L-loop pattern of internal organization, and an absent left atrioventricular connection.[39–42] The common and rare cardiac anomalies seen in the patient with tricuspid atresia have been fully catalogued. Some of these include atrioventricular septal defect; dextrocardia; anomalies of systemic and pulmonary veins; aortic atresia, fifth aortic arch; unroofed coronary sinus; divided left atrium; double-outlet ventricle; anatomically corrected malposition of the great arteries; juxtaposition of the atrial appendage, etc. Sanchez-Quintana and colleagues have studied the myoarchitecture and connective tissue in hearts with tricuspid atresia.[43] The overall architecture of the muscle fibers and its connective tissue matrix in hearts with tricuspid atresia

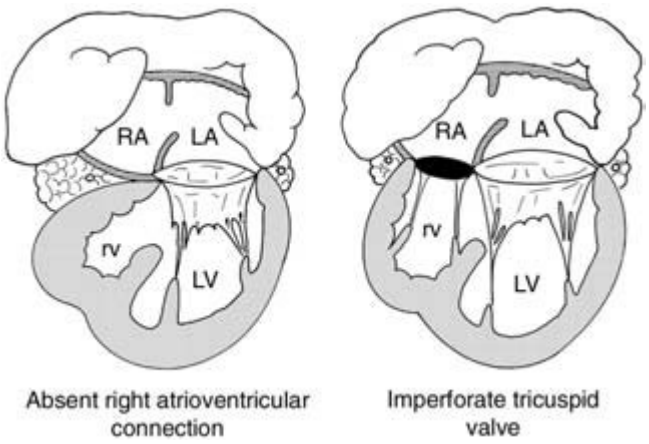

Fig. 29-1 Two forms of tricuspid atresia. It is more commonly due to absence of the right atrioventriuclar connection and much less commonly is an imperforate tricuspid valve. LA = left atrium; LV = left ventricle; RA = right atrium; rv = small right ventricle.

differs from normal with increased muscle and connective tissue. How this particular finding impacts on the long-term function of the left ventricle is unclear, but concerning.

Outcome analysis

Tricuspid atresia can be recognized in the fetus, as well as the usual coexisting abnormalities including ventricular septal defect, pulmonary stenosis and abnormalities of ventriculoarterial connection.[43A] Sharland has reported on the outcome of 84 fetuses with tricuspid atresia studied before the end of 1997.[43A] Twenty-two of these were found to have transposition of the great arteries and 7 of these 22 had aortic arch anomalies. Of the total group 54 sets of parents opted for termination of pregnancy; there were 2 intrauterine deaths, and 4 infant deaths.

Any number of clinical studies have attempted to define the natural and modified history of the patient with tricuspid atresia.[44–57] The outcome of patients with tricuspid atresia depends on the nature of the blood supply to the lungs and associated anomalies. Since the majority of patients with this condition have normal ventriculoarterial connections, and restrictive flow to the lungs, it is not surprising that progressive reduction in size of the VSD defines the clinical course of progressive cyanosis and the sequelae of hypoxemia.[58,59] Babies with tricuspid atresia and pulmonary atresia will usually present the earliest, coincident with ductal closure. About 20% of those with tricuspid atresia have a discordant ventriculoarterial connection or transposed great arteries.[59] Those without important pulmonary stenosis will usually die in infancy with congestive heart failure and pulmonary artery hypertension. This group tends to have an associated obstructive anomaly of the aortic arch, and this would of course accelerate clinical deterioration.

Until 1971, patients with tricuspid atresia with very reduced pulmonary blood flow were palliated with a variety of systemic-to-pulmonary shunts, and those past infancy with the classic Glenn or cavopulmonary shunt.[47–54] We reported on our early clinical experience with these shunts in 1975 and then in 1980.[50,51] The classic Blalock–Taussig shunt, Potts' shunt between the descending thoracic aorta and left pulmonary artery, Waterston shunt between the ascending aorta and right pulmonary artery were all used to augment pulmonary blood flow. The Potts' and Waterston shunts were often made too large, or grew, resulting in congestive heart failure and pulmonary artery hypertension. These shunts tended as well to distort by narrowing the pulmonary artery, often resulting in a substantially different pulmonary blood flow between right and left lung. Unfortunately, the complications of the Waterston and Potts' shunt, especially the propensity for causing pulmonary artery hypertension, excluded many of these patients from Fontan palliation.[60] Today, the Potts' and Waterston shunts are rarely used. None the less these shunts did provide acceptable palliation, and after all kinds of shunt, about 91% were alive 7 years after the shunting operation. For those patients with concordant ventriculoarterial connections and a very large ventricular septal defect, pulmonary blood flow could be controlled with banding of the main pulmonary trunk. However, most patients with concordant ventriculoarterial connections and increased pulmonary blood flow can be managed medically as the ventricular septal defect is usually only of moderate size and tends to narrow spontaneously.[59] Pulmonary artery banding could be used in the patient with discordant ventriculoarterial connections, and some of these patients required repair of an associated coarctation of the aorta. Progressive reduction in the size of the ventricular septal defect following pulmonary banding in those with transposition frequently resulted in systemic outflow tract obstruction (Fig. 29-3).[61–67] Data published some years ago from the Toronto Hospital for Sick Children showed that the classical Glenn shunt afforded excellent long-term palliation,[50–52] and in some of these palliation could be extended with creation of an axillary artery–vein fistula,[68] a maneuver first reported by Glenn and Fenn and others.[69,70] We reported our experience with this procedure in 11 patients.[68] Oxygen saturations generally increased and symptomatology improved, at the expense of course of volume loading the

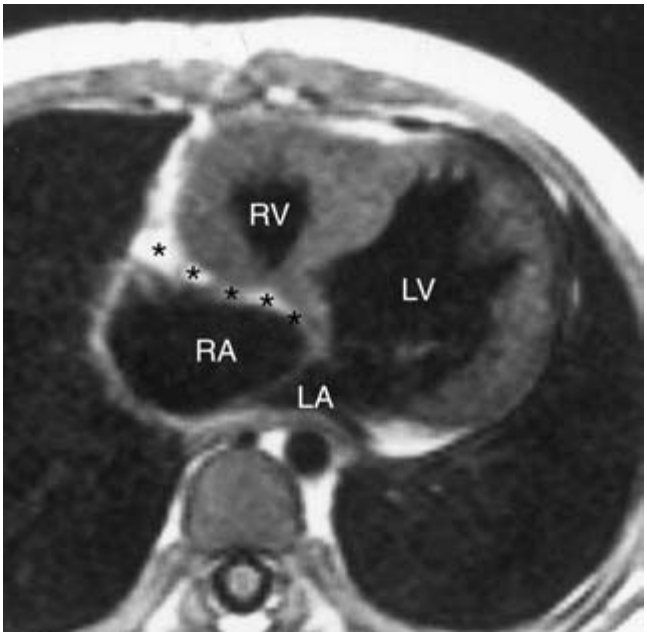

Fig. 29-2 Absent right atrioventricular connection seen in T1-weighted MR image. Notice that the epicardial fat tissue (asterisks) invaginates toward the center of the heart between the right atrium (RA) and the right ventricle (RV). LA = left atrium; LV = left ventricle.

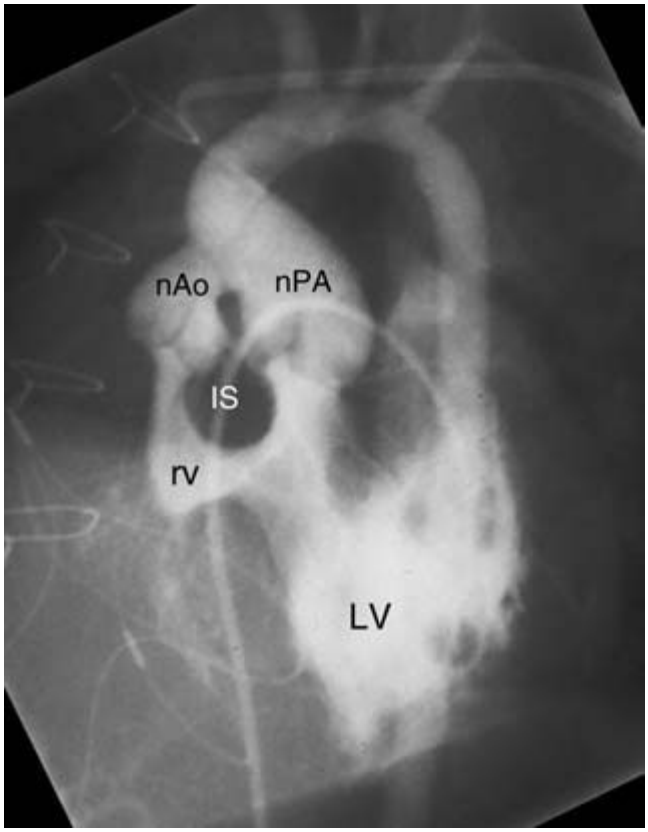

Fig. 29-3 Effect of pulmonary artery banding in a patient with tricuspid atresia with discordant ventrioculoarterial connection. The subaortic stenosis became severe with reduced size of the ventricular septal defect (d) and hypertrophy of the infundibular septum (IS). Damus–Kaye–Stansel operation was performed. LV = left ventricle; nAo = native aorta; nPA = native pulmonary artery; rv = right ventricle.

dominant left ventricle. For patients with concordant ventriculoarterial connections palliated only with a classical Glenn shunt, progressive diminution or closure of the VSD could effectively isolate the left pulmonary artery, a very important and serious complication.[50–52,59] Some patients have a very restrictive ovale foramen and this would limit cardiac output as well. In a rare patient the flap of the ovale foramen assumed aneurysmal proportions, herniating like a "ping-pong" ball into the left atrium and left ventricle.[71] There is ample clinical experience with balloon atrial septostomy in the patient with tricuspid atresia.[72]

Relatively little clinical information on the natural history of substantial cohorts of patients with tricuspid atresia who have received no therapy, either medical or surgical, has been published.[44–47] A rare individual with tricuspid atresia may survive many years without surgical intervention.[44–46,57] In this regard, Gerlis and his colleagues reported the case of a man who died at 60 years of age with a complex form of tricuspid atresia without any surgery.[45] But such long-term survival without surgical intervention is very uncommon. Fesslova and colleagues reported on 111 patients with tricuspid atresia seen from 1972 to 1982, most of whom had been palliated.[54] Nine per cent died during the first month; 13% within the first 3 months; and 20% during the first 6 months. Sixty-nine per cent of all deaths occurred during the first year of life. Six patients in this series died without surgery at a mean age of 32.2 ± 12.3 days. Similar results have been published by Patel and his colleagues.[48] Dick and his colleagues reported on the clinical course of 101 patients with tricuspid atresia seen at the Boston Children's Hospital from 1941, several years before the introduction of the Blalock–Taussig operation and 1973, just before the Fontan era began at their hospital.[47] Overall survival of this cohort to 15 years of age was *c*. 50% (Fig. 29-4). The overall surgical mortality in this review was 23% and this review did not include the Fontan experience. For those patients with reduced pulmonary blood flow and no surgical palliation, 90% died within the first year of life. The Prospective Bohemia Survival Study identified 39 children at birth with tricuspid atresia from the 815 569 children born between 1980 and 1990.[73] This gives a prevalence of 0.048 per 1000 live births or 0.78% of all heart malformations. Nearly 72% reached the age of 1 month; between the first and sixth month of age, the mean survival curve continued to decline to 48.72%, and at 1 year of age, the survival rate was 46.15%. The decline in the survival curve stopped at 10 years to 35.90% and remained at this level to 15 years of age.[73]

In 1989, we reported on the course of 84 infants with tricuspid atresia seen at the Toronto Hospital for Sick Children in the first year of life between 1970 and 1984 (Fig. 29-5).[55] This time period embraced the beginning of the Fontan era at our institution and the earliest clinical experience with prostaglandin administration. During this era, our Fontan mortality for tricuspid atresia was 6%, but we felt it important to examine the outcome of the entire cohort. For the entire cohort, an estimate of the probability of surviving for 1 year was 64% (95% CL, 54% to 74%) and to 8 years was 55% (95% CL, 44% to 66%). The overall surgical mortality for the palliative procedures was 35.8%, with 11 deaths in the first month of life. Of the nearly 40% of our entire cohort who died or who were excluded from the Fontan, the reasons included early death following initial palliative procedures, sudden cardiac death, or the development of subaortic stenosis, severe pulmonary artery distortion, and/or ventricular dysfunction. Over the past decade our institutional mortality for the Fontan procedure has fallen to < 3% and mortality for all forms of palliation leading to the Fontan for patients with tricuspid atresia has declined as well. Franklin and

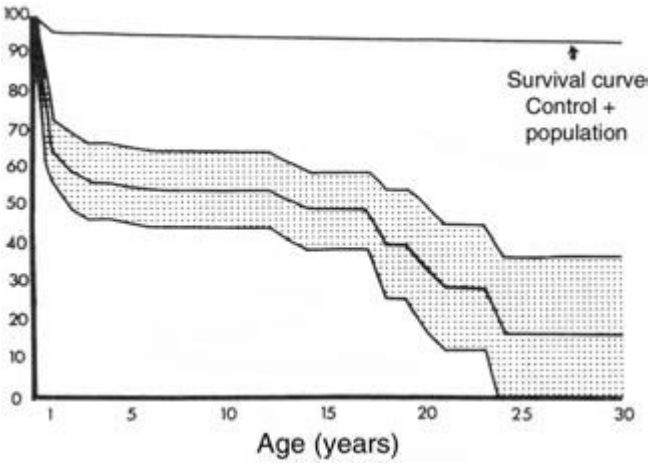

Fig. 29-4 Survival curve of 101 patients with tricuspid atresia seen at the Children's Hospital, Boston, from 1941 to 1973. (Reprinted from Dick *et al.*,[47] Copyright (1975), with permission from Excerpta Medica, Inc.)

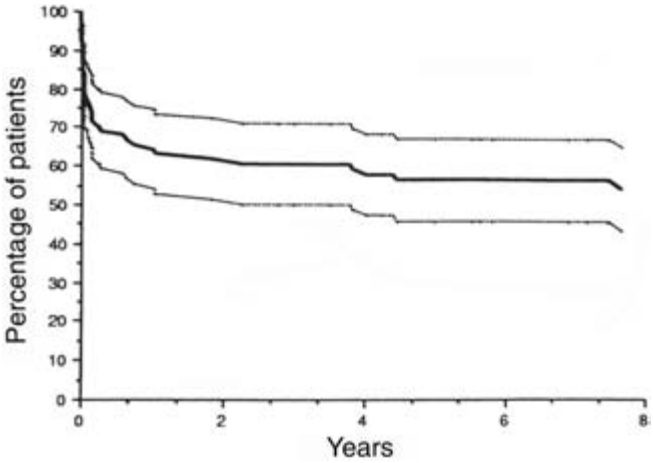

Fig. 29-5 Survival of patients presenting in infancy with tricuspid atresia to the Toronto Hospital for Sick Children. (Reprinted from Tam *et al.*,[55] Copyright (1989), with permission from Excerpta Medica, Inc.)

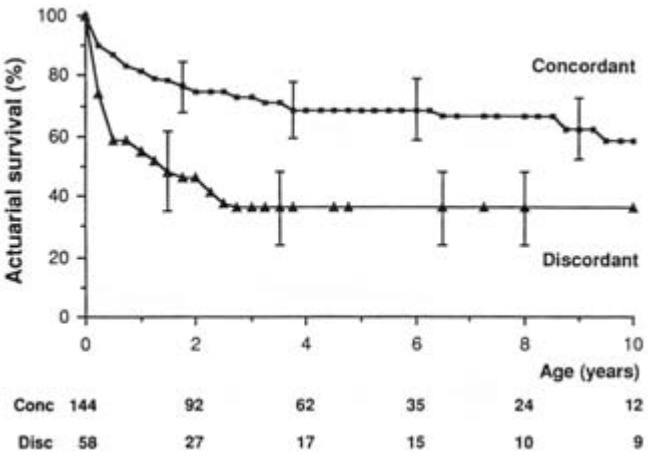

Fig. 29-6 Survival curves showing actuarial survival for patients with tricuspid atresia before definitive repair, comparing those with concordant to discordant ventriculoarterial connections. (Reprinted from Franklin *et al.*,[56] Copyright (1993), with permission from Lippincott Williams & Wilkins.)

his colleagues carried out a similar study, reviewing the survival and suitability for the Fontan procedure of 237 patients with tricuspid atresia presenting in infancy.[56] This very large clinical experience included patients seen at the London Great Ormond Street Hospital for Sick Children and the Royal Brompton within the first year of life from 1972 to 1987. Overall actuarial survival was 72% at 1 year, 53% at 5 years, and 46% at 10 years. Univariate risk-factor analysis established that discordant ventriculoarterial connections, pulmonary atresia, aortic arch obstruction, and subaortic stenosis were associated with poor survival (Fig. 29-6), virtually identical to our observations, while balanced pulmonary blood flow and older age at presentation were beneficial. In the consideration of palliative procedures, survival was worse for patients requiring banding of the pulmonary trunk with aortic arch repair. On retrospective review of 204 patients judged suitable for the Fontan at presentation, 99 (48%) are known to have died before a Fontan procedure or became unsuitable for such surgery during the follow-up.

We have recently extended our observations to 225 patients with tricuspid atresia diagnosed between 1971 and 1999 at the Toronto Hospital for Sick Children.[74] Twenty-one per cent had discordant ventriculoarterial connections; 75% of the entire cohort pulmonary outflow tract obstruction and 11% aortic outflow tract obstruction. There were a total of 72 deaths (32%), with 10 deaths before any intervention. Palliative procedures were performed in 203 patients, including 151 systemic shunts; 27 pulmonary artery banding; and 60 venous shunts; and overall 44 of these 207 patients died. 137 patients underwent a Fontan procedure with 7 early and 8 late deaths. Before Fontan, at least one procedure was performed in 90% of patients (n = 203). Forty-four deaths occurred after an initial palliation, 7 early deaths after Fontan procedure and 11 late deaths after the Fontan procedure. Total survival for the cohort was 81% at 1 year and 64% at 15 years. There were no significant changes in mortality with the Fontan procedure over the study time period. Survival following the Fontan procedure was 93%, 87% and 81% at 1, 5, and 10 years (Figs 29-7, 29-8). The Fontan procedure was performed in 137 (61%) of 225 patients. In 9 of these patients the Fontan operation was performed in a single stage, without any prior palliation. The types of connections that were

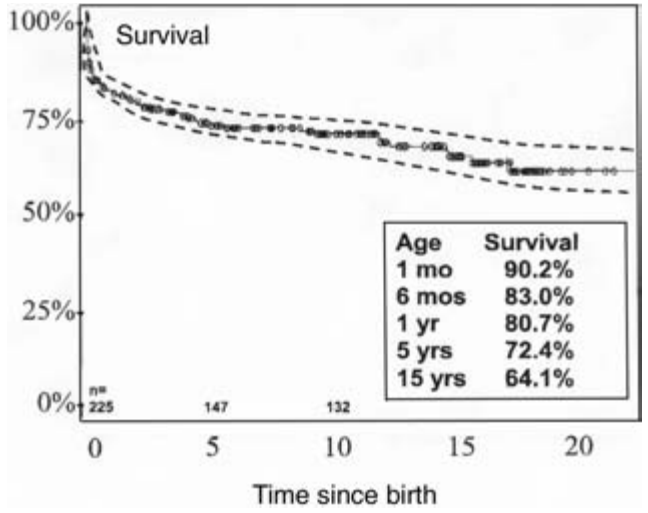

Fig. 29-7 Kaplan–Meier actuarial survival curve depicting survival from birth of Toronto cohort.

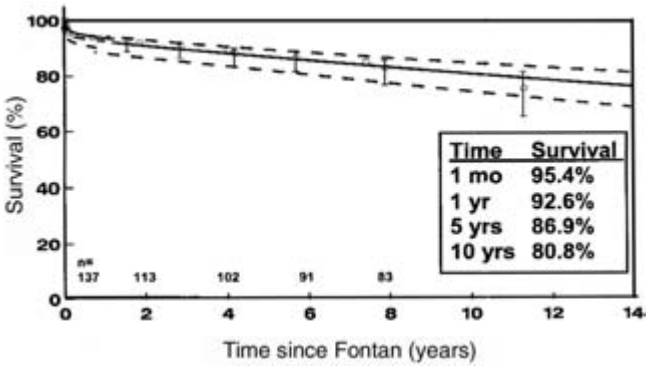

Fig. 29-8 Kaplan–Meier actuarial survival curve depicting survival from time since Fontan of Toronto cohort.

used for construction of a Fontan circuit changed over time. Early in the experience, atriopulmonary ($n = 54$, 40%) or right atrioventricular conduit ($n = 44$, 32%) connections were constructed. A lateral tunnel ($n = 24$, 18%) or extracardiac conduit ($n = 14$, 10%) connection were favored in the more recent and current eras. A fenestration was used in 33 patients (24%). With each consecutive birth cohort, the median age at which the Fontan was performed declined significantly. Reoperation or subsequent interventions were required in 53 patients (39%). Two patients after the Fontan required cardiac transplantation. This experience confirms our earlier observations and those of Franklin and colleagues;[55,56] namely that while outcomes for children with tricuspid atresia are improving, an important proportion of patients continue to die before intervention or Fontan palliation, or are not suitable candidates for the Fontan procedure. Multiple procedures and interventions are required in the majority of patients before the Fontan procedure, in order to regulate pulmonary blood flow, maintain an unrestrictive atrial communication, address systemic outflow tract outflow obstruction, rehabilitate pulmonary arterial stenoses and stage with cavopulmonary connections. Ashburn and his colleagues for the Congenital Heart Surgeons Study have studied the outcomes of 112 infants with tricuspid atresia and concordant ventriculoarterial connections seen at the participating institutions within the first 3 months of age.[56A] The mean birthweight was 3.1 kg and 15% had noncardiac anomalies. Twenty per cent had pulmonary atresia; 50% had restricted pulmonary blood flow, and 20% excessive pulmonary blood flow. An arterial shunt was performed as an initial shunt in 67%; cavopulmonary shunt as the initial shunt in 24%, and pulmonary artery banding in 9%. By the conclusion of the study, 11 patients had died, 10 before the Fontan. With a variety of strategies to reach a Fontan, current survival was estimated to be 92% and 88% at 1 and 3 years, respectively. Thus results for patients with the "ideal" form of tricuspid atresia continue to improve. Warnes and Somerville have commented on the outcomes of 17 adolescents and adults with tricuspid atresia and transposition.[75] Most of the patients in this series had either died or were disabled, and subaortic stenosis and pulmonary vascular obstructive disease contributed to morbidity and mortality. There is another group of patients with a form of tricuspid atresia who fare very poorly. This is the group with an absent pulmonary valve, imperforate tricuspid valve, and regional defective myocardial development with myocardial noncompaction.[76–82] This entity is discussed in Chapter 17 and isolated myocardial noncompaction in Chapter 41G. Suffice it to say, patients with this combination of anomalies only rarely survive to Fontan palliation.[82]

The concept by Fontan and Baudet of performing an atriopulmonary connection and atrial separation for the patient with tricuspid atresia is one of the signal contributions for patients with congenital heart disease during the last half of the 20th century (see Chapter 36).[12,83] This procedure and its many modifications has extended the quality and length of life for those patients not amenable to a biventricular repair.[84] From the earliest report of the Fontan procedure for the patient with tricuspid atresia to contemporary results, surgical results have continued to improve with a risk of perioperative death in most centers of 5% or less and predicted survival to 10–15 years of 70% or more (see Chapter 36). The Mayo Clinic reported on early and late results of a 25-year experience with the Fontan in 216 patients with tricuspid atresia.[85] The median follow-up of this cohort was 13 years and 79% of the patients survived. In the most recent decade, the operative mortality was only 2%. Eighty-nine per cent of surviving patients were in New York Heart Association class 1 or 2. The improved surgical results are predicated on a variety of issues including strict adherence to the criteria for performing this operation, perhaps staging with a bidirectional cavopulmonary shunt, better anaesthetic, intraoperative care, atrial fenestration, and care in the critical care unit postoperatively[84] (see also Chapter 36). In addition, early takedown of the failing Fontan contributed to better surgical results. The Fontan procedure, its evolution in technique and ongoing evaluation of the criteria for performing this operation are reviewed in detail in Chapter 36. But the aftermath of the Fontan may be characterized in some patients by one or more potentially life-threatening complications (see Chapter 37).

All references can be found at the end of the book. See pp. 770–2 for Chapter 29.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom, Shi-Joon Yoo, and Umesh Dyamenahalli

Pulmonary Atresia and Intact Ventricular Septum

First described by Hunter in 1783 and then by Peacock in 1869,[1,2] this uncommon form of congenital heart disease has intrigued many of us over the years.[3] In its simplest definition, pulmonary atresia and intact ventricular septum is a disorder characterized by complete membranous and in many patients muscular atresia of the right ventricular outlet.[1–6] The ventricular septum is intact, or nearly so. But pulmonary atresia and intact ventricular septum is a profoundly complex disorder encompassing tremendous morphologic heterogeneity (Figs 30-1, 30-2).[3–19] It is perhaps this wide diversity in structure that has both challenged and stimulated surgical and catheter-based therapies. The coronary artery abnormalities that are so important in many patients with pulmonary atresia and intact ventricular septum have evolved from pathologic curiosity to that of signal importance in surgical management and prognosis (Figs 30-3 to 30-6).[9,10,12,13,15,20–38] In this diversity, one feature also correlating with a poor outcome is a low pressure right ventricle reflecting gross tricuspid regurgitation and defective right ventricular muscularization.[9,10,12–15,39–41] And these two features, namely important abnormalities of the coronary circulation and a low pressure right ventricle are mutually exclusive.

Incidence and patterns of inheritance

Pulmonary atresia and intact ventricular septum is an uncommon form of congenitally malformed heart, accounting for only about 3% of newborns with serious congenital heart disease.[42] Data published in the report from the New England Regional Infant Cardiac Program identified 75 patients with this disorder, accounting for 3.3% of all babies encompassed by this study.[43] The more recently completed Baltimore–Washington Infant Study found the prevalence for pulmonary atresia and intact ventricular septum as 0.083 per 1000 live births.[44] The prospective Bohemia Survival Study identified 53 patients with pulmonary atresia and intact ventricular septum amongst 815 569 children born between 1980 and 1990 in Bohemia.[45] These accounted for a prevalence of 0.06 per 1000 live births and 1.05% of all heart malformations surveyed during this study. This lesion accounts for 0.71% of all patients seen with congenital heart disease at the Toronto Hospital for Sick Children.[42] As one surveys cyanotic neonates with congenital heart disease, this disorder ranks third, following transposition of the great arteries and pulmonary atresia and ventricular septal defect.[46] Data provided by the Pediatric Cardiac Care Consortium found that pulmonary atresia accounted for 2.6% of the patients surveyed.[47] They reported that in Arkansas, the prevalence/1000 live births for this malformation was 0.065, Iowa 0.085, and Minnesota 0.058. The incidence of pulmonary atresia and intact ventricular septum for the United Kingdom and Eire was 4.5/100 000 live births based on the survey of this disorder from 1991 to 1995.[48,48A] Leonard and coworkers identified from one health region in the United Kingdom 29 patients with pulmonary atresia and intact ventricular septum from a birth cohort of 601 635 live births between 1980 and 1995, for a prevalence of 0.049 per 1000 live births.[49] Important extracardiac malformations in patients with pulmonary atresia and intact ventricular septum are uncommon.[43,48] Rarely, cases of pulmonary atresia and intact ventricular septum have been noted in patients with trisomy 18 or 21.[48]

There are a few reports of familial aggregation of this disorder, but we have not identified siblings with this disorder among > 170 families with one affected child seen in our institution.[50,51] No gender or genetic disposition amongst patients with pulmonary atresia and intact ventricular septum has been firmly established, although Chitayat and his colleagues speculate that this could be a single gene disorder.[50]

Morphogenesis

Kutsche and Van Mierop suggest that pulmonary atresia with ventricular septal defect occurs earlier in cardiac morphogenesis than pulmonary atresia and intact ventricular septum.[52] Their conclusion is based on an analysis of a number of morphologic factors including the diameter of the pulmonary trunk, the morphology of the pulmonary valve, and the morphology and topography of the arterial duct. Kutsche and Van Mierop suggest that pulmonary atresia and ventricular septal defect occurs early in cardiac morphogenesis, at or shortly after partitioning of the truncoconal part of the heart, but before partitioning of the ventricular septum. Based on these morphologic variables, they suggest that pulmonary atresia and intact ventricular septum likely occurs after cardiac septation, speculating that this disorder might reflect a prenatal inflammatory disease rather than a congenital malformation. It is possible that their conclusions of the timing of the maturational arrest are correct for some forms of hearts with pulmonary atresia and intact ventricular septum, specifically those with a nearly normal-sized right ventricle and an imperforate well-formed tricommissural pulmonary valve. Indeed, there is evidence based on serial fetal echocardiographic studies that pulmonary atresia may be acquired in some patients, and these hearts tend to have better developed right ventricles. However, there are few data to support an inflammatory process as hearts with this disorder obtained from fetuses and from the immediate newborn have

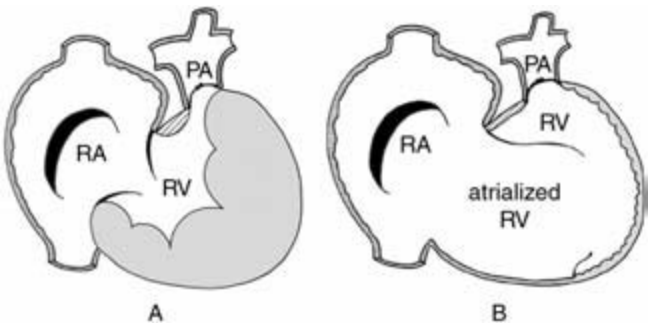

Fig. 30-1 Two forms of pulmonary atresia with intact ventricular septum. **A**. The classic form is characterized by hypoplastic and hypertensive right ventricle (RV). The tricuspid valve is small and not severely regurgitant. This form tends to be associated with ventriculocoronary arterial connections. **B**. The dilated form is associated with severe tricuspid regurgitation. Both right atrium (RA) and right ventricle are dilated. In this form, the ventriculocoronary arterial connection is not a feature. PA, pulmonary artery.

been studied histopathologically without providing any conclusive evidence of acute or subacute inflammation.[53–57] Furthermore, one would wonder whether those hearts with a diminutive right ventricle and ventriculocoronary artery connections represent an earlier insult or maturational arrest than those with a well-formed right ventricle and a well-formed though imperforate pulmonary valve. There is less certainty about the view advocated by Kutsche and Van Mierop in those patients with a tiny right ventricle and whose pulmonary valve is unicommissural and in whom there are extensive ventriculocoronary connections. Further confounding this hypothesis are those hearts with pulmonary atresia, intact ventricular septum, aortopulmonary collateral, and a right-sided aortic arch.[58–61]

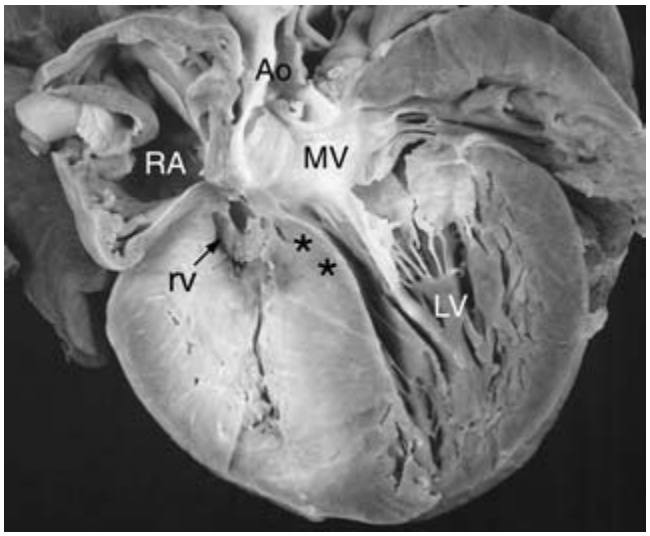

Fig. 30-2 Severely hypoplastic right ventricle (rv) in pulmonary atresia with intact ventricular septum. The right ventricular free wall and interventricular septum are very thick. The right ventricular cavity is tiny. The interventricular septum bulges into the left ventricular outflow tract (asterisk).

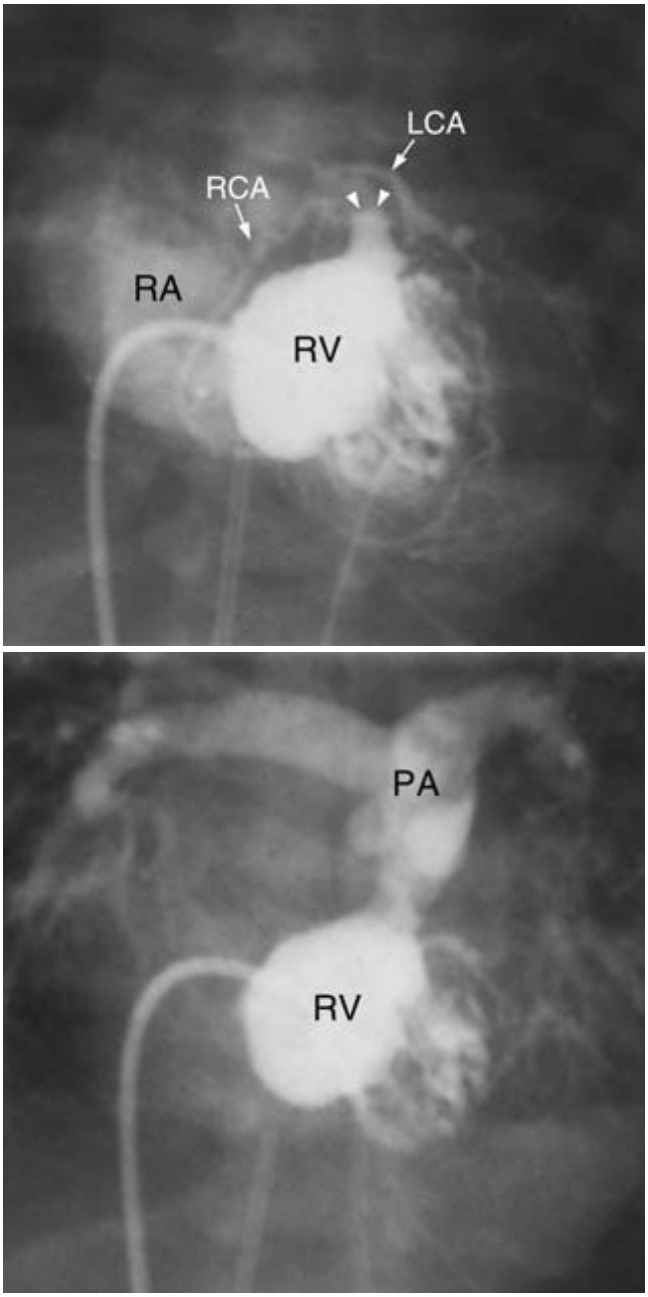

Fig. 30-3 Pulmonary atresia with intact ventricular septum. **A**. The right ventricle (RV) is moderately hypoplastic, and there is mild tricuspid regurgitation. The arrow indicates the atretic pulmonary valve. Both the right and left coronary arteries (RCA and LCA, respectively) are opacified through the ventriculocoronary connections. **B**. The patient underwent laser ablation of the atretic pulmonary valve and balloon valvuloplasty. Injection into the right ventricle after the procedure does not fill the ventriculocoronary arterial communications. PA, main pulmonary artery; RA, right atrium.

Segmental analysis

The atrial situs is normal and the atrioventricular and ventriculoarterial connections are concordant. Levocardia is present in > 98% of hearts exhibiting pulmonary atresia and intact ventricular septum. Dextrocardia with solitus atria is infrequent as

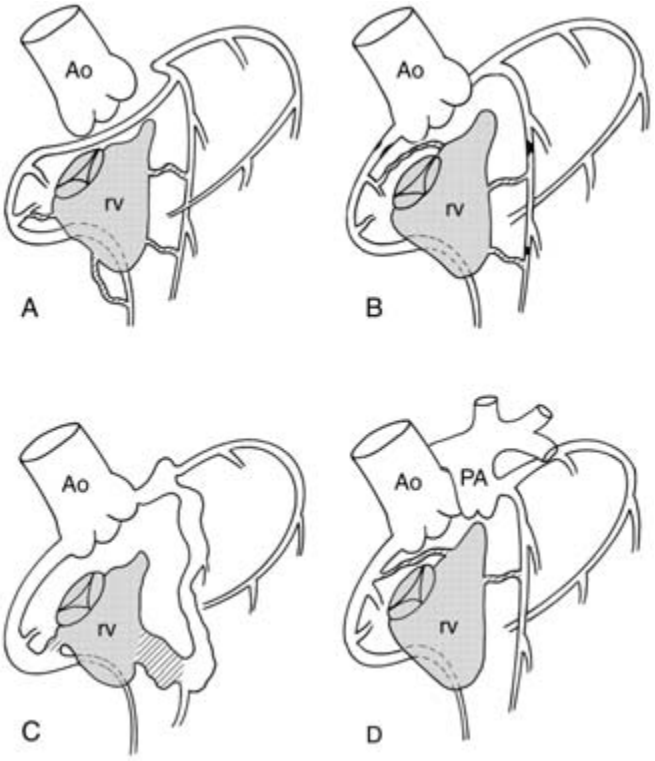

Fig. 30-4 Various forms of ventriculocoronary arterial communications causing right ventricle (RV)-dependent coronary circulation. **A**. Absent connections between the coronary arteries and aorta (Ao) with multiple ventriculocoronary connections. **B**. Proximal narrowing or interruption with multiple ventriculocoronary connections. **C**. Large fistulous communications with ectatic coronary arteries. **D**. Origin of one coronary artery from the pulmonary artery (PA) with multiple ventriculocoronary connections.

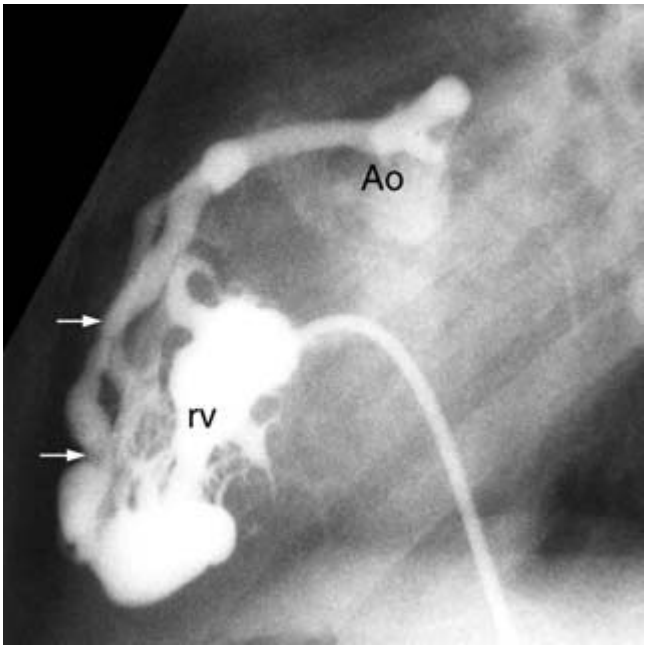

Fig. 30-5 Very large ventriculocoronary arterial communications. Right ventriculogram in lateral view shows opacification of dilated left anterior descending coronary artery (arrows) with retrograde filling of the aorta (Ao). Note the caliber changes in the left anterior descending coronary artery. The infundibular component of the right ventricle (rv) is not formed.

is pulmonary atresia and intact ventricular septum with double discordance.[3,61–65] The aortic arch is usually left-sided.

The pulmonary circulation in pulmonary atresia and intact ventricular septum

The pulmonary arteries are almost always confluent in patients with pulmonary atresia and intact ventricular septum.[3,5,48,61] The pulmonary circulation in the overwhelming majority is maintained by a left-sided patent arterial duct, although very rarely by large direct aortopulmonary collaterals.[58–61] There is usually a main pulmonary trunk with imperforate continuity with the atretic pulmonary valve. Severe underdevelopment of the branch pulmonary arteries is uncommon.[3,5] Left pulmonary artery stenosis at the site of ductal insertion has been observed in these patients.[61,66] In this regard, Marino and his colleagues suggest that the arterial duct in patients with pulmonary atresia and intact ventricular septum constricts earlier than the arterial duct in patients with pulmonary atresia and ventricular septal defect.[67] Rarely the pulmonary arteries in pulmonary atresia and intact ventricular septum are non-confluent, each supported by its arterial duct.[61,68] In one case which we reported the right pulmonary artery originated from a right-sided arterial duct, while the main pulmonary trunk and left pulmonary artery were connected to a fifth aortic arch.[69] A pulmonary sling has also been observed in the patient with pulmonary atresia and intact ventricular septum.[70] The lungs are often compressed in those babies with the largest hearts, and thus extremely severe tricuspid regurgitation.[3,10,61,71–75] Once thought to be underdeveloped in this situation, the histopathologic study of Tanaka and

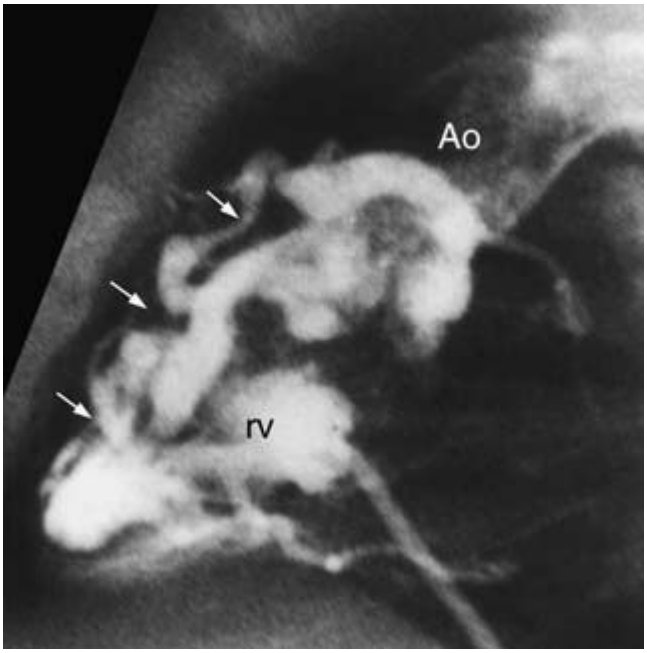

Fig. 30-6 Interruption of major coronary artery with ventriculocoronary arterial communications. Right ventriculogram in lateral view shows opacification of the left anterior descending coronary artery showing multiple levels of interruption (arrows). rv, right ventricle.

colleagues has indicated that unlike the lungs from patients with diaphragmatic hernias, lungs from neonates with massive tricuspid regurgitation and extreme cardiomegaly are not underdeveloped, nor do they demonstrate abnormal vascular extension.[75]

In the surgical and therapeutic history of this disorder, a number of anatomical considerations have been considered risk factors for poor outcome either in isolation or in combination. These include tricuspid valve size, right ventricular size, ventriculocoronary connections and a right ventricular dependent coronary circulation, amongst others.[39–41] Some have suggested that histopathological changes in the left ventricle may have an effect on long-term outcome.[76,77]

The tricuspid valve

The tricuspid valve in many patients with this disorder is severely stenotic (Fig. 30-1A), while in others the tricuspid valve is massively regurgitant (Fig. 30-1B), with a very dilated annulus, at times virtually devoid of valvular tissue.[4–11,61,78] In those patients with the most stenotic tricuspid valve, the annulus is obstructive, muscularized and all components of the valve apparatus are abnormal with a thickened free-valve margin; thickened and shortened and attenuated chordae tendineae; and abnormal papillary muscles, including a parachute configuration. The massively regurgitant tricuspid valve shows a very dilated annulus. In this situation, the tricuspid valve demonstrates features of displacement and/or dysplasia, and a portion or the entirety of the annulus may be unguarded.[8,61,71–73,78–82] Ebstein's anomaly of the tricuspid valve has been found in about 10% of autopsied patients with pulmonary atresia and intact ventricular septum.[83] Displacement without dysplasia is virtually unknown in patients with Ebstein's anomaly complicating pulmonary atresia and intact ventricular septum.[8,61,79] An obstructive form of Ebstein's valve has been observed in some patients with pulmonary atresia and intact ventricular septum.[61,84,85] The population-based study of pulmonary atresia and intact ventricular septum identified 18 patients (10%) with Ebstein's anomaly of the tricuspid valve.[48A]

A number of methodologies have been used to attempt to quantify the diameter of the tricuspid valve. Hanley and his colleagues have advocated the use of the so-called tricuspid *Z*-value as a measure of the normalized tricuspid valve diameter.[41] This is the diameter of the tricuspid valve normalized to body surface area and based on the data of Rowlatt, Rimoldi, and Lev initially published in 1963.[86] The more negative the *Z*-value of the tricuspid valve, the smaller and more obstructive the tricuspid valve. The larger the *Z*-value of the tricuspid valve, the larger the tricuspid valve diameter, and the more severe the regurgitation. These authors showed that the *Z*-value was highly correlated with right ventricular cavity size; the more negative the *Z*-value, the smaller the right ventricle. This correlation was highly significant with the presence of ventriculocoronary connections as well. More recently, Drant and colleagues have provided data supporting the observation that infundibular diameter was a better predictor of right ventricular–coronary communications than the *Z*-value of the tricuspid valve.[87] Others have used a ratio between the tricuspid and mitral valves in helping to define management pathways.[88]

The right ventricle

Numerous categorizations of the right ventricle have been made in this disorder, including attempts to capture its volume.[4–7,12–15,89–103] These classifications have evolved from a qualitative assessment of cavity size (from small to very large), to a semi-morphologic characterization of the ventricle in term of its morphologic components (inlet, apical trabecular, and outlet zones), to semi-quantitative assessment of the inlet–outlet dimensions. Others have provided a ratio between inlet-to-outlet dimensions.[91] Right ventricular volume determinations have also been attempted,[101] but whatever the methodology in these determinations, such techniques are challenged by the marked myocardial hypertrophy that attenuates the apical trabecular part and infundibulum. The right ventricle in some of these patients is very underdeveloped, seemingly formed only of an inlet portion.[7,11,61,89,90] In others, the right ventricle has an inlet and trabecular portion, while in others the right ventricle is represented by inlet, apical trabecular, and infundibular components. The degree of investment of the components in any given patient varies considerably, and muscular hypertrophy and overgrowth may obviate recognition of the trabecular and outlet portions of the right ventricle.[7,11,61] The right ventricular myocardium in those babies with the severest forms of tricuspid regurgitation may be very thinned and may transilluminate, and in others the deficiency of the myocardium may be so severe as to suggest Uhl's anomaly.[6,61] There is no doubt that with relief of outflow tract obstruction, many right ventricles demonstrate growth, stimulated in part by post-interventional pulmonary regurgitation and from remodeling with regression of hypertrophy.[91–95,100,101]

The coronary circulation

A remarkable evolution in our understanding of the coronary artery circulation in patients with pulmonary atresia and intact ventricular septum has occurred, and the disordered coronary circulation has had a profound effect on surgical management and outcome (Figs 30-3 to 30-6).[3,9,12–15,19–38] Ventriculocoronary connections and myocardial sinusoids are an important aspect of this disorder. Though these peculiar connections between the cavity of the right ventricle and the coronary arteries were observed at the autopsy table > 75 years ago,[20,103] it is just about three decades ago when Freedom and Harrington suggested that such connections might promote myocardial ischemia.[29] A substantial literature has subsequently been published defining the character of the coronary arteries, their pathology, and the coronary circulation in these patients, and surgical strategies have been defined on the basis of the coronary circulation. Gittenberger-de Groot and her colleagues have recently published a comprehensive review of the histopathology of ventriculocoronary arterial communications.[35] In the UK National Collaborative Study of pulmonary atresia and intact ventricular septum, of 140 patients identified since 1991, the coronary arteries were considered normal in 58% and minor and major coronary artery fistulae were identified in 15% and 17% respectively. Ten patients were considered to have coronary artery stenosis.[48] The median tricuspid *Z*-value for this cohort of patients was minus 1.6. Kaufman and Anderson in 1963 commented on the frequent association between hearts with ventriculocoronary connections, and pulmonary atresia and intact ventricular septum, but no specific functionality was assigned to

these peculiar communications.[104] These observations have been more recently confirmed by Schutte and her colleagues.[105] An extensive literature has documented the vast array of changes in the coronary arteries in patients with pulmonary atresia and intact ventricular septum.[3,9,12–15,19–38] The histopathologic alterations of those coronary arteries participating in the ventriculocoronary communication is not characterized by inflammation as once thought. Rather the process demonstrates myointimal hyperplasia with a rich background of glycosoaminoglycans.[3,9,12,13,15,61] There is a wide spectrum of histopathologic lesions of both the extramural and intramural coronary arteries. These lesions range from mild degrees of intimal and medial thickening in which a continuous internal elastic lamina and normal lumen is present to a loss of normal arterial wall morphology with replacement of the arterial wall by fibrocellular tissue containing irregular, non-organized elastin strands and severe stenosis or obliteration of the arterial lumen. Some have designated these changes "fibroelastosis" of the coronary arteries, but it is clear that the emphasis should be placed on myointimal hyperplasia.[27] Staining for glycosaminoglycans shows the prominence of ground substance formation by the activated smooth muscle cells, rather than reduplicated elastica and collagen that is characteristic of fibroelastosis. This pathologic process results in profound distortion of the normal architecture, eventuating in endothelial irregularity, stenosis or interruption. These coronary arterial changes occur only in patients with ventriculocoronary connections, and by inference, with a hypertensive right ventricle. We have speculated that the pathogenesis of these arterial lesions is predicated on the repeated and sustained injury to the coronary arterial intima from high-pressure right ventricular systolic turbulent blood flow mediated by the presence of the ventriculocoronary connections.[124] Intra- or extramural coronary arteries remote from the ventriculocoronary connections demonstrate less severe arterial lesions. These lesions have been found in fetal hearts with pulmonary atresia and intact ventricular septum and in hearts of the immediate newborn.[53] The abnormalities of coronary origin and distribution in patients with pulmonary atresia and intact ventricular septum embrace the same spectrum of those abnormalities as seen in patients with otherwise normal hearts, including abnormalities of origin, epicardial course, and number. A single coronary artery may originate from the aorta, or rarely from the pulmonary trunk.[106,107] There are a number of congenital and acquired conditions of the coronary circulation specific to pulmonary atresia and intact ventricular septum that impact on surgical management. These include absence of proximal aortocoronary connection between one or both coronary arteries; coronary arterial stenosis or interruption; or a so-called coronary–cameral fistula with a major fistula between right or left coronary artery and the right ventricle.[3,9,12–15,19–38,53,54,61,64,95,108–116] In the population-based study published by Daubeney and his colleagues, coronary arterial abnormalities were identified in 45.8% of 183 liveborn infants with pulmonary atresia and intact ventricular septum.[48A] Ten patients (7.6%) were considered to have a right ventricular-dependent circulation.

A right ventricular-dependent coronary artery circulation

As the characterization of the unusual coronary circulation in patients with pulmonary atresia and intact ventricular septum increased, it became evident that surgical outcomes were related to, or determined at least in part by the involvement of the coronary arteries. Clearly important to surgical management was recognition of the concept of a right ventricular-dependent coronary artery circulation and its integration into surgical algorithms (Figs 30-4 to 30-6).[3,9,12–15,19–38,53,54,61,64,95,108–116] In the normal circulation, the aortic diastolic pressure is the driving pressure for coronary blood flow. Those factors reducing aortic diastolic pressure, shortening diastole, reducing aortic compliance, etc., will compromise coronary blood flow. The presence of ventriculocoronary artery connections promotes coronary artery stenosis and interruption and aortic diastolic pressure is often insufficient to drive coronary blood flow when there are obstructive lesions within the coronary circulation. Thus in a coronary circulation that is wholly or in part right ventricular dependent, it is both the blood that gets into the right ventricle and the systemic or suprasystemic systolic right ventricular pressure that drive the coronary circulation in a retrograde fashion. Yet this process may lead to further coronary arterial distortions. The coronary circulation was considered wholly right ventricular dependent in 9% of the 145 patients enrolled in the Congenital Heart Surgeons Study.[41] These data are very similar to those published from this institution in a series of papers addressing the coronary circulation.[3,12–15,19,39,40,61] The management corollary to this is clear: interference with blood flow into the right ventricle or reduction of right ventricular systolic pressure in those situations in which the coronary circulation is right ventricular dependent could result in myocardial ischemia, infarction, and death. These observations were clearly substantiated by our own observations published by Coles and his colleagues as well as in the Congenital Heart Surgeons multi-institutional study of pulmonary atresia and intact ventricular septum.[39,41] One hundred and seventy-one neonates with pulmonary atresia and intact ventricular septum were entered into a prospective, multi-institutional study between January 1, 1987 and January 1, 1991 under the aegis of the Congenital Heart Surgeons Study.[41] Multivariable analysis of their data showed that small diameter of the tricuspid valve, a coronary circulation that was severely right ventricular dependent, birthweight, the date and type of initial surgical procedures were risk factors for time related death. The data on the deleterious effects of ventriculocoronary connections and a right ventricular-dependent coronary circulation as defined in the publication of Hanley *et al.* are similar to the data published from Toronto. Giglia and her colleagues from the Children's Hospital in Boston studying the influence of right heart size on outcome in patients with pulmonary atresia and intact ventricular septum have come to similar conclusions: "These results support our current hypothesis that coronary artery anatomy and not right ventricular or tricuspid valvar hypoplasia predicts which patients with pulmonary atresia and intact ventricular septum will do well after early right ventricular decompression."[100] While this study did not find a correlation between small right heart size and survival, the data of Giglia and her colleagues appropriately places the emphasis on the risk of right ventricular decompression on the nature of the coronary circulation. Those patients with a massive coronary artery–cameral (right ventricular) fistula are also right ventricular dependent. If the right ventricular pressure is reduced, such patients will develop a fatal steal, rapidly leading to coronary artery insufficiency, and myocardial ischemia and/or infarction.[38,61] We have reported the most unusual findings in one patient who lacked

any proximal aortocoronary connection. Unique to this patient a direct systemic artery connected the descending thoracic aorta to the left coronary system in this baby.[36]

The left ventricle

Akiba and Becker in a study of the left ventricle in patients with pulmonary atresia and intact ventricular septum found that four of eight hearts in their study showed short and almost dysplastic chords of the mitral valve, and one heart exhibited a small central cleft of the anterior mitral leaflet.[76] The left ventricle may exhibit variable degrees of hypertrophy, especially in those patients surviving past infancy. Some years ago, Zuberbuhler and Anderson called attention to a convexity of the outlet portion of the interventricular septum occurring in those patients with small and very hypertensive right ventricles.[7] We and others have also noted this convexity of the ventricular septum in patients with the hypertensive form of pulmonary atresia and intact ventricular septum (Figs 30-2, 30-7).[76,117,118] This subaortic bulge only rarely is thought to promote left ventricular outflow tract obstruction before Fontan's operation. We have observed severe left ventricular outflow tract obstruction resulting in death occurring after Fontan's operation when there is an unfavorable change in the ratio between left ventricular mass/end-diastolic volume.[118] Aortic valve stenosis has also been well described in patients with pulmonary atresia and intact ventricular septum, including the neonate with critical aortic stenosis, or the somewhat older child with severe aortic valve stenosis.[119,120]

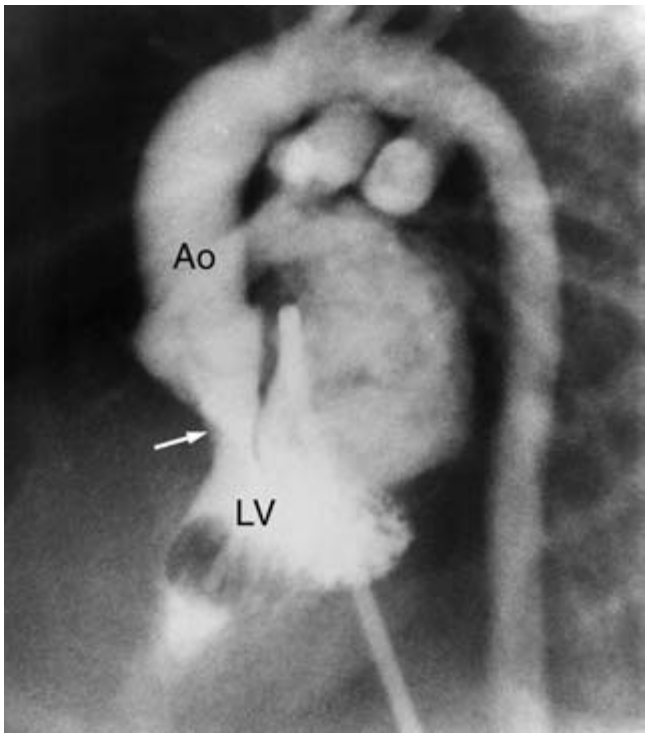

Fig. 30-7 Left ventriculogram after biventricular repair in a patient with pulmonary atresia and intact ventricular septum shows convexity (arrow) of the outlet portion of the ventricular septum. Ao, aorta; LV, left ventricle.

Myocardial abnormalities

The myocardium of patients with pulmonary atresia and intact ventricular septum demonstrates a wide range of myocardial abnormalities.[3,10,12–15,19,32,33,35,53–57,61,76,77,121–131] In view of the profound disturbances in the coronary circulation, it is not surprising that frank ischemia, fibrosis, infarction and myocardial rupture have been identified in these patients. In a provocative paper, Akiba and Becker suggest that disease of the left ventricle might be the limiting factor for long-lasting successful surgical intervention.[76] They found in the eight hearts that they studied grossly and microscopically signs of acute myocardial ischemia, and the volume density of interfiber collagen showed high levels in all, within the range of normal in five patients, but exceeding twice the standard deviation of normal in three patients. The subendocardium was disproportionately disadvantaged with higher levels of interfiber collagen than the subepicardium. They suggest that the high levels of endomysial collagen are consistent with chronic ischemia in relation to left ventricular hypertrophy, and that these abnormalities may render the left ventricle less able to cope with a volume load, and thus the left ventricle might be the limiting factor for long-lasting successful surgical intervention. Other abnormalities include myocardial disarray, the appearance of so-called spongy myocardium, and ventricular endocardial fibroelastosis. There is certainly ample clinical and morphologic evidence that the left ventricle in patients with pulmonary atresia and intact ventricular septum is abnormally hypertrophied and non-compliant. The capillary distribution in the ventricles of hearts with pulmonary atresia and intact ventricular septum has been studied by Oosthoek and colleagues.[77] Disarray and other disturbances of capillaries and myocytes were found in hearts with pulmonary atresia and intact ventricular septum, a hypoplastic right ventricle and ventriculocoronary connections. They found that these changes were more extensive when coronary artery interruptions were present.[77] The right ventricular myocardium may be particularly thinned in those babies with severe tricuspid regurgitation.

Outcome analysis

A number of studies of the prenatal recognition of pulmonary atresia and intact ventricular septum have been published, with some reports as well as fetal recognition of ventriculocoronary connections.[71–73,120,132–136] There is increasing evidence that fetuses with florid tricuspid regurgitation do not fare well.[71–73] Such fetuses are known to develop right-sided heart failure with pleural and pericardial effusions, ascites, pulmonary hypoplasia, and fetal death. Thus fetal loss might be anticipated in the specific subset of patients with pulmonary atresia, intact ventricular septum, extremely severe tricuspid regurgitation, and a low pressure right ventricle. Rarely, the fetus with a hypertensive right ventricle and a tenuous coronary artery circulation may experience progressive left ventricular dysfunction, with a fetal death. We have also seen one fetus who died because of a nearly sealed ovale foramen. Maeno and his colleagues reported in 1999 the Toronto Hospital for Sick Children's experience from 1989 to December 1997 with the prenatal recognition of right ventricular outflow tract obstruction with intact ventricular septum and also commented on the detection of ventriculocoronary connections.[135] For the purpose of this review, they excluded cases with severe tricuspid regurgitation where such

connections would not be anticipated. Of 15 fetuses with pulmonary atresia and intact ventricular septum, eight families chose to terminate the pregnancy; seven underwent some form of intervention and six of these survived. Of 13 patients assessed for ventriculocoronary communications, seven were diagnosed correctly, consistent with other recent reports on the role of fetal ultrasonography in the recognition of ventriculocoronary connections. Others have also reported their experience with prenatal recognition of coronary arterial abnormalities in this group of patients.[135A] Sharland, in her personal series of 70 cases of pulmonary atresia and intact ventricular septum with a small right ventricle detected prenatally, 58% elected to terminate the pregnancy.[134] There were a further 6 spontaneous fetal deaths, and another 6 deaths in the neonatal period. Thus this particular cohort recognized prenatally is substantially reduced by the time the neonatal period has concluded. The outlook for the group with the dilated right ventricle and gross tricuspid regurgitation was terrible. Again, from the observations of Sharland, 31 fetuses were recognized with this expression of the disorder. Eighteen families chose termination of pregnancy; there were 5 intrauterine deaths, and 8 neonatal deaths. Daubeney and his colleagues studied the impact of fetal echocardiography on incidence of pulmonary atresia and intact ventricular septum at birth and on postnatal outcome.[48] There were 86 fetal diagnoses made at a mean age of 22 weeks of gestation, leading to 53 terminations of pregnancy (61%), 4 intrauterine deaths (5%), and 29 live births (34%). The liveborn incidence of this disorder would have been 5.6 per 100 000 births in England and Wales, 5.3 in Scotland, and unchanged in Eire and Northern Ireland, if there were no termination of pregnancy and assuming no further spontaneous fetal loss. Twenty of the fetuses (23.3%) had severe tricuspid regurgitation, and in 9 of these were thought to have Ebstein's deformity of the tricuspid valve. There was no difference in outcome between the 29 liveborn cases with fetal recognition and the remaining 154 liveborn infants not diagnosed prenatally. Because the pulmonary circulation in the overwhelming majority of these patients is duct mediated, without intervention the majority will die coincident with ductal closure.[3,14,46,61] Rarely survival without intervention is documented, usually with a more stable source of pulmonary blood flow (aortopulmonary window or coronary-to-pulmonary artery fistula).[137,138]

The history of palliation of patients with pulmonary atresia and intact ventricular septum begins with the systemic-to-pulmonary arterial shunt; cavopulmonary shunt; open and closed pulmonary valvotomy; right ventricular outflow tract reconstruction with a transannular patch; right ventricular overhaul; the Fontan procedure, the one-and-a-half ventricle repair with or without ligation of the right pulmonary artery proximal to the site of the cavopulmonary anastomosis.[39,41,47,89–93,100,114,115,139–151] There is small experience with stenting of the arterial duct as a maneuver to palliate these patients.[152,153] More recently transcatheter perforation of the imperforate pulmonary valve has been accomplished with reasonable outcome in the patients so treated (Fig. 30-3).[154–157] From the 1950s to the early 1970s these babies were palliated with a variety of systemic-to-pulmonary artery shunts, including the Blalock–Taussig shunt, the Potts and Waterston shunt. The mortality for these very hypoxic babies was substantial, but some survived to benefit from a cavopulmonary shunt.[158] Open and closed pulmonary valvotomies had limited success, but some babies, particularly those with a well-formed ventricle, did well. Fortunately the medical and surgical outlook for many patients with pulmonary atresia and intact ventricular septum continues to improve. The reasons for this are complex and reflect amongst many factors the ever-improved "platform" for neonatal care. The introduction of prostanoid therapy in 1976 allowed one to stabilize these babies before any form of intervention was considered. It became clear that some babies were severely compromised and died as a result of the combination of a systemic-to-pulmonary artery surgical shunt and a patent arterial duct, and that the duct should be ligated at the time the shunt is constructed.[159] Pacileo and his colleagues have shown that in patients without ventriculocoronary connections left ventricular contractility indices are compromised after a systemic to pulmonary arterial shunt.[159A] The recognition of the disordered coronary circulation and the concept of a right ventricular dependent coronary circulation which evolved through the late 1970s and 1980s led to different surgical algorithms. Clearly while some of these patients are not candidates for a biventricular repair for a variety of reasons, univentricular palliation of the Fontan type or the one-and-a-half ventricle repair has certainly salvaged some of these children, as has cardiac transplantation. The concept of a right ventricular overhaul benefited some of these patients as well.[93] Radiofrequency or laser perforation of the imperforate pulmonary valve has also been an important development for some of these patients (Fig. 30-3). However, for the baby with very severe tricuspid regurgitation and gross cardiomegaly, the outlook is still poor despite the innovative approach of Starnes and his colleagues, and now others.[160–162] Many have published therapeutic/surgical algorithms over the years, reporting varying degrees of success in relatively small numbers of patients. Some have interposed a conduit between the right ventricle and aorta to equilibrate right ventricular and aortic pressure and to perfuse the right ventricle and the coronary arteries with oxygenated blood.[139–141]

Samanek and Voriskova have reported on the outcome of 53 patients with pulmonary atresia and intact ventricular septum identified in Bohemia born between 1980 and 1990.[45] Twenty-four and a half per cent of these died during the first week of life and by 5 years survival was only 7.55% where it remained stable to 15 years of age.[45] The outcome of children born with pulmonary atresia and intact ventricular septum in Sweden from 1980 to 1999 has just been reported.[163] A total of 84 children were born with pulmonary atresia and intact ventricular septum, giving an incidence of 4.2 per 100 000 live births. In all, 77 were operated on with a 1-year survival rate of 75%. Thirty-six children had ventriculocoronary communications, with a 1-year survival rate of 50%. At the end of the study period, 52 children were alive, 32 with biventricular repair, and 19 with univentricular repair. Follow-up time was 14 days to 20 years (median 6 years). Statistical analysis of incremental risk factors for death showed statistical significance for low birth weight, male sex, muscular pulmonary atresia, and having a systemic-to-pulmonary shunt as the sole initial intervention. For the cohort undergoing surgery, survival analysis revealed a survival rate of 81% at 1 month, 69% at 4 years, and 68% at 10 years after the initial surgery. Leonard and coworkers have provided some interesting data on the natural and unnatural history of patients with pulmonary atresia.[49] They reported the outcomes of 129 patients born with pulmonary atresia from 1980 to 1995 in the Northern Health Region of England. Twenty-nine had pulmonary atresia and an intact ventricular septum, 60 had

pulmonary atresia with a ventricular septal defect, and 40 had complex pulmonary atresia.[49] The total mortality was 72 of the 129 (56%), with 15 deaths during the first week and 49 in the first year. There were 23 surgical deaths, 33 hospital deaths not related to surgery, and 16 sudden deaths, 12 of these remaining unexplained. For the group of 29 patients with pulmonary atresia and an intact ventricular septum, 15 (52%) died in the first year. This group experienced 6 surgical deaths at a mean age of 65 days, ranging from 3 to 345 days; 7 hospital deaths at a mean age of 125 days, and there were 3 sudden deaths at a mean age of 975 days.[49]

Just as surgical algorithms continued to evolve so did clinical and imaging investigations of congenital heart patients as well. This is not the appropriate forum to discuss all those imaging modalities that have been used to investigate patients with pulmonary atresia and intact ventricular septum as there is an extensive literature devoted to this aspect.[14,61] There is compelling clinical evidence that outcome of surgical intervention is irrevocably linked to a precise assessment of the coronary circulation. This assessment is not sufficient if only the presence of ventriculocoronary connections is determined. The specific calibre of the coronary arteries, areas of stenosis or interruption, ectasia, etc., must be defined. While there is ever increasing experience with echocardiography in the recognition of ventriculocoronary connections (even in the fetus), at the present time this methodology is not precise enough to forgo cardiac catheterization with angiocardiography, including selective coronary arteriography if indicated.[164–170] One cannot be reassured by the echocardiographic appearance of a normal right ventricle that ventriculocoronary connections with a right ventricular-dependent coronary circulation is excluded as we have learned from the experience of Mair and his colleagues.[146,171]

Hanley and his colleagues presented in 1993 the observations of the Congenital Heart Surgeons Study on this disorder.[41] A total of 171 neonates with pulmonary atresia and intact ventricular septum were entered into a prospective study in 31 institutions between January 1, 1987 and January 1, 1991. Survival was 81% at 1 month after the first intervention and 64% at 4 years. The incremental risk factors for death after entry were lower birth weight, smaller dimensions of the tricuspid valve and a right ventricular-dependent coronary circulation. Eighteen per cent of the living patients had received a one-ventricle repair within 3 years and 32% a two-ventricle repair; the remainder 50% had incompletely separated pulmonary and systemic circulations. Only 8 patients in this series had gross right ventricular enlargement, and the outcome for this small group was unfavorable. Reviewing updated and additional patients enrolled in the Congenital Heart Surgeons Study in 1996 Blackstone and his colleagues asked what proportion of 346 neonates with pulmonary atresia and intact ventricular septum reach definitive repair.[172] Within 5 years of enrollment, 21% went directly or in stages to a biventricular repair; 4% to a one-and-a-half ventricle repair, and 41% died before definitive repair. In their analysis, tricuspid valve size was the most important risk factor in predicting outcome. The data from the Congenital Heart Surgeons Study has recently been extended by Ashburn and colleagues.[172A] Between 1987 and 1997, 408 neonates with pulmonary atresia and intact ventricular septum were entered into a prospective study by 33 institutions. Overall survival was 77% at 1 month, 70% at 6 months, 60% at 5 years, and 58% at 15 years. Prevalence of end states 15 years after entry were: two-ventricle repair, 33%; Fontan, 20%; one-and-a-half ventricle repair, 5%; heart transplant, 2%; death before reaching definitive repair, 38%; alive without definitive repair, 2%. As one might expect, patient-related factors discriminating among end-states primarily included adequacy of right-sided heart structures, degree of aberration of coronary circulation, low birth weight, and tricuspid valve regurgitation. There was improvement in overall survival across the study period. Holding other factors constant, predicted 5-year overall survival for neonates enrolled in 1987, 1992, and 1997 was 49%, 63%, and 79%, respectively. The coronary artery anatomy in this cohort is interesting. Right ventricle-to-coronary artery fistulae were present in 126 patients (31%). Right ventricle-dependent coronary circulation, defined as supply of a major portion of left ventricle from the right ventricle through the fistulae, was present in 19 (5%) neonates. These observations are interesting considering that in 20% of the patients the end-point was the Fontan operation.

The Pediatric Cardiac Care Consortium provided outcome data on 462 operations carried out in 365 patients with pulmonary atresia and intact ventricular septum.[47] There were 60 deaths (25.6%) among 234 operations carried out in the first year of life, and 13 deaths (5.8%) for 225 operations performed in patients between 1 and 21 years of age. Of 51 Fontan procedures carried out by members of the consortium, 10 patients (19.6%) died. In this regard, Mair reported on the results of the Fontan operation in 40 patients with pulmonary atresia and intact ventricular septum.[146,171] Three early and three late deaths were encountered. In only 5 patients were ventriculocoronary connections observed, and no patient in this series had a right ventricular-dependent coronary circulation. In 1997, we reported on the outcome of 22 patients with pulmonary atresia and intact ventricular septum who had undergone a Fontan at the Toronto Hospital for Sick Children between 1980 and 1994.[147] Ventriculocoronary connections were identified in 15 of these and the coronary circulation was considered right ventricular-dependent in 5. There were 3 early and 1 late deaths. The actuarial survival at 10 years after the Fontan was 80%. There is relatively little information on the outcome of patients with pulmonary atresia, an intact ventricular septum and a right ventricular-dependent coronary circulation. Powell and his colleagues reported on 12 patients with a right ventricular-dependent coronary circulation in 2000.[173] Of 49 patients with pulmonary atresia, an intact ventricular septum diagnosed since 1986, 12 had a right ventricular-dependent coronary circulation. All underwent a modified Blalock–Taussig shunt with 1 intraoperative and 1 late sudden death. Eight patients went on to a bidirectional cavopulmonary shunt, and of these 5 have undergone a fenestrated Fontan and 3 are awaiting a fenestrated Fontan. The 5-year actuarial survival rate for this small cohort of patients was 83%. Rychik and his colleagues reviewed the surgical experience of 67 patients with pulmonary atresia and intact ventricular septum operated on at the Children's Hospital of Philadelphia between 1981 and 1998.[174] These patients were divided into three groups on the basis of the initial surgical strategy: group 1, aortopulmonary shunt alone in 31 patients; group 2, right ventricular recruitment in 32; group 3, cardiac transplant in 4. Overall actuarial survivals at 1, 5, and 8 years were 82%, 76%, and 76%, respectively. As one would anticipate, death was highest in infancy, 10 of 16, but the outcome was equivalent for all three strategies. Only one-third had a successful biventricular repair, and the tricuspid valve *Z*-score was

significantly higher in this group when compared to those who had the Fontan operation.

Fyler in 1992 showed that surgical results for pulmonary atresia and intact ventricular septum operated on at the Boston Children's Hospital had continued to improve over time.[175] More recently, Jahangiri and his colleagues also from Boston Children's Hospital extended these observations, reporting on the outcome of 47 patients who underwent surgery between January 1991 and September 1998.[176] Sixteen of these patients (34%) had a right ventricular-dependent coronary circulation, and all of these underwent a modified Blalock–Taussig shunt with one death. Fourteen of 16 patients underwent a bidirectional cavopulmonary shunt at a median of 9 months after their first operation, and nine of these had a subsequent Fontan operation without any mortality. In the 31 patients without a right ventricular-dependent coronary circulation, 6 patients underwent only a systemic-to-pulmonary artery shunt, 23 had a shunt and right ventricular decompression, and 2 had only a transannular patch. In this group of 31 patients, 10 patients had a biventricular repair, 6 a one-and-a-half ventricle repair, and 8 patients a Fontan operation, with only 1 death. The overall survival was 98% at 1 year, 5 years, and 7 years. McCrindle in a commentary on this paper does not dispute the excellence of these results, but urges some caution in the interpretation of these results as some patients were probably excluded.[177] Recently Laks and Plunkett reviewed the surgical experience with disorder at the University Of Calfornia in Los Angeles (UCLA).[178] Between 1982 and 1997, 111 patients with pulmonary atresia and intact ventricular septum underwent surgery at UCLA. They excluded 6 patients with Ebstein's anomaly of the tricuspid valve and pulmonary atresia and intact ventricular septum. A total of 63 patients with pulmonary atresia and intact ventricular septum underwent palliative procedures as neonates. Of these 20 patients had severe right ventricular hypoplasia and/or severe coronary abnormalities with a right ventricular-dependent coronary circulation. There were three early deaths in this group. The remaining 43 patients had mild to moderate right ventricular hypoplasia without a major abnormality in the coronary circulation. All of these underwent procedures to open the right ventricular outflow tract with or without a shunt. Three early and 2 late deaths occurred in this group. Early survival in this group was 90% and late survival 87%. A total of 80 patients surviving palliative procedures from UCLA and referring institutions underwent further interventions at UCLA. Of these, 19 underwent a one-and-a-half ventricle repair with a bidirectional cavopulmonary shunt, with 3 deaths. Twenty-two patients underwent a Fontan operation as later intervention, with 2 early and 1 late death. Actuarial survival for this entire group was 96% at 1 year, 89% at 5 years, and 83% at 10 years.[178] These results are excellent, acknowledging that the fate and well-being of the entire cohort was not presented.

The group in Toronto has had a long interest in pulmonary atresia and intact ventricular septum. We have focused attention on the striking morphological heterogeneity of this disorder, defined the pathologic and clinical findings of the disordered coronary circulation and those types of coronary circulation contributing to a right ventricular-dependent coronary circulation (Fig. 30-4), and have reported on the results of selective coronary arteriography in these patients. Those important changes in the myocardium and the nature of the occlusive coronary pathology have been extensively described as well. A number of papers have emanated from the Toronto Hospital for Sick Children providing our surgical experience with pulmonary atresia and intact ventricular septum. Shams and his colleagues reported on the outcome of 50 patients with pulmonary atresia and intact ventricular septum seen between 1950 and 1967.[158] The overall experience was very poor, with most of the patients dying without surgery, or in the immediate postoperative period. The majority of the patients in this series had a direct attack on the pulmonary valve or/or infundibulum and all died. The survival was considerably better for those who underwent a systemic-to-pulmonary artery shunt ± balloon septostomy as reported by Aziz and his colleagues in 1975 who documented the outcome of this approach for 15 neonates with pulmonary atresia and intact ventricular septum from 1950 to 1972.[179] The mortality in this era (just before the introduction of prostanoid therapy) for this approach was 27%. Coles and our colleagues reported in 1989 on the long-term results in neonates with pulmonary atresia and intact ventricular septum seen from 1965 through 1987.[39] This experience included 115 patients, 16 of whom died before surgical intervention. Fifty-six per cent of the patients undergoing surgery had ventriculocoronary connections. The early surgical mortality was 27.2% and the actuarial survival was only 24.7 ± 6% at 13 years postoperatively. Multivariate analysis indicated the presence of a right ventricular-dependent coronary circulation, a decreasing ratio between right ventricular and left ventricular pressure at the initial catheterization and lower weight at operation were incremental risk factors for a postoperative death. Ebstein's anomaly of the tricuspid valve was also an additional risk factor for early death. The presence of a right ventricular-dependent coronary circulation was uniformly fatal for those patients undergoing any form of right ventricular decompression or thromboexclusion of the right ventricle, but it required a number of years for this concept to mature and to be integrated into clinical practice.

We have just reviewed again our clinical experience with 210 consecutive patients with pulmonary atresia and intact ventricular septum (102 males (49%) and 108 females) seen from 1965 to 1998 at the Toronto Hospital for Sick Children.[180] Overall survival was 72% at age 1 month, 57% at 1 year, 48% at 5 years and 43% at 10 years (Fig. 30-8). Survival improved with subsequent birth cohorts ($P < 0.001$), with overall survival for 1992–98 85% at age 1 month, 75% at 1 year and 67% at 5 years (Fig. 30-9). Only earlier date of birth and the presence of Ebstein's malformation and prematurity were significant independent factors associated with decreased overall survival. After controlling for

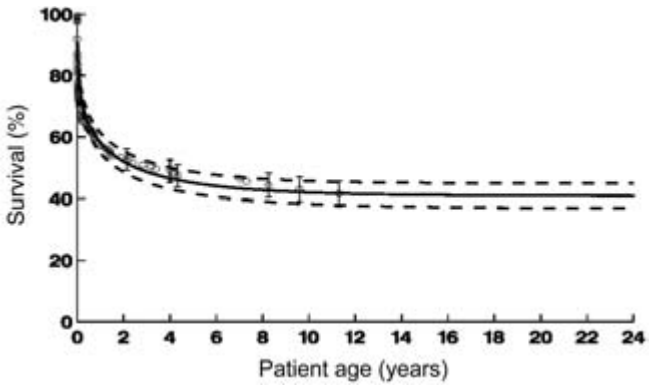

Fig. 30-8 Kaplan–Meier estimate of survival of entire cohort of patients with pulmonary atresia and intact ventricular septum.

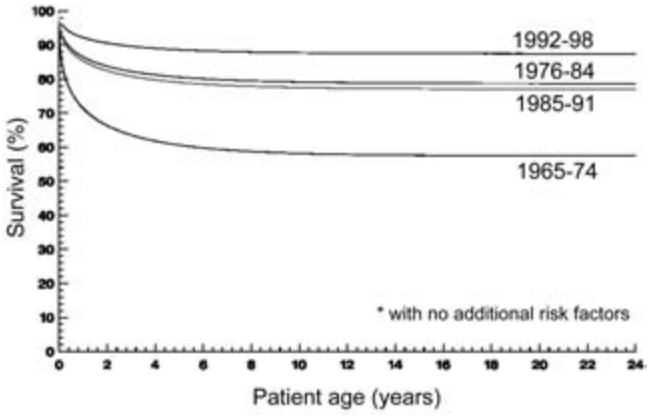

Fig. 30-9 Kaplan–Meier estimates of survival of patients with pulmonary atresia and intact ventricular septum by era. Note the improvement in the more recent time period.

these 2 factors, no other factors significantly impacted survival. Right ventricular sinusoids ($n = 182$) were present in 125 (69%) and absent in 57 (31%). Ventriculocoronary connections ($n = 180$) were present in 100 (55%) and absent in 80 (45%). These connections ($n = 95$) was confined to the left coronary artery in 13 (14%) and to right coronary artery in 5 (5%) and both to left and right coronary arteries in 77 (81%) of patients. Detailed analysis of coronary arteries was possible in 172 patients. We found normal coronary arteries in 118 (69%), proximal coronary arterial stenoses only in 20 (12%), coronary arterial dilation in 4 (2%) and proximal coronary interruption in 29 (17%). A total of 39 (23%) patients were considered to have a right ventricular-dependent coronary circulation. This experience shows how one's understanding of the disordered coronary circulation can effectively neutralize this as a risk factor for poor outcome. Those patients with a low right ventricle to left ventricle pressure ratio and Ebstein's anomaly of the tricuspid valve continued to have a poor outcome and patients with severe tricuspid regurgitation accounted for 17% of the entire cohort. Predicted actuarial survival for any era would be enhanced if these had been excluded from analysis.

Humpl and his colleagues at the Toronto Hospital for Sick Children have examined our experience in 30 patients with percutaneous balloon pulmonary valvotomy for pulmonary atresia and intact ventricular septum (Fig. 30-3).[181] From April 1992 to August 2000, 50 neonates were diagnosed with pulmonary atresia and intact ventricular septum. Of this group, 30 underwent attempted percutaneous radiofrequency-assisted pulmonary valvotomy and balloon dilatation of the pulmonary valve. The remaining 20 patients were surgically treated on the algorithm of univentricular palliation either because of an absent infundibulum,[7] a right ventricular-dependent coronary circulation,[13] or both. The median age of catheter-based intervention was 2 days, with a median weight of 3.28 kg. Perforation was successful in 27 patients. Fourteen of these eventually required a modified Blalock–Taussig shunt between 2 and 24 days after balloon dilatation. There were 3 early and 2 late deaths. At a follow-up time of 1 to 87 months, 16 patients have a biventricular circulation, 3 a one-and-a-half ventricle circulation, and 1 patient a Fontan circulation. Four patients are awaiting further palliation (current status: modified Blalock–Taussig shunt, $n = 1$ or biventricular cavopulmonary shunt $n = 3$).[182] There was no significant change of the tricuspid valve Z-score or right ventricular length Z-score with time. Agnoletti and her colleagues reported the long-term follow-up of perforation of 33 patients with pulmonary atresia and intact ventricular septum.[183] The median age and weight of these patients were 3 days and 3 kg. Of the 33 patients, 17 required neonatal surgery. At a median follow-up of 5.5 years, survival was 85% and freedom from surgery was 35%. Five patients required a partial cavopulmonary connection.[183]

The myocardium of the patient with pulmonary atresia and intact ventricular septum is thought to be intrinsically abnormal, and it is conceivable that progressive left ventricular dysfunction may become evident during continued long-term follow-up.[76,77] For those patients undergoing single ventricle palliation because of a right ventricular-dependent coronary circulation, the form and function of the coronary circulation is of course of great concern. Despite the fact that pulmonary venous blood enters the coronary circulation during right ventricular systole, the coronary vascular bed is exposed to very abnormal shear forces and turbulent flow, both of which may promote endothelial damage, contributing to coronary insufficiency. We have found that patients with ventriculocoronary connections and coronary abnormalities have a higher incidence of wall motion abnormalities than those without these findings.[130] We speculated that these wall motion abnormalities reflect ongoing myocardial ischemia and furthermore that such patients are at risk for late, sudden death. There is little information on resting or exercise myocardial perfusion studies in these patients and because of the peculiar coronary circulation, one would have to be most careful in the interpretation of the results. Sudden death has been reported in patients with pulmonary atresia and intact ventricular septum,[49] and this has been attributed to an ischemic myocardium. Furthermore, in the same group of patients there is always the substrate for a dynamic form of left ventricular outflow tract obstruction because of the potential for the interventricular septum to bulge into the left ventricular outflow tract (Figs 30-2, 30-7).[7,118] One would be concerned about the functionality of the septal perforators in this setting, again as a substrate for myocardial ischemia. These patients require very careful long-term surveillance, with particular attention to detecting important ventricular rhythm disturbances and for left ventricular dysfunction. One must be careful or cautious in the use of afterload reducing agents because of the reality of dynamic left ventricular outflow tract obstruction. There might be a role in selected cases for the judicious use of cardiospecific beta blockers.

In summary. the outcomes for patients with pulmonary atresia and intact ventricular septum continue to improve, although the surgical management of those patients with a low right ventricle/left ventricle pressure ratio continues to be difficult. The follow-up issues for these patients are also complex, depending on the underlying morphological substrate and type of repair. Those undergoing a Fontan-type of univentricular palliation are potential hosts to a wide range of complications (see Chapter 37). For those undergoing a surgical biventricular repair or one based on catheter therapy, long-term issues will likely be related to the form and function of the right ventricle, impact of chronic pulmonary regurgitation on the right ventricle and secondarily on the form and function of the tricuspid valve, and on the functional integrity of the tricuspid valve itself. Many of the same issues are germane to the patient undergoing a one-and-a-half ventricle repair.[181] In this group, attention must be paid to the form and function of the bidirectional cavopulmonary connection, remembering that aneurysmal changes have been

described in those with forward pulsatile pulmonary blood flow (see Chapter 35). The patient palliated only with a systemic-to-pulmonary artery anastomosis will likely demonstrate progressive hypoxemia as the shunt is outgrown, but chronic volume loading and a disordered coronary circulation may lead to a functional deterioration in left ventricular contractility. Some patients will evolve from a systemic-to-arterial shunt to a bidirectional cavopulmonary shunt. In those patients who do not become Fontan candidates, the development of pulmonary arteriovenous fistulae or venous collateralization may result in progressive hypoxemia and clinical deterioration (see Chapter 35).

In summary:

- Pulmonary atresia and intact ventricular septum is a disorder with profound heterogeneity.
- Termination of pregnancy and spontaneous fetal loss (especially in those with severe tricuspid regurgitation) will continue to reduce liveborn prevalence.
- Numerous catheter-based and surgical algorithms are necessary to establish either a biventricular repair, one-and-a-half ventricle repair, or univentricular palliation.
- Laser-assisted perforation of the right ventricular outflow tract with subsequent balloon dilatation has proven in some modest-sized series to provide excellent short- and medium-term results.
- Patients with a right ventricular-dependent coronary circulation have been treated successfully with univentricular palliation. The long-term effect of the disordered coronary circulation on left ventricular function is to be determined. Whether such patients are especially at risk for coronary-mediated sudden cardiac death is unclear. But the issue is worrisome.
- Some patients with particularly egregious coronary artery abnormalities are best treated with transplantation.
- Outcomes of patients with pulmonary atresia and Ebstein's anomaly of the tricuspid valve with florid cardiomegaly continue to be poor despite some limited success with conversion to tricuspid atresia, and plication of the gigantic right atrium, etc.[160–162]
- Overall, with the exception of the pulmonary atresia/Ebstein group, outcomes continue to improve.

All references can be found at the end of the book. See pp. 772–7 for Chapter 30.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

31

Robert M. Freedom and Shi-Joon Yoo

Hypoplastic Left Heart Syndrome

While some have considered aortic atresia "the worst heart disease,"[1] the accomplishments of many over the past one-quarter century have proved this incorrect. Keith and his colleagues attribute to Dilg in 1883 and Martens in 1890 some of the earliest reports of aortic atresia, although there was an even earlier report.[1A] However real progress began just over 50 years ago when the late Dr Maurice Lev (1908–94) characterized hearts with so-called hypoplasia of the aortic tract complex (Fig. 31-1). These hearts shared in common normal situs and connections, but the left heart demonstrated varying degrees of underdevelopment.[2] Many others have subsequently studied these hearts which are united by:[3–16]

- aortic stenosis or atresia
- mitral stenosis or atresia
- varying degrees of left ventricular hypoplasia
- a patent ovale foramen or less commonly an intact atrial septum
- patent arterial duct
- hypoplasia of ascending aorta
- left ventricular endocardial sclerosis.

The right heart and main pulmonary trunk are dilated and hypertrophied and the arterial duct is the tenuous conduit to the systemic and coronary circulation. The designation "hypoplastic left heart syndrome" for this constellation of anomalies was first used by Noonan and Nadas who described the clinical profile of these patients.[17] Survival for even a short time in these patients was dependent on patency of the arterial duct and on the caliber and patency of the ovale foramen.[17,18] The "programmed" closure of the arterial duct leads invariably to death, usually within the first hours or days after birth.[17–19] Those with a very restrictive interatrial communication, or an intact atrial septum usually die within hours of birth, often with pulmonary lymphangiectasia.[20–33]

Incidence and etiology

The New England Regional Infant Cardiac Program gave a prevalence of 0.164/1000 live births for the hypoplastic left heart syndrome,[34] while the Baltimore–Washington Infant Study provided a somewhat higher prevalence of 0.267/1000 live births,[35] similar to that reported by Francannet *et al.* and their coworkers[35A,35B,35C] The prevalence for left-sided obstructive lesions obtained from the Alberta Heritage Pediatric Cardiology Program was 0.677/1000 live births, but it is unclear from their data whether this category includes lesions less severe than "hypoplastic left heart syndrome."[36] The prevalence of the hypoplastic left heart syndrome in Oregon from 1971 to 1986 was 0.162 per 1000 live births. Of the affected children in the Oregon study, 15% ± 4% died on the first day of life; 70% ± 5% within the first week; and 91% ± 3% died within 30 days.[37] Data from the prospective Bohemia Survival Study identified 172 patients with the hypoplastic left heart syndrome from 815 569 children born from 1980 to 1990.[38] This gives a prevalence of 0.21 per 1000 live births and these accounted for 3.42% of all congenital heart malformations encountered in this study.[38] This constellation of cardiac anomalies is the most common cardiac cause of congestive heart failure in the first week of life.[6,17,18]

There are several lines of evidence summarized by Grossfeld that support a genetic cause of the hypoplastic left heart syndrome.[39] The hypoplastic left heart syndrome has been recorded in siblings, and both autosomal recessive inheritance and multifactorial inheritance have been implicated.[39–55] Holmes and colleagues found a recurrence risk in siblings of 0.5% for hypoplastic left heart syndrome and 2.2% for all cardiac malformations.[47] Brenner and his colleagues found that amongst probands with one affected sibling with the hypoplastic left heart syndrome, there is a predilection for bicuspid aortic valves in first degree relatives.[48] The inference from this observation is that genetic factors likely contribute to the cause of left-heart blood-flow lesions. In addition to familial occurrences, a number of chromosomal abnormalities have been identified in patients with the hypoplastic left heart syndrome, perhaps the most common being Turner's syndrome.[45,51,54,55] Anderson more than a quarter of a century ago discussed congenital heart malformations among 109 sets of twins and triplets.[55A]

The New England Regional Infant Cardiac Program characterized babies with the hypoplastic left heart syndrome as usually full-term, of normal birth weight and for the most part free of important extracardiac malformations.[34] These observations were part of the impetus to define palliative intervention for these patients. As stated earlier, recent data are concerning, indicating that some of these patients do have chromosomal abnormalities including among others Turner's syndrome.[55,56] In addition the central nervous system of these babies has been scrutinized since increasing numbers of infants with the hypoplastic left heart syndrome are now surviving univentricular palliation. Concerning information about congenital brain anomalies associated with the hypoplastic left heart syndrome has been published by Glauser and colleagues, from the institution where Norwood and his colleagues have achieved so much with this group of patients.[57,58] Of 41 infants with the hypoplastic left heart syndrome dying in this institution from 1980 to 1985, 29% had either a major or minor central nervous system abnormality, including 3 cases of agenesis of the corpus

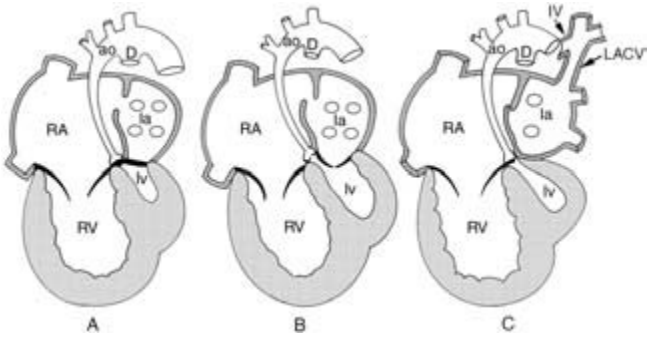

Fig. 31-1 Various forms of hypoplastic left heart syndrome. The connection between the left atrium (LA) and left ventricle (LV) can be through an atretic (**A**) or stenotic (**B**) mitral valve, or the connection can be absent (**C**). The aortic valve is atretic or critically stenotic. The ascending aorta (Ao) shows variable degree of hypoplasia and shows retrograde filling in most cases. The patent ductus arteriosus (D) is essential for survival. Interatrial communication is also essential but often restrictive and rarely absent. The left atrium (LA) can be decompressed through a levoatriocardinal vein (LACV) as in C. IV, innominate vein RA, right atrium; RV, right ventricle.

callosum, 1 case of prosencephaly. Micrencephaly was recorded in 27% of patients and a thin cortical mantle in 21%. These findings were differentiated from those acquired neuropathological changes in this group of patients.[58] The neurodevelopmental outcome of 11 patients who underwent the first stage of Norwood's palliation showed 7 had major difficulties, perhaps in retrospect reflecting some aspect of surgical technique.[59] Mutations in the cardiac homeobox gene NKX2-5 are an infrequent cause of sporadic cases of hypoplastic left heart syndrome.[59A]

Outcome analysis: evolution in diagnosis and treatment

In the era before routine application of echocardiographic imaging, and before pharmacological manipulation of the arterial duct, the majority of these babies presented in a moribund state and either without a pulse, or with diffusely weak arterial pulses.[6,14,17,18,30] There was relentless metabolic acidosis, and death quickly ensued. For those who seemed somewhat more stable or those who responded even transiently to resuscitation, a limited cardiac catheterization with angiography confirmed the diagnosis. All-too-often, passage of the catheter through the arterial duct resulted in a profound bradycardia that degenerated into a terminal ventricular dysrhythmia.[18,60–63] The application of m-mode echocardiography in the mid 1970s and then cross-sectional echocardiographic imaging of the 1980s virtually replaced the invasive methodologies to establish this diagnosis in typical cases.[18,30]

The diagnosis of the hypoplastic left heart syndrome in the 1950s and 1960s carried a uniformly fatal prognosis. Rarely, a patient with aortic atresia would survive a few years or even into the third decade of life without surgical intervention,[63–68] but the majority of babies with the hypoplastic left heart syndrome died within the first days or few weeks of life.[18,19,30] Some attempts to palliate these babies were made in this era and such palliation took the form of bilateral banding of the branch pulmonary arteries with interposition of a tube graft between the main pulmonary trunk and the descending aorta.[69–72] A few patients survived these heroic attempts, but most centers offered only compassionate care.

Several events in the contemporary history of congenital heart disease were important in providing the impetus to consider a staged approach to surgical palliation. The reality of the Fontan operation for patients with one ventricle hearts published in 1971; the ability to pharmacologically promote and maintain ductal patency by the administration of an E-type prostaglandin and thus stabilize the baby with a duct-dependent systemic circulation and the New England Regional Infant Cardiac Program that described patients with the hypoplastic left heart syndrome in a positive way all gave emphasis to a staged surgical initiative.[34,73,74] Stimulated by a surgical interest in this disorder hearts with varying degrees of left heart hypoplasia and thus potential candidates for univentricular palliation were re-examined and the many common and less common associated cardiac anomalies were fully catalogued (see Table 31-1). New knowledge emerged and older information reviewed about the anatomy of the hypoplastic left heart syndrome. This included information about coarctation of the aorta, initially considered uncommon in the hypoplastic left heart syndrome, but very common on re-examination, and its form.[75–77] The anatomy of the Eustachian valve (hypoplastic and malaligned),[78,79] tricuspid valve,[80] patterns of anomalous pulmonary venous connection,[81] alternate pathways to pulmonary venous return in the setting of premature closure of the ovale foramen, and the status of the atrial septum were all examined in detail.[82–85] Those uncommon cardiac anomalies seen in association with aortic atresia were also catalogued, including aorto-left ventricular tunnel;[86–88] atrioventricular septal defect,[71,89,90] right and left atrial isomerism,[91–95] bilateral arterial ducts, right aortic arch;[96,97] aortopulmonary window;[98,99] aortic arch interruption;[98–104] fifth aortic arch;[102–104] abnormal coronary artery origin (single, one or both),[105–107] scimitar syndrome,[108] hearts with double discordance;[109–114] univentricular hearts, absent aortic valve leaflets with left heart hypoplasia, etc.[62,97,115–121]

Throughout the mid-to-late 1970s and early 1980s, there was considerable interest in the peculiar coronary circulation often seen in the patient with pulmonary atresia and intact ventricular septum (see Chapter 30). In this setting those conditions that jeopardized normal coronary dynamics and surgical outcome were studied in detail and a number of abnormalities were described including those contributing to a right ventricular-dependent coronary circulation. Hearts with left-sided hypoplasia were then examined for similar abnormalities of the coronary circulation and evidence of coronary microvascular pathology. A similar expression of abnormalities was seen, but were invariably less severe than in those patients with right

Table 31-1 Unusual cardiac anomalies and aortic atresia

Aorto-left ventricular tunnel
Aortopulmonary window
Atrioventricular septal defect
Double discordance
Fifth aortic arch
Heterotaxia
Interruption of aortic arch
"Single" ventricle
VSD and normal left ventricle

heart obstruction.[122–129] Ventriculocoronary connections were seen primarily in those patients with a perforate mitral valve, and were rarely observed in specimens with aortic and mitral atresia.[122,124–126] Clearly one could explain this difference by the reciprocal relationship between the presence of coronary artery pathology and ventricular endocardial sclerosis.[128] But what is fascinating is why is the dense, "sugar-coating" type of ventricular endocardial sclerosis is so uncommon in patients with pulmonary atresia and intact ventricular septum and yet so prevalent in those patients with aortic atresia and a perforate mitral valve?[124] Is this related to the "color" or level of oxygenation of blood entering the ventricle and elastin synthesis? The myocardium of patients with the hypoplastic left heart syndrome was also studied, and varying degrees of myocardial disarray, ischemia and frank fibrosis with dystrophic calcification was found.[122–128]

It was William Norwood, initially at the Children's Hospital in Boston and later at the Children's Hospital of Philadelphia, who pioneered the staged approach to the palliation of babies with the hypoplastic left heart syndrome (Fig. 31-2).[130,131] Acknowledging his contributions, the designation "Norwood operation" is now firmly entrenched in our literature. The basic tenants to the initial operation as advocated and performed by Norwood included:

- provide unobstructed systemic blood flow
- provide a stable and controlled source of pulmonary blood flow
- provide a widely open atrial septum.

The operation has undergone multiple modifications from that pioneered by Norwood. Basically, the small ascending is opened and the pulmonary trunk divided. The main pulmonary artery is anastomosed and augmented by homograft tissue to the ascending aorta and the anastomosis extended distally enough to treat any aortic coarctation. Any ductal tissue that could lead to a recurrent coarctation is excised. Most now perform a modified Blalock–Taussig shunt from the base of the innominate artery or right subclavian artery to the right pulmonary artery. The pulmonary artery confluence is now routinely patched to prevent late pulmonary arterial stenosis.[132,133] Because of lack of growth of homograft material, distortion and lack of availability, Brawn and his colleagues modified the repair of the aortic arch as follows: all duct tissue is excised and the descending aorta is anastomosed to the aortic arch, which is opened back into the ascending aorta.[134] Then to this confluence is anastomosed the proximal main pulmonary artery. In some patients continuity of the aortic arch was maintained and the repair was performed with a Damus–Kaye–Stansel anastomosis. The size of the systemic-to-pulmonary shunt has also evolved over time, with most surgeons having abandoned the 4.0 mm graft, preferring to use either a 3.5 or 3.0 mm graft. From clinical trial and error, the judicious management of these patients required careful balancing of the systemic and pulmonary blood flow. Too large a shunt and hence pulmonary blood flow promoted a coronary steal, jeopardizing the myocardium and this all-too-often resulted in death.[132,135–139] Some cardiologists felt that from postoperative blood gas analysis excessive pulmonary blood flow was not implicated as a cause of death, but in nonsurvivors, low cardiac output and hypoxemia were assumed to be the major culprits.[139] A smaller systemic-to-pulmonary artery anastomosis allowed easier management of this aspect of care, acknowledging that with a smaller shunt, many of these babies would be quite hypoxic in the immediate post-operative period. Some using the larger shunt attempted to control pulmonary blood flow by ventilating the patient in a hypoxic gas mixture.[140] More recently, pulmonary venous desaturation early after Norwood palliation has been found to contribute to the degree of hypoxemia.[141] Others have shown that an anaerobic threshold was reached when the systemic venous saturation fell below 30%, and that clinical management to maintain superior caval saturation above this threshold yielded low first-stage Norwood mortality.[142] An adjustable tourniquet to manipulate pulmonary blood flow after the Norwood operation has been advocated.[143] Many factors, both physiologic as well as anatomic, obviously contribute to the level of systemic oxygenation at first stage Norwood palliation, among these the status of the pulmonary vascular bed as well as the status of the atrial septum.[30,31,33,144–149] It became clear from many clinical experiences that excessive pulmonary blood flow usually from too large a shunt increases ventricular volume work in the face of inadequate systemic cardiac output, low aortic diastolic blood pressure, and inadequate coronary perfusion, this cascade resulting all-too-frequently in death. Some have advocated the use of a small saphenous vein homograft as a superior conduit for the systemic arterial shunt in the Norwood procedure, finding this graft limits flow without the risk of thrombosis.[149A]

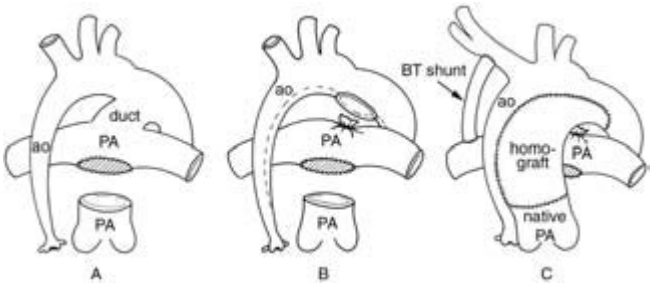

Fig. 31-2 Norwood operation. **A**. The main pulmonary artery (PA) is divided and the floor of the confluent pulmonary artery is closed with a patch or by direct suture. **B**. The ductus arteriosus is divided and completely excised, and its pulmonary arterial side is closed. The aortic incision is extended along the ventral side of the aortic arch and adjacent ascending (Ao) and descending aorta. **C**. The pulmonary artery is anastomosed to the incised aorta either directly or by using a homograft patch. A modified Blalock–Taussig (BT) shunt is placed on the right side.

Patients with severe pulmonary valve stenosis, severe congenital tricuspid regurgitation (organic, not functional), and unilateral hypoplasia of a pulmonary artery were usually deemed not candidates for staged single ventricle palliation.[150–152]

In the first years after Norwood and his colleagues initiated the staged surgical approach, many other centers also began to palliate these patients, but surgical results were often disappointing. This led many centers to question the wisdom of this approach. Because of the poor surgical results, many continued to counsel only compassionate care. Just two decades ago in 1983, Norwood and his coworkers reported in the *New England Journal of Medicine* the successful staged palliation of a patient with aortic atresia culminating in a Fontan procedure.[153] This provoked even more interest in the salvage of babies with hypoplastic left heart syndrome. Taking another approach, Bailey and his colleagues transplanted a baboon heart into Baby Fae, a newborn with the hypoplastic left heart syndrome, in 1985, but this baby did not survive.[154] This experience none the less ushered in the era of cardiac allotransplantation as another

dramatic therapy for babies with the hypoplastic heart syndrome, again experience pioneered by Bailey and his colleagues in Loma Linda, California. From the late 1980s some centers advocated the Norwood approach while others, neonatal cardiac allotransplantation, or both.[155] And some still counseled only compassionate care, a view considered by some unethical.[132]

But the Norwood procedure was not performed by surgeons in isolation. During the late 1970s and into the 1980s, centers around the world were gaining considerable experience in the Fontan operation, applying this operation to many forms of congenital heart disease (see Chapter 40). Many investigations were performed in various centers after first stage palliation. These shed light on the nature of the reconstituted ascending aorta; adequacy of repair of the distal aortic arch/coarctation; pulmonary arteries to define residual/recurrent obstruction, and the status of the atrial septum (restrictive or nonrestrictive).[132,133,156] There was considerable interest in right ventricular function and the implication of tricuspid regurgitation on short and medium-term outcome.[156,157] These findings led to continued refining and modification of surgical technique, with gradually improving surgical results. Various maneuvers were being employed to improve overall surgical results with the Fontan operation, including fenestration of the Fontan with later closure of the fenestration. Others felt that surgical outcome could be enhanced by staging to the Fontan (see Chapters 35 and 36). This staging took the form of a second operation interposed between the initial Norwood and the final Fontan.[158–164] The intermediate operation that staged to the Fontan was the performance of bidirectional cavopulmonary connection or hemi-Fontan with repair of associated anatomical hazards. The staging procedure unloaded the systemic right ventricle, changed its geometry, tended to improve a mild degree of tricuspid regurgitation and improved coronary dynamics.[165–167] These maneuvers were lauded by some as very important to reducing mortality at the time of the Fontan, but this opinion and experience were not universally shared (see Chapters 35 and 36).

By the late 1980s and early 1990s, some centers were achieving very reasonable surgical results with the Norwood procedure for babies with the hypoplastic left heart syndrome. Among those surgeons whose results were extolled included Norwood in Philadelphia; Bove of Ann Arbor, Castaneda and Jonas in Boston, Spray and his coworkers, Quaegebeur, Mee, Brawn and their respective colleagues, amongst others. As surgical results for the hypoplastic left heart syndrome continued to improve, the Norwood procedure was then applied to other forms of congenital heart disease with critical and complex forms of left ventricular outflow tract obstruction. Paralleling these accomplishments with the Norwood procedure, Bailey and his group continued to report an ever increasing and gratifying experience with neonatal transplantation.[168] Because donor hearts were often not immediately available for neonatal transplantation, the Loma Linda group became quite expert at keeping babies alive, some for weeks or even months, until a heart became available. Some required a maneuver to widen in a limited way a very restrictive atrial septal defect[33] and others while waiting for a donor organ, required stenting of the arterial duct as prostanoid therapy had become inadequate to prevent ductal closure.[169–171] As more experience with the Norwood procedure or cardiac transplantation accumulated, it became evident that those with a terribly restrictive atrial septum or in fact an intact atrial septum had an exceptionally poor outlook (Figs 31-3, 31-4).[31,33] This aspect led to a renewed interest in the nature of the pulmonary vascular bed in patients with the hypoplastic left heart syndrome. It became clear that a modest degree of obstruction at the atrial septum by promoting pulmonary venous hypertension had a salutory effect on pulmonary blood flow.[147] However Graziano and colleagues have published data suggesting that patients with the hypoplastic left heart syndrome and a restrictive atrial septal defect have pulmonary vascular abnormalities that place them at higher risk for

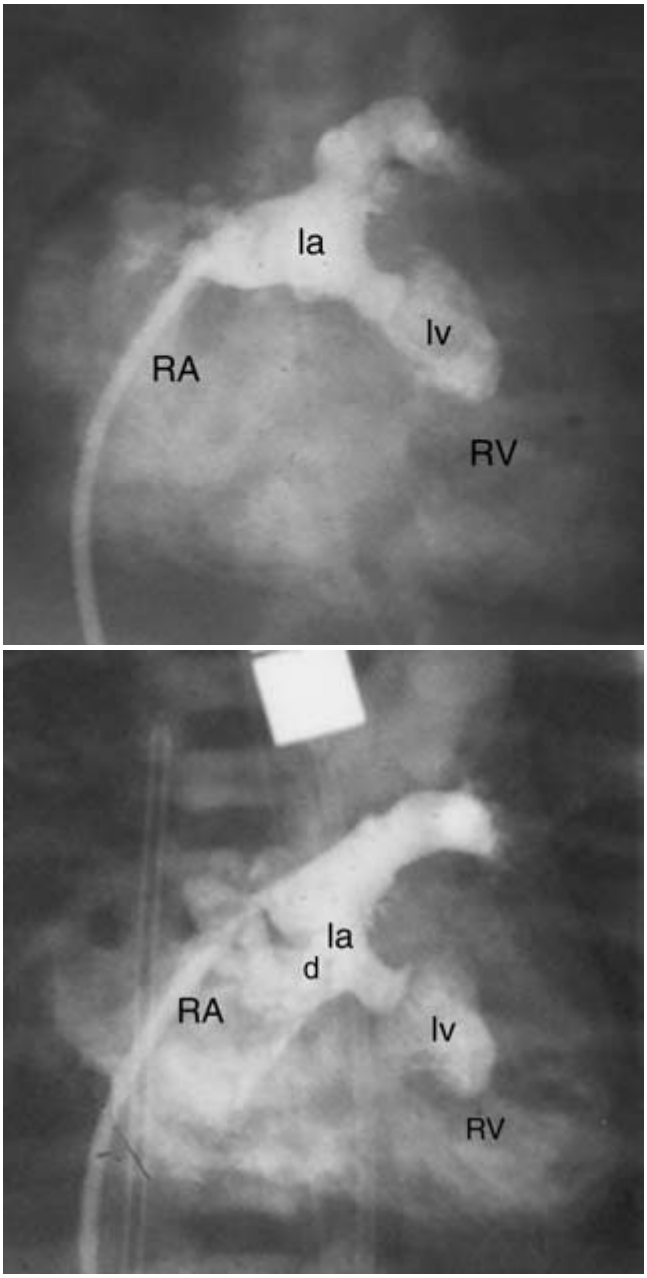

Fig. 31-3 Aortic atresia with severely hypoplastic mitral valve and restrictive patent foramen ovale. **A**. Injection into the tiny left atrium (la) visualizes the tiny left ventricle (lv). Only a small amount of left-to-right interatrial shunt is seen. **B**. Injection into the left atrium after balloon atrial septostomy demonstrates a large defect (d) created in the atrial septum. RA, right atrium; RV, right ventricle.

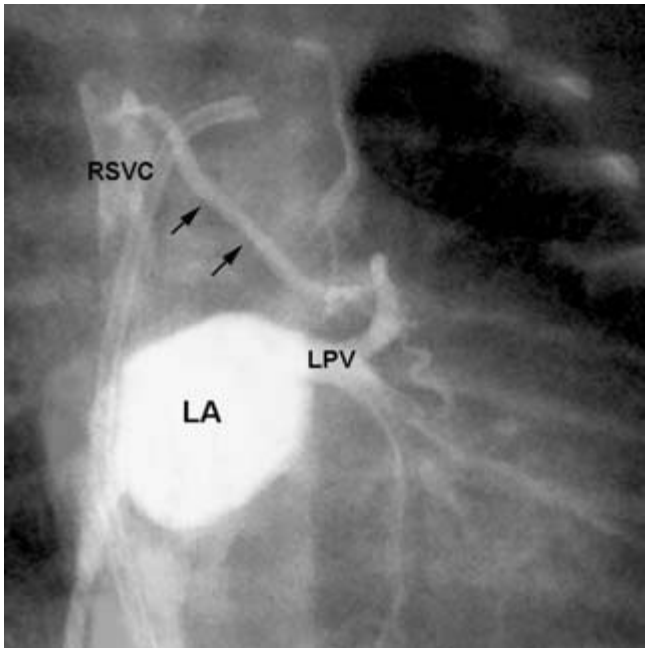

Fig. 31-4 Hypoplastic left heart syndrome with restrictive atrial septum. A collateral vein (arrows) arising from the left pulmonary vein (LPV) decompresses the hypertensive left atrium (LA) to the right superior vena cava (RSVC).

current surgical interventions.[147A] Kuhn and colleagues from Loma Linda with its extensive experience with transplantation as its primary form of therapy for these babies has suggested that those requiring atrial septal decompression are at greater risk for overall morbidity and mortality.[147B]

Today, one can only look back to the mid to late 1980s and wonder what all the fuss was about. Care givers were challenged by ethicists in offering therapy, or indeed withholding it.[172–179] There was no easy solution or answer and institutional choices were often mandated by their own individual experiences. Where surgical outcome was poor, it seemed that compassionate care was more commonly the usual option. During the same era, fetal echocardiography was providing a unique window to early recognition of congenital heart disease, and the choice for termination of pregnancy. In some parts of the world, fetal recognition and termination of pregnancy led to a reduced liveborn incidence of the hypoplastic left heart syndrome.[180] Attrition for the patient with the hypoplastic left heart syndrome continues to be substantial. Many families opt for termination of pregnancy once the fetal diagnosis is established. Sharland and her colleagues have had considerable experience with the prenatal recognition and outcome of fetuses with the hypoplastic left heart syndrome.[181–183] She has reviewed the fetal experience of Guy's Hospital in London, UK, with the hypoplastic left heart syndrome. The percentage of parents choosing termination of pregnancy was 75% in 1994; 55% in 1995; and 60% in 1996 and 1997.[182] Of the 354 cases with some form of the hypoplastic left heart syndrome in her series, there were 227 pregnancy terminations (64%), 22 intrauterine deaths (6.2%) 69 neonatal deaths (19.5%), and 6 deaths later in childhood (1.7%). Only thirty-five or 30% of the cohort survived. Some have asked whether prenatal diagnosis of the hypoplastic left heart syndrome effects preoperative status, surgical outcome and neurodevelopmental status.[184–190] The answer is not clear-cut. Chang and his colleagues some years ago suggested that prenatal diagnosis and earlier transport resulted in better preoperative condition and likely improved survival.[184] Mahle and his colleagues reviewed the very large experience of the Children's Hospital of Philadelphia.[186] With the use of multivariable analysis, their data indicated that prenatal diagnosis was associated with fewer adverse perioperative neurologic events than in those whose hypoplastic left heart syndrome had been diagnosed postnatally (odds ratio = 0.46). They go on to conclude that prenatal diagnosis has a favorable impact on treatment of patients who have hypoplastic left heart syndrome and are undergoing staged palliation, reducing as well early neurologic morbidity. In their experience, however, prenatal diagnosis was not associated with reduced hospital mortality. Kumar and coworkers also found that prenatal diagnosis did not improve the outcome of intervention when compared to those diagnosed postnally.[187] But prenatal diagnosis did improve the preoperative status of babies with the hypoplastic left heart syndrome, a finding supported by Satomi and coworkers.[185] This issue has also been addressed by Tworetzky and his colleagues.[188] They concluded that prenatal diagnosis of hypoplastic left heart syndrome was associated with improved preoperative clinical status and with improved survival after first-stage palliation in comparison with patients diagnosed after birth. Allan and her colleagues reviewed the experience of the Columbia Babies Hospital in terms of outcome after prenatal diagnosis of the hypoplastic left heart syndrome.[189] There was a survival rate of 70% in infants undergoing surgery with no complicating features; a 50% survival of all the surgical candidates; and only a 37.5% survival from an intention to treat position.[189] Brackley and coworkers reviewed the outcome of all 87 fetuses with the hypoplastic left heart syndrome referred to the Fetal Medicine Unit at Birmingham Women's Hospital between 1994 and 1999.[190] They were referred at a median gestational age (95% CI) of 23 (19–37) weeks. Of these, 53 (61%) chose prenatal karyotyping. The overall frequency of abnormal karyotype was found in 7 of 59 cases (12%) and associated structural anomalies in 18 of 87 (21%). After counseling, 38 of 87 couples (44%) chose termination of pregnancy. Of the remaining 49 fetuses, 11 (23%) were not considered for postnatal surgery because of parental choice and they died after compassionate care. Of the 36 babies who had surgery postnatally, only 12 survived (33%). Thus they recorded a survival rate of 38% for the stage 1 Norwood procedure in the prenatally diagnosed patients with hypoplastic left heart syndrome seen in their center. These data suggest that at the point of prenatal detection, the overall survival rate for fetuses with hypoplastic left heart syndrome is 25% (if terminated pregnancies are excluded). Friedman and his colleagues have provided a useful summary of the issues related to the prenatal diagnosis of the hypoplastic left heart syndrome.[186A]

Even today there remains considerable attrition for those fetuses and liveborn babies identified with the hypoplastic left heart syndrome. Termination of pregnancy, decision for nontreatment of the liveborn, mortality at the various surgical procedures and between the stages, and morbidity and mortality after Fontan or transplant all serve to reduce the outcome of the entire cohort.[162,180–202] The inevitable outcome of so-called compassionate care is death as well. For those babies listed for transplant, death on the waiting list can be 20% or higher, with a 30-day surgical mortality of 10–15%.[203–205] The post-transplant survival for patients is reasonably good, with 70–80%, or even

higher at 5 years. Dr Lori West of the Toronto Hospital for Sick Children introduced the concept of ABO-incompatible heart transplants in the neonate and young infant and has reported her initial experience with 10 patients with encouraging results.[206] This strategy may reduce the time on the waiting list and pre-transplant morbidity and mortality as well. Clearly at this time donor availability remains an important issue.

There remains discussion and debate as to which is the better surgical strategy: staging with the Norwood to the Fontan, or transplantation.[207,207A] Some patients starting out on a transplant algorithm may switch to a Norwood–Fontan tract if a heart does not become available, and some having undergone first stage Norwood palliation or second stage palliation will cross over to a transplant algorithm because of poor right ventricular function, severe tricuspid regurgitation; pulmonary artery hypertension, etc. Some have advocated decision analysis in defining the optimum treatment strategy.[208] Gutgesell and Massaro reported the results of management strategies of 636 neonates with the hypoplastic left heart syndrome in a consortium of 40 university hospitals from 1989 to 1993.[202] In 374 patients (59%), no surgical procedure was carried out, and presumably all these patients died. A Norwood procedure was performed in 222 with 53% mortality, and a cardiac transplant in 40, with 42% mortality. Gutgesell and Gibson have recently reported[202A] the results of the management of the hypoplastic left heart syndrome from a University Hospital Consortium from 1990 to 1999, thus slightly overlapping with their earlier report.[202] Of the 2264 patients with the hypoplastic left heart syndrome admitted to hospitals participating in this study (27 institutions in 1990 and 56 by 1999), 1203 underwent a Norwood procedure with a 42% mortality.[202A] Cardiac transplantation was performed in 72 with 38% mortality. Interestingly, in the hospitals participating as members of the University Hospital Consortium, the proportion of patients managed by the Norwood procedure increased from 43% during the first half of the decade to 59% in the second half, with a corresponding decrease in the proportion managed either by transplantation or non-intervention. Five of the participating institutions performed > 50 Norwood procedures during the study period, and a mortality rate ≤ 40% was achieved by all 5, and by 9 of 40 institutions performing < 50.

Some years ago the Congenital Heart Surgeons Study addressed intermediate survival in neonates with aortic atresia.[201] Three hundred and twenty-three neonates with aortic atresia were entered into a 21-institution prospective, nonrandomized study between January 1, 1994 and January 1 1997.[201] Three protocols were used: (1) staged reconstructive therapy with initial Norwood palliation concluding in the Fontan in 253; (2) heart transplantation in 49; (3) non-surgical management in 21. For the patients entered into the two surgical protocols, survival at 1, 3, 12, 24, and 36 months after entry was 67%, 59%, 52%, 51%, and 50%, respectively. A multivariable analysis found incremental risk factors for death at any time after entry to be lower birthweight (P = 0.04); associated noncardiac anomaly (P = 0.007) and entry into the non-surgical protocol (P < 0.0001). In the overall study, there did not appear to be an important difference in the outcome of the two surgical strategies. Differences were recognized, however, between those institutions designated as high or low risk ones.[201] These observations were recently extended by the 2003 publication of Ashburn and his colleagures for the Congenital Heart Surgeons Study who reported on the outcomes of 710 neonates with either critical aortic stenosis or aortic valve atresia undergoing Norwood palliation.[202B] These patients were enrolled prospectively by 29 participating institutions between 1994 and 2000. Overall survivals after the Norwood operation were 72%, 60% and 54% at 1 month, 1 year and 5 years, respectively. Risk factors for mortality included lower birth weight, smaller ascending aorta, older age at Norwood operation and a number of institutional and procedural variables. Of the neonates surviving initial Norwood palliation, risk factors for death occuring before subsequent transition included younger age at cavopulmonary shunt and need for right atrioventricular valve repair.

Cohen and Allen have reported data from the Pediatric Cardiac Care Consortium (PCCC).[209] In this database, from 1984 to 1995, 438 patients with the hypoplastic left heart syndrome underwent as an initial operation either a Norwood procedure or cardiac transplant. In 380 of the 438, the initial operation was the Norwood procedure, and of these 270 (55%) died postoperatively, and 170 survived. Mortality was greatest for the smallest infants; 87.5% for those under 2.5 kg. and 16.7% for those over 5.0 kg. In this regard, Weinstein and his colleagues reviewed the experience of early survival of infants weighing 2.5 kg or less undergoing first-stage reconstruction for hypoplastic left heart syndrome, finding an early mortality within 30 days of operation or before hospital discharge of 51%.[210] Of the 170 survivors of first-stage palliation in the PCCC, 20 died following another operation. These 150 survivors underwent an additional 60 operations with several more deaths. Thus, of the 380 infants undergoing staged palliation, 230 died following an operation, for a cumulative operative mortality rate of 60%. Cardiac transplantation was the initial operation in 58 neonates, and 17 (29%) died. In data from the PCCC, the mortality rate for the Norwood procedure declined to 45.6% for 79 operations performed in 1994.[209] Pylees and colleagues have recently extended the experience of the Pediatric Cardiac Care Consortium with the outcome of staged palliation of the hypoplastic left heart syndrome. In the interval from 1985 to 1989, 38% survived first stage palliation; 1990–1994, 45%; and from 1995 to 1999, 49% survived first stage palliation. For the entire cohort of 1147 babies with the hypoplastic left heart syndrome enrolled from 1985 to 1999, 46% survived first-stage palliation. Second stage palliation survival improved from 74% in 1985–89 interval to 94% in 1995–99. Fontan survival was 81% in the earliest interval, improving to 97% in the 1995 to 1999 interval. Interestingly in this analysis, stage 1 survival correlated poorly with center volume in the group possessing a maximum of 9.6 cases/year.[209A]

Indeed, experience reported from a number of centers has reported declining mortality rates for first-stage palliation in recent years.[193,195–198,200,201] Jenkins and her colleagues published in 2000 interesting data comparing the two treatment strategies for the hypoplastic left heart syndrome.[211] They obtained data on 231 infants with hypoplastic left heart syndrome, born between 1989 and 1994 and intended for surgery from four pediatric cardiac surgical centers. The patient's status at last contact was used for survival analysis and mortality at one year for risk factor analysis were the outcome measures. Survival curves showed improved survival for patients intended for transplantation over patients intended for staged surgery. One-year survival was 61% for transplantation and 42% for staged surgery (P < 0.01); 5-year survival was 55% and 38%, respectively (P < 0.01). Survival curves adjusted for preopera-

tive differences were also significantly different ($P < 0.001$). Waiting-list mortality accounted for 63% of first-year deaths in the transplantation group. Mortality with stage 1 surgery accounted for 86% of that strategy's first-year mortality. Birth weight < 3 kg (odds ratio [OR] 2.4), highest creatinine > or = 2 mg/dL (OR 4.7), restrictive atrial septal defect (OR 2.7) and, in staged surgery, atresia of one (OR 4.2) or both (OR 11.0) left-sided valves produced a higher risk for 1 year mortality. Their data showed that transplantation produced significantly higher survival at all ages up to 7 years. Furthermore, patients with atresia of one or both left-sided valves did poorly in staged surgery and had significantly better survival with transplantation.[211] Chang and colleagues have addressed the clinical management of infants with the hypoplastic left heart syndrome treated in the United States from 1988 to 1997 using the National Inpatient Sample Dataset.[211A] For the entire time period they enrolled 1986 patients with the hypoplastic left heart syndrome, with 812 in-hospital deaths (40.9%). The in-hospital mortality rate decreased from 54.4% in 1988 to 38.1% in 1997. The proportion of patients treated with the Norwood operation increased from 8% in 1988 to 34% in 1997. The proportion of patients dying in hospital without surgery decreased over time. Their data also showed a lower mortality for patients undergoing cardiac transplantation compared with the Norwood procedure (26.2% vs. 46%). Tweddell and his colleagues have shown a remarkable improvement with first stage palliation, with hospital survival in the years 1992 to 1996 of 44%, compared to 93% from July 1996 to October 2001.[211B] Survival to stage two palliation also significantly improved in the current era, 81% (66/81) vs. 44% (15/34), $P < 0.01$. Anti-inflammatory treatment strategies demonstrated improved survival by univariate analysis ($P < 0.001$). Multivariate analysis identified continuous venous oxygen saturaion monitoring as a factor favoring first stage palliation survival ($P = 0.02$) and use of POB as a factor favoring survival to stage two palliation ($P = 0.003$). In the current era shorter duration of deep hypothermic circulatory arrest was associated with improved survival to second stage palliation ($P = 0.02$). In this experience improved survival following first stage Norwood palliation was achieved with strategies that allowed for early identification of decreased systemic output and the use of afterload reduction to stabilize systemic vascular resistance and therefore the pulmonary to systemic flow ratio.

The Norwood circulation is for many infants unstable with the potential for adverse events especially in the first year of life.[191,192] Retrospectively, data from the Children's Hospital of Philadelphia were reviewed to determine the incidence of unexpected death among 536 patients with hypoplastic left heart syndrome who were discharged to home after stage I surgical procedure.[192] To identify potential risk factors, a nested case–control analysis was undertaken. Unexpected death occurred in 22 of 536 patients (4.1%) discharged to home after stage I surgical procedure. The median age at unexpected death was 79 days (range, 25 to 227 days). Seizures preceded cardiac arrest in 2 patients, and ventricular arrhythmias were documented in 3 additional patients during attempted resuscitation. Autopsy studies were performed in 12 patients and identified residual lesions that may have contributed to death in 2 patients. In multivariate analysis documented perioperative arrhythmia and earlier year of stage I surgical procedure were associated with an increased risk for unexpected death ($P = 0.03$ and $P = 0.04$, respectively). There were 4 additional patients who had unexpected death after subsequent cavopulmonary operation at a median age of 1.6 years (range, 0.9 to 3.8 years). Unexpected death occurred in > 4% of patients with hypoplastic left heart syndrome who were discharged to home after stage I surgical procedure and was most common in the first several months of life. This group concluded that factors that may contribute to unexpected death included residual lesions, arrhythmias, and neurologic events, although in the majority of cases the cause remained largely unknown. The group from the Children's Hospital in Boston studied the post-mortem findings of 122 patients who died after undergoing the Norwood procedure from 1980 to 1995 to establish the causes of death and consider their therapeutic applications.[191] The most important causes of death were found to be impairment of coronary perfusion (33 patients, 27%); excessive pulmonary blood flow (23 patients, 19%); obstruction of pulmonary arterial blood flow (21 patients, 17%); neoaortic obstruction (17 patients, 14%); right ventricular failure (16 patients, 13%); bleeding (9 patients, 7%), infection (6 patients, 5%); tricuspid or common atrioventricular valve dysfunction (6 patients, 5%); sudden death from presumed arrhythmias (6 patients, 5%); and necrotizing enterocolitis (3 patients, 3%). In 26 patients (21%) the leading causes of death after the Norwood procedure were found to be largely correctable surgical technical problems associated with perfusion of the lungs (36%), of the myocardium (27%), and of the systemic organs (14%).

Data recently published from Toronto reported evolving strategies and improving outcomes of the modified Norwood procedure over the past decade.[193] The overall 5-year survival rate for 171 infants undergoing staged reconstruction was 43%. The mortality rate for first stage reconstruction from 1990 through 1993 was 59%; in the period from 1994 through 1997, 39%, and from 1998 into 2000 19%. Kaplan–Meier survival curves at 1 month, 1 year, and 5 years were at follows: 43%, 31%, and 28% in the earliest era; 60%, 49%, and 45% in the middle era, and 80% at 1 month and 68% at 1 year from 1998 into 2000.[193] In Cox proportional modeling, the only significant independent risk factors associated with an increased risk of time-related death were earlier date of Norwood operation; lower weight at the Norwood operation, and preoperative use of mechanical ventilation. After controlling for these variables, no other variable was associated with total mortality. There was a trend toward an increased risk of mortality with greater degrees of preoperative tricuspid regurgitation.[193] De Rose and colleagues described the findings of a newborn dying at first stage palliation with intractable left ventricular ischemia. Causal to this was severe hypoplasia of the left coronary artery and an abnormal coronary artery branch contributing to a myocardial steal. We and others have documented thrombus in the aortic root which occluded one or both coronary ostia and acute shunt occlusion has been documented clinically and at post-mortem.[191,192,212,213] Contributing to morbidity and mortality after first-stage palliation is recurrent obstruction of the aortic arch.[191,192,213–222] We have documented precoronary stenosis in the reconstructed ascending aorta and have surgically revised this area successfully.[223] Evidence has been provided that the reconstituted transverse aortic arch grows after the Norwood operation.[224] The incidence of coarctation after stage I Norwood procedure varies between 11% and 37% and this contributes to late morbidity and death after this operation (Fig. 31-5).[214–221] Balloon angioplasty has been shown to be very effective in treating this complication.[214–221] One should be aware that in

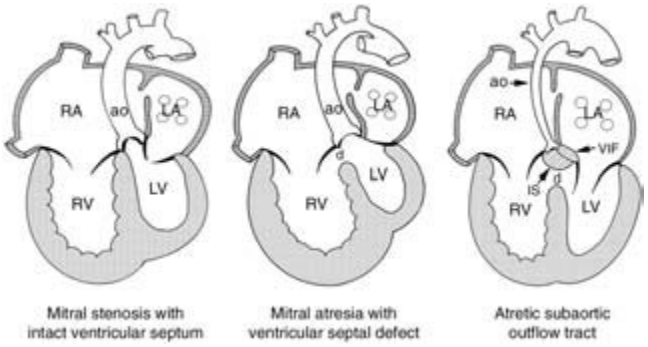

Fig. 31-5 Aortic atresia with normal left ventricle. The left ventricle (LV) can be normally developed in the presence of aortic atresia. ao, aorta; d, ventricular septal defect; LA, left atrium; RA, right atrium; RV, right ventricle; VIF, ventriculoinfundibular fold.

some patients acute cyanosis can develop following balloon angioplasty of recurrent aortic arch obstruction after the Norwood operation.[219] This likely reflects the response to the acute drop in driving pressure across the systemic-to-pulmonary artery shunt. In those patients with an aberrant right subclavian artery, blood pressure measurements from upper and lower limbs may be confusing because the origin of both vessels may be compromised in the repair of the distal aortic arch. Similarly, the origin of the innominate artery can be compromised after stage I palliation as reported by Garabedian and colleagues, promoting an innominate artery steal.[225] Rarely in the patient with aortic atresia the innominate artery will be isolated as in the patient reported by Papagiannis *et al.*[94] In any patient not doing well after first stage palliation it is mandatory that the distal aortic arch be completely imaged. In the presence of the tortuosity of the reconstructed aortic arch, cross-sectional echocardiography and color Doppler may not be adequate to define the status of the aortic arch.[226] Fraisse and coworkers advocate angiographic imaging. We would often first perform MRI-imaging and then either to treat or to confirm we would resort to an invasive procedure.[217] Acute shunt thrombosis is sadly a reality for some babies after first stage palliation, contributing to the attrition.[191–193] This seems more common in the smaller shunt and when there is associated pulmonary artery stenosis. There has been some experience with aortopulmonary shunt reconstitution using balloon angioplasty and placement of an endovascular stent.[227,228] Tricuspid valve regurgitation also exerts its toll on patients with the hypoplastic left heart syndrome.[80,151,159,160,191,192,201] Virtually all studies addressing tricuspid valve form and function in patients with the hypoplastic left heart syndrome showed that important regurgitation affected in a negative way outcome at the Fontan (see Chapter 47). Intrinsic anatomic abnormalities of the tricuspid valve are more common than previously thought, and certainly tricuspid regurgitation is often both functional and anatomic in origin.[80,151] Mild tricuspid regurgitation may be reduced in severity by those surgical maneuvers reducing right ventricular volume overload, namely the hemi-Fontan or the bidirectional cavopulmonary shunt.[159,160,191,192,195–199,229] There is less clinical evidence that these maneuvers exert an influence in those patients with severe tricuspid regurgitation, and surgical repair/annuloplasty or replacement is necessary if these patients are to become candidates for the Fontan.[230–233] The group from Ann Arbor has had a large experience with tricuspid valvuloplasty in patients with the hypoplastic left heart syndrome, describing the pathology as either or both abnormal leaflet morphology or incomplete leaflet coaptation.[231,232] Some patients will certainly be improved by these procedures and will become satisfactory candidates for the Fontan, while others will cross over to a transplant protocol.

In the evolving strategies to enhance first-stage outcomes, some have revisited bilateral pulmonary artery banding with stenting of the arterial duct as first-stage palliation.[233B] This limited experience allowed survival in some patients to heart transplantation or to neoaortic reconstruction and a bidirectional cavopulmonary shunt. Even more recently, Pizarro and Malec and their colleagues have reported that the use of a right ventricle to pulmonary artery conduit at the first stage reconstruction improves outcome.[233C,D] This procedure conferred better and more stable postoperative hemodynamics as the patient is not shunt-dependent. While their observations about enhanced early outcome seem compelling, the impact of this maneuver on the function of the single, systemic right ventricle must be carefully defined. This group reported much improved hemodynamics using this approach.[233C,D] This issue is particularly germane for the patient with the hypoplastic left heart syndrome who will undergo a Fontan procedure. Concern about the morphologically right ventricle as the systemic ventricle has been discussed elsewhere in this volume (see Chapters 25A and 26A). Pearl and his colleagues have provided a recent discussion of the many surgical strategies employed for patients with the hypoplastic left heart syndrome.[233E] Ishizaka and colleagues have also reported the role of bilateral pulmonary artery banding to resuscitate the newborn with the hypoplastic left heart syndrome.[233F]

Any number of risk factors have been identified for poor outcome at the initial staging Norwood operation.[233A] These include low birth weight, a diminutive ascending aorta; atresia of both aortic and mitral valves as compared to those with patent valves; severe extracardiac anomalies; preoperative clinical status; Turner syndrome, right ventricular dysfunction, age at the time of first stage palliation, etc. Most now exclude patients with severe extracardiac malformations from either surgical protocol. Turner syndrome has been shown to be a risk factor for poor outcome of the Norwood procedure.[234] Reis and his colleagues reviewed the implications of this association from the 406 cases of hypoplastic left heart syndrome seen from 1990 to 1997 at the Children's Hospital of the University of Michigan.[227] Ten (2.5%) also had Turner syndrome. Nine infants were delivered at term and one at 36 weeks. The mean (± SD) gestational age at delivery was 38 ± 1.2 weeks, and mean (± SD) birth weight was 2991 ± 438 g. The karyotype was 45, X in seven cases, and 45, X mosaic in three. Most infants had dysmorphic features at birth. All 10 infants had first-stage reconstruction surgery for hypoplastic left heart syndrome. Only two survived and underwent second-stage palliation; both are alive currently, although with significant medical problems. From this experience they concluded that while staged reconstruction surgery has improved survival for neonates with isolated hypoplastic left heart syndrome, for those with Turner syndrome, survival appears markedly reduced.[234] There is not general agreement as to the issue of the tiny ascending aorta as a risk factor.[132,201] Some do not open the diminutive ascending aorta to its root in the Norwood repair as initially advocated by Norwood,[235,236] but rather connect the pulmonary trunk to the undersurface of the transverse aortic arch, thereby "neutralizing" this

factor.[134,198] Right ventricular dysfunction has not proven to be a risk factor for first stage palliation, but has proven a risk factor at staging and at subsequent Fontan.[157] There are certain patients with very severe right ventricular dysfunction even after effective resuscitation, or those with a prenatal right ventricular myocardial infarction,[237] and both groups would be anticipated to do poorly.[160,161,195–198,201] Older age at the time of first stage palliation has been suggested to be a risk factor for poor outcome, although there is not unanimity of opinion about this.[195,201,238] Pizarro and colleagues have published data that low birth weight babies have an increased early surgical risk but have acceptable intermediate survival for subsequent palliation including the Fontan.[201A] This group concludes that prematurity and low birth weight should not contraindicate Norwood palliation.

There is ever increasing experience both with outcomes of the bidirectional cavopulmonary shunt and with the Fontan procedure for the hypoplastic left heart syndrome.[183,193,196,201,239–243] As we discuss in Chapter 35, mortality at the intermediate staging operation is in the range of 5–6%.[160,165,201] Mosca and his colleagues reported the Ann Arbor experience with the Fontan procedure in 100 consecutive patients with the hypoplastic left heart syndrome between February 1992 and April 1998.[239] The hospital survival for the entire cohort was 89% (95% CL, 83% to 95%). During this time period, two different surgical techniques were used: cardiopulmonary bypass with moderate systemic hypothermia, and in the latter half of the experience, circulatory arrest with profound hypothermia. Survival was 98% for the second technique, and 79% for the first. Azakie and his colleagues from the Toronto Hospital for Sick Children reported the results of the Fontan procedure in 45 patients palliated with the Norwood procedure from 1993 to 2000.[242] There were 2 early and 2 late deaths in this modest-sized series. Mahle and his colleagues have reviewed a 15-year experience of the Children's Hospital of Philadelphia with 840 patients with the hypoplastic left heart syndrome who underwent first stage palliation between 1984 and 1999 focusing on survival.[243] The 1-, 2-, 5-, 10-, and 15-year survival for the entire cohort was 51%, 43%, 40%, 39%, and 39%, respectively. Late death occurred in 14 of the 291 patients discharged to home after the Fontan procedure, although only 1 patient has died beyond 5 years of age. Heart transplantation after stage I reconstruction was performed in 5 patients. Later era of stage I surgery was associated with significantly improved survival ($P < 0.001$). Three-year survival for patients undergoing stage I reconstruction from 1995 to 1998 was 66% vs. 28% for those patients undergoing surgery from 1984 to 1988. Age > 14 days at stage I and weight < 2.5 kg at stage I were also associated with higher mortality ($P = 0.004$ and $P = 0.01$, respectively). Other variables, including anatomic subtype, heterotaxia, and age at subsequent staging procedures, were not associated with survival. Late death after the Fontan and the need for cardiac transplantation were uncommon in this very large experience.[243] The overall survival from a modest-sized series of patients with the hypoplastic left heart syndrome diagnosed antenally from 1995 to 2000 was 48%, with virtually all the surgical mortality occurring at the Norwood operation.[190] In another series of prenatally diagnosed hypoplastic left heart syndrome reported by Munn and colleagues, the survival rate following surgery for infants felt to be the best candidates was only 25%.[244]

In follow-up, the survivors of the Fontan will experience the entire range of potential complications described in these patients (see Chapter 37). Because the morphologically right ventricle supports the systemic circulation in the patient with the hypoplastic left heart syndrome, the long-term performance of the single right ventricle is of considerable interest. The form and function of the morphologically right ventricle as the systemic ventricle after atrial repair of complete transposition has been dealt with in Chapter 25A. In addition, progressive dysfunction of the systemic morphologically right ventricle in patients with double discordance has been amply documented (see Chapter 26A). In this regard, Van Praagh *et al*. has summarized those reasons why the morphologically right ventricle is inherently disadvantaged as the systemic ventricle.[245] Perhaps there is even more to be concerned with in the Fontan survivor group with the hypoplastic left heart syndrome. Many of these patients do indeed have only a single right ventricle. Others have a small, hypertensive left ventricle with the potential for ventriculocoronary connections and coronary artery occlusive pathology. In this regard, the study of Sugiyama and colleagues is relevant.[246] Their findings suggested that ventricular function appeared to be greatly influenced by left heart structure. The presence of larger left ventricular muscle bulk and frequent myocardial damage seen in mitral stenosis/aortic atresia seems disadvantageous to right ventricular end-diastolic volume and right ventricular wall motion. Fogel and his colleagues have reported a number of differences in contractility in patients with single right ventricles compared with systemic right ventricles in a dual-chamber circulation.[247] The long-term implications of Fogel's findings are unclear at this time. However publications from Matsuda and Mahle and their respective coworkers do provide worrisome information about the functionality of the single right ventricle.[248,249] Mahle and his colleagues published their findings in 2001 showing that the systolic and diastolic properties of the functionally single right ventricle differ considerably from those of the normal systemic ventricle.[248]

In the cascade of data to be included in any outcome analysis of patients undergoing univentricular palliation is the issue of neurodevelopmental status. One should not be surprised that neurodevelopmental outcome may not be entirely normal when one reflects on the findings of Natowicz, Glauser, Rogers and their respective colleagues.[56–59] A number of studies have addressed neurodevelopmental outcome of patients who have undergone the Fontan procedure and more specifically those with the hypoplastic left heart syndrome (see Chapter 36). First, as reminded by Limperopoulos and her colleagues neurodevelopmental abnormalities are common in young infants with congenital heart defects and are often present before as well as after open heart surgery.[250–252] Mahle and his colleagues from the Children's Hospital of Philadelphia studied the outcome of 115 school-aged children with the hypoplastic left heart syndrome who had undergone staged palliation before 1992.[253] Over 30% of patients were receiving some form of special education. Although the majority of patients scored within the normal range on standardized neurocognitive testing, the median full-scale IQ (86) was significantly lower than the general population. Of further concern was that 18% of the subjects had IQ scores in the mentally retarded range. Minor neurologic abnormalities were also detected in 55% of patients and 60% had problems with attention. Multivariate analysis revealed the occurrence of clinical seizures at the time of presentation was associated with lower full-scale IQ scores. Similar findings were published by Goldberg and her colleagues who showed that the

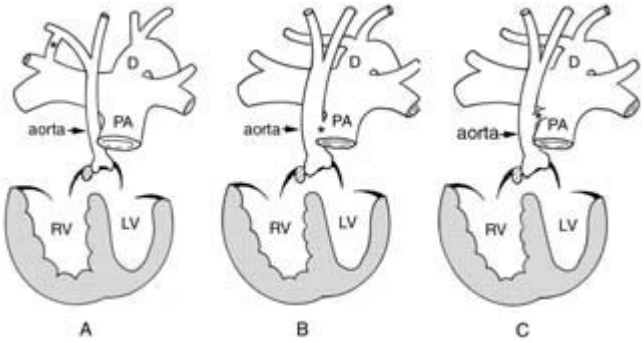

Fig. 31-6 Aortic atresia with interrupted aortic arch. The source of blood supply (asterisk) to the ascending aorta is the right-sided arterial duct (**A**), aortopulmonary window (**B**) or fistulous tract of the fifth aortic arch origin (**C**). LV, left ventricle; PA, pulmonary artery; RV, right ventricle.

hypoplastic left heart syndrome patients scored less well on the Full Scale Wechsler test than patients with other forms of single ventricle pathology.[254] None the less, what a drama since the first description of the physiology of this disorder in 1851;[255] the initial descriptive morphologies and clinical descriptions of the 1950s, attempts at palliation in the 1960s and 1970s, and the first Fontan in 1983. There is no doubt about it: despite ongoing challenges with and for patients with the hypoplastic left heart syndrome [256] we must value the survivors.[257] The learning curve for many of us was steep, but surgical and medical ingenuity has made it clear that aortic atresia is no longer the "worst heart disease."[1]

Aortic atresia and normal left ventricle

Aortic atresia is not synonymous with left ventricular hypoplasia. There are a group of patients with aortic atresia and a normal left ventricle (Fig. 31-5),[70,97–100,102–104,258–262] and > 25 years ago we speculated that some of these patients may be candidates for ventriculoaortic reconstitution.[71] Some of these patients have a complex form of univentricular heart or double discordance.[109–121] However there is a group with normal situs and connections, usually a large, malalignment-type of ventricular septal defect, and aortic atresia.[70,258,260] Although a variety of ventricular septal defect morphologies have been described, the most common is characterized by caudal displacement of the infundibular septum that fused posteriorly with the left-sided ventriculoinfundibular fold ventricle (Fig. 31-5C).[70,260] This completely blocks the subaortic vestibule. The combination of aortic atresia with a normal left ventricle has been described in combination with an associated interruption of the aortic arch. Blood supply to the ascending aorta has been mediated by an aortopulmonary window,[62,98,99,104] right-sided arterial duct,[100] and proximal aortopulmonary fistulous connection (likely a fifth aortic arch with a systemic-to-pulmonary artery connection) ventricle (Fig. 31-6).[102,103]

In 1981, Norwood and Stellin reported a reparative operation for a patient with aortic atresia, interruption of the aortic arch, ventricular septal defect and bilateral arterial ducts.[100] The ventricular septal defect was patched; the aortic arch reconstituted, and an apical left ventricle–descending aorta conduit was used to provide continuity between the left ventricle and the systemic circulation. Duffy and coworkers next reported in 1983 the initial palliation of a baby with aortic atresia and ventricular septal defect at 23 days of age.[263] The first procedure included bilateral banding of the branch pulmonary arteries similar to the patient reported from Toronto in 1977,[70] and replacement of the ductus arteriosus with a Goretex conduit. At 23 months of age, corrective surgery was accomplished by closure of the ventricular septal defect, insertion of a valved conduit between the apex of the left ventricle and the subdiaphragmatic aorta, removal of the pulmonary artery bands and division of the pulmonary–aortic conduit. In follow-up the patient had a mild coarctation of the aorta but remained asymptomatic at 2 years of age.

A single-stage repair in the neonate without the use of an apical left ventricle-to-descending aortic conduit was first reported by Austin and colleagues in 1989,[264] and there have been a number of other reports since that time.[265–271] Repair is accomplished by tunneling the left ventricle through the ventricular septal defect to the pulmonary artery. The pulmonary

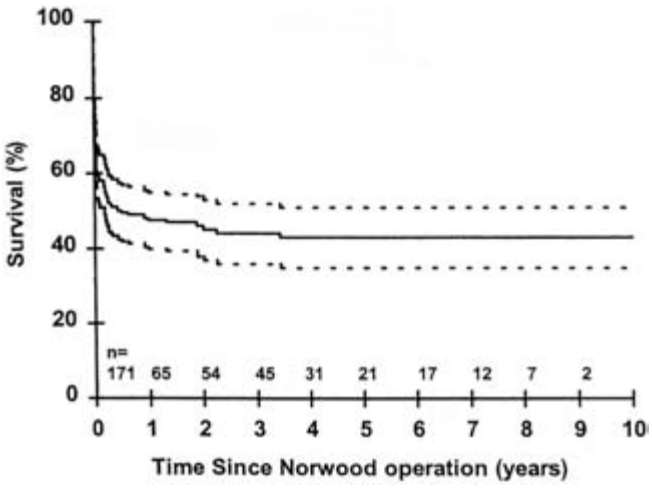

Fig. 31-7 Kaplan–Meier survival curve for 171 patients undergoing modified Norwood procedure at Toronto's Hospital for Sick Children from 1990 to 2000. The overall mortality rate was 41%. (Reprinted rom Azakie *et al.*,[193] Copyright (2001), with permission from the Society of Thoracic Surgeons.)

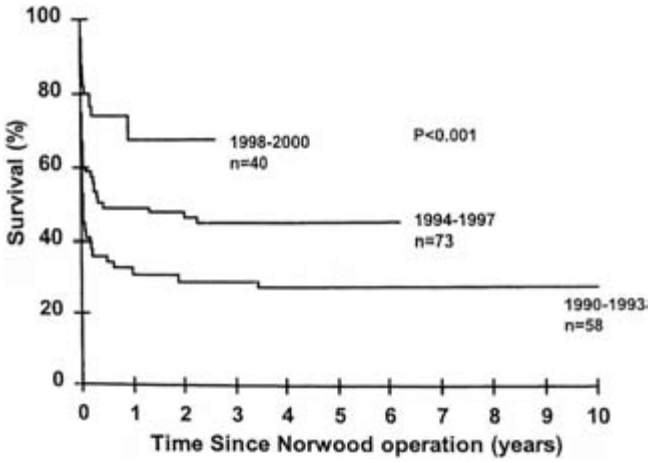

Fig. 31-8 Data from Toronto's Hospital for Sick Children. Kaplan–Meier curves demonstrate improving outcome between the different eras. (Reprinted from Azakie *et al.*,[193] Copyright (1999), with permission from the Society of Thoracic Surgeons.)

trunk is divided and the proximal pulmonary trunk is connected to the ascending aorta. Continuity between the right ventricle and distal pulmonary artery confluence is achieved with a conduit. We have experience with the repair of six patients with one death. The late mechanical issues relate to the performance of the native pulmonary valve in the systemic circulation and the "usual" problems encountered with a conduit in the neonate and infant. There is one patient with aortic atresia, ventricular septal defect and discordant ventriculoarterial connections who underwent a successful one-stage biventricular repair using a similar technique.[272]

Patients with the hypoplastic left heart syndrome complicated by absent aortic valve leaflets have tended to do very poorly at first-stage Norwood and cardiac transplantation is a better treatment strategy.[273–278] Finally, as we will discuss elsewhere (see Chapters 25A and 37), patients with a single or systemic right ventricle are known to develop ventricular dysfunction and heart failure, indeed a sobering and concerning consideration for those on or those who have completed Fontan palliation.[279] One must be impressed by ever-improving results with Norwood palliation as shown in Toronto (Figs 31-7, 31-8) and elsewhere.[163,193,198,211B] Yet a recent survey showed that given a prenatal diagnosis of the hypoplastic left heart syndrome 48% of physicians surveyed would terminate pregnancy, only 22% would continue pregnancy and 30% were uncertain. Given a neonatal diagnosis, physicians were evenly split between surgical treatment, comfort care without surgery, and uncertainty.[280]

Thus in the > 25 years since systematic palliation of the patient with hypoplastic left heart syndrome began:

- Hearts with typical morphology of the hypoplastic left heart syndrome are amenable to univentricular palliation and there is increasing experience with staged reconstruction concluding in the Fontan operation.
- There is still discussion and evolution as to what approach affords the best first stage palliation. There is increasing experience in catheter-mediated palliation and as well evolution from an arterial shunt with its intrinsic instability to a right ventricle to pulmonary artery conduit to afford better postoperative hemodynamics. Some have reverted to bilateral pulmonary banding, but whether this approach will gain wider acceptance is only speculative.
- Surgical results of first-stage palliation continue to improve in many centers.
- Termination of pregnancy will continue to have an effect on liveborn prevalence of this disorder.
- In those patients undergoing staged palliation, there is attrition at and between every stage, with most of the attrition at or about and between the first and second stages.
- Neonatal cardiac transplantation also affords reasonable palliation. It is unclear at this time whether staged palliation or transplantation in the long term will be most advantageous to the patient born with hypoplastic left heart syndrome.
- For patients surviving staged palliation, a morphologically right ventricle will be the systemic ventricle. Thus many of the concerns about the long-term functionality of the morphologically right ventricle are similar to those of patients with transposition of the great arteries surviving the Mustard or Senning operation (see Chapter 25A) or the patient with double-discordance who has undergone physiologic repair (see Chapter 26A).
- Cohen and colleagues have found that amongst patients followed up to 21 years after staged reconstruction for the hypoplastic left heart syndrome the neo-aortic root progressively dilated out of proportion to body size over time, with 98% of their cohort having a Z-score > 2 at most recent follow-up.[281] Neo-aortic regurgitation was present in 61% of patients at most recent follow-up, with progression over time in about half of their study group (49%). However, neo-aortic regurgitation was more than mild in only a few patients. They found that significantly larger neo-aortic root Z-scores were observed in patients with any degree of neo-aortic regurgitation at most recent follow-up.
- As in any patient undergoing repair of a complex cardiac malformation in the neonatal period using profound hypothermia and cardiac arrest, longitudinal neurodevelopmental and cognitive function assessments are important.
- Considerable new knowledge has evolved directly from the challenges to salvage babies with the hypoplastic left heart syndrome.
- This malformation complex should no longer be considered the "worst heart disease."[1]

All references can be found at the end of the book. See pp. 777–84 for Chapter 31.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

32

Robert M. Freedom and Shi-Joon Yoo

Double-Inlet Ventricle

Double-inlet ventricle is the most common form of so-called "single or univentricular hearts." In double-inlet ventricle, the ventricular inlet is unseptated (Fig. 32-1). It sounds so simple, ventricular septation, for hearts with basically one unseptated ventricular chamber, but the results, early and late for the most part were disappointing, and thus this approach has been largely abandoned.[1–8] Something better had to come along, and it did: atrial separation and an atriopulmonary connection, the Fontan operation or complete right heart bypass, first performed in 1968 and with the wisdom of restraint published in 1971.[9–11] This operation dramatically altered the outcomes for many patients with a "single ventricle" malformation. The thrust of contemporary management strategies is to protect the integrity of the myocardium and pulmonary vascular bed so that the patient will meet the criteria for the Fontan operation (see Chapter 36). Fundamental to this strategy then is to preserve the systolic and diastolic function of the myocardium, prevent disproportionate myocardial hypertrophy and disadvantageous ventricular compliance, maintain functional integrity of one atrioventricular valve, and very importantly to protect the pulmonary vascular bed from hypertensive changes.[8,9] Perhaps as well, it is important to maintain the functional integrity of the pulmonary valve in those patients with a single ventricle malformation either with or at risk for subaortic stenosis for later palliation.[12–16]

Prevalence

The prospective Bohemia Survival Study identified 67 children with a single ventricle from a total live-born cohort of 815 569 children born between 1980 and 1990.[17] This gave a prevalence of 0.08 per 1000 live births and in this study these accounted for 1.37% of all congenital heart disease.[17] The New England Regional Infant Cardiac Program identified 58 infants with single ventricle from 2381 infants with congenital heart disease.[18] These accounted for 2.4% of all congenital heart disease and a prevalence of 0.054 per 1000 live births.[18] Data from the Toronto Hospital for Sick Children revealed that "common ventricle" accounted for 1.65% of all congenital heart defects.[19] O'Leary reviewing the available literature to 2002 suggests a birth incidence of single ventricle of between 4 and 8 per 10 000 live births.[19A] Steinberger and colleagues using data collected from the Baltimore–Washington Infant Study have carried out a population-based epidemiological study of single ventricle.[17A] This survey addressed infants born from 1981 to 1989, finding that single ventricle occurred in 1.25%. Of the 55 patients with single ventricle, the authors interviewed 48 families. Of these 48, 33 had normal situs and 15 had abnormal situs.[17A] Paternal alcohol consumption (OR = 2.0, 95% CI, 1.1–3.9%) and paternal cigarette smoking (OR = 2.4, 95% CI, 1.1–5.1%) were associated with all cases of single ventricle. These associations were even stronger in the subset of infants with abnormal situs. A maternal history of a previous induced abortion was also associated with infants born with abnormal situs (OR = 3.2, 95% CI, 1.1–11.5%). Paternal marijuana use was associated with cases of single ventricle in normal situs (OR = 2.2, 95% CI, 1.0–5.2%).[17A]

A single ventricle malformation has been reported in siblings and in other familial aggregations. In one such report a single ventricle and common arterial trunk were documented in siblings.[20,20A] Weigel and his colleagues have studied the occurrence of congenital heart defects in siblings of patients with univentricular hearts and tricuspid atresia.[21] Eleven of the total 388 siblings (2.8%) of the 189 patients with univentricular heart had a congenital heart defect (see Table 32-1).

Nomenclature

There is still no agreement as to how best to designate those hearts with a functional single ventricle: common ventricle, primitive ventricle, single ventricle, one ventricle hearts, dominant ventricle, univentricular heart, hearts with univentricular atrioventricular connection, double-inlet ventricle, etc. At least some of the difficulty rests with the definition of what is or constitutes a ventricle. Most of us caring for patients with congenital heart disease sort of know what it is when we see it. But the transatlantic discussion regarding nomenclature was quite polarized, at times pejorative, entertaining to a point, and even informative:

Anderson RH, Becker AE, Freedom RM *et al.* Problems in the nomenclature of the univentricular heart. *Herz* 1979; 4: 97–106.[22]

Anderson RH, Becker AE, Tynan M *et al*. The univentricular atrioventricular connection: getting to the root of a thorny problem. *Am J Cardiol* 1982; **54**: 822–8.[23]

Anderson RH, Macartney FJ, Tynan M *et al*. Univentricular atrioventricular connection: the single ventricle trap unsprung. *Pediatr Cardiol* 1983; **4**: 273–80.[24]

Van Praagh R, David I, Van Praagh S. What is a ventricle? The single ventricle trap. *Pediatr Cardiol* 1982; **2**: 79–84.[25]

Van Praagh R, David I, Wright GB, Van Praagh S. Large RV plus small LV is a not a single RV [letter]. *Circulation* 1980; **61**: 1057.[26]

Anderson RH. Problems in nomenclature: bulboventricular foramen vs. ventricular septal defect. *J Am Coll Cardiol* 1988; **11**: 674–5.[27]

Lincoln C, Anderson RH. Nomenclatura obscura: subaortic obstruction in double-inlet left ventricle and related lesions. *Ann Thorac Surg* 1991; 52: 730–1.[28]

Anderson RH. Weasel words in paediatric cardiology. *Int J Cardiol* 1983; **2**: 425–9.[29]

Well, I guess you get the idea, the flavor of the discussion and the "players!"

But beyond the obvious differences, the specific types of hearts that we recognize as having a "single ventricle" are important to management and to one's understanding of the natural and modified history. Most agree that the three morphological types of single ventricle hearts include (Fig. 32-1):

- left ventricle type with/without rudimentary right ventricle
- right ventricle type with/without rudimentary left ventricle
- indeterminate or undifferentiated type.

One can construct a complex matrix of the various types of these hearts according to the following morphological variables:

- atrial situs (solitus, inversus, indeterminate)
- type of atrioventricular connection (double-inlet, absent right or absent left)
- right or left hand pattern of ventricular organization
- ventriculoarterial connection (concordant, discordant, double-outlet, single-outlet aorta, single-outlet pulmonary trunk, common arterial trunk).

The concept of a univentricular atrioventricular connection and the 50% rule has certainly added even more complexity to this already complex situation.[30–33] Some hearts with important straddling of the atrioventricular valves, dominant forms, right or left, of the atrioventricular septal defect, hearts with twisted atrioventricular connection, etc., may be best treated with univentricular palliation rather than a high risk biventricular repair (Table 32-2).[34]

One might argue that under the "umbrella" of the 50% rule and the concept of the univentricular atrioventricular connection that some of these hearts belong to the family of single ventricle. Yet there are still some unequivocally biventricular hearts best and perhaps only amenable to univentricular palliation.[35,36] Among these are many forms of hypoplastic left heart syndrome, with aortic atresia or critical stenosis, severe mitral stenosis and a diminutive left ventricle; pulmonary atresia, intact ventricular septum, and a right ventricular-dependent coronary circulation; extreme Ebstein's anomaly for malformation of the tricuspid valve in the newborn with/without organic pulmonary atresia. In addition some forms of double-outlet right ventricle with a remote ventricular septal defect; hearts with an imperforate tricuspid valve with congenitally absent pulmonary valve, etc., are all better treated on the algorithm of univentricular palliation.[35–39] From a variety of studies carried out in the West, a uni-

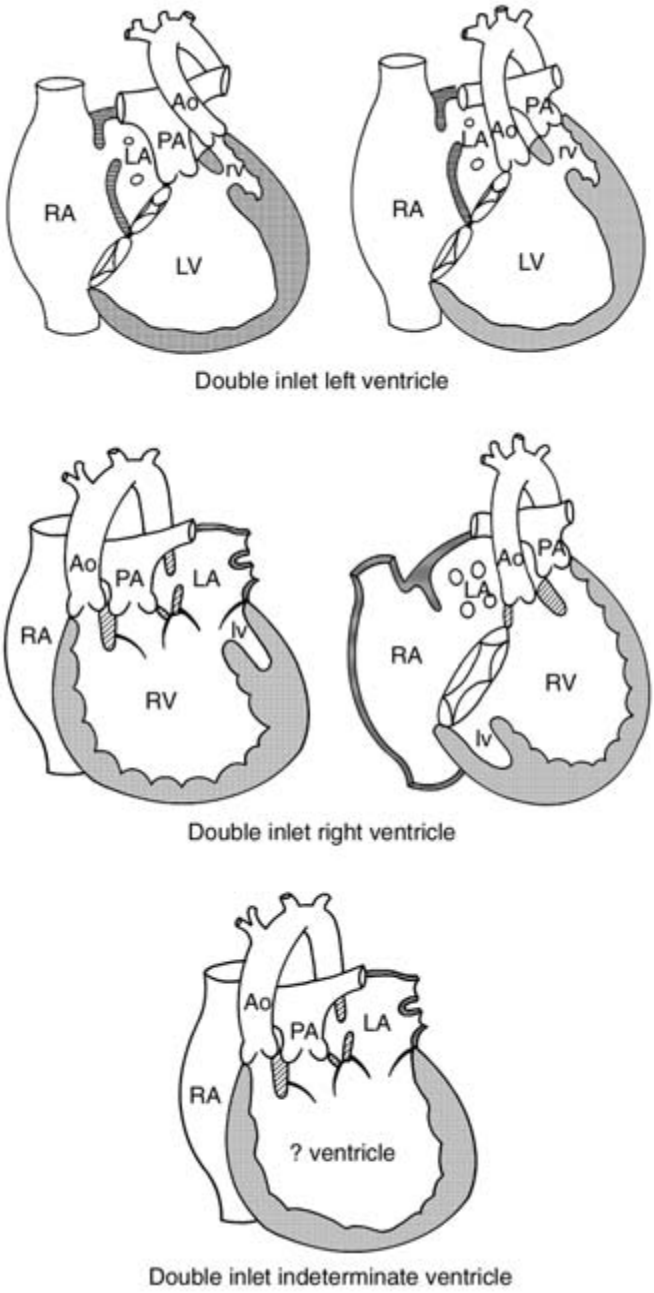

Fig. 32-1 Various forms of double-inlet ventricles in situs solitus. Ao, aorta; LA, left atrium; LV or lv, left ventricle; PA, pulmonary artery; RA, right atrium; RV or rv, right ventricle.

Table 32-1 Occurrence of congenital heart defect in siblings of patients with ventricular heart or tricuspid atresia

Type of univentricular heart	DILV	Complex UVH	Complex UVH and asplenia	Complex UVH and polysplenia
No. of patients	102	69	14	4
No. of siblings in each group	202	140	29	7
No. of siblings with CHD	1	7	1	2
Siblings with CHD (%)	0.5	5.0	3.4	28.6

CHD, congenital heart defects; DILV, double-inlet left ventricle; UVH, complex univentricular heart.
(From Weigel *et al.*[21] with permission)

Table 32-2 Conditions requiring univentricular palliation, so-called functionally single ventricles

Double-inlet ventricles
Tricuspid atresia with absent right atrioventricular connections or imperforate tricuspid valve
Other forms of absent right or left atrioventricular connections
Important straddling of an atrioventricular valve or valves
Significantly unbalanced forms of atrioventricular septal defect
Twisted atrioventricular connections with a straddling atrioventricular valve or significant hypoplasia of a ventricle
Hypoplastic left heart syndrome
Most cases of aortic atresia or critical stenosis
Severe mitral stenosis with diminutive left ventricle
Pulmonary atresia with intact ventricular septum, significantly hypoplastic right ventricle, and/or right ventricular-dependent coronary circulation
Extreme form of Ebstein's anomaly of the tricuspid valve with functional or anatomical pulmonary atresia
Double outlet right ventricle with a remote ventricular septal defect that cannot be routed to a ventricular outlet

ventricular atrioventricular connection of left ventricular type is found in 60–70% of patients.[2,8,22,23,30,31,33,40–49] In any of these studies, again in an occidental patient population, the single right ventricle is considerably less common, ranging from *c.* 5% to 25% of cases, and those with an indeterminate ventricle usually < 5%. In an angiographic study of ventricular morphology from the Mayo Clinic published by Julsud and colleagues, the ventricular morphology was determined in 476 patients undergoing a Fontan procedure.[50,51] A dominant left ventricle was identified in 72%, a dominant right ventricle in 16%, and a ventricle of indeterminate morphology in 1%.[51] In an autopsy study of 205 hearts with a double-inlet ventricle, Anderson and his colleagues found double-inlet left ventricle in 140 (56%), double-inlet right ventricle in 25 (12.2%), and double-inlet indeterminate ventricle in 40 (19.5%).[30,52] The incidence of double-inlet indeterminate ventricle in this compilation is considerably higher than most other surveys conducted in an occidental population. Van Praagh and his colleagues found of 31 autopsied cases of single ventricle 23 had a single left ventricle (74.2%) and 8 (25.8%) had a single right ventricle.[41] Wang and coworkers have reviewed the ventricular morphology as determined by echocardiography in 60 Chinese patients with double-inlet ventricle.[53] Interestingly, they found both atria connected to a dominant right ventricle in 36 patients (60%), to a dominant left ventricle in 17 (28%), and to an indeterminate ventricle in 7 (12%).[53] Right isomerism was identified in 30 patients (83%) with double-inlet right ventricle; in 5 (29%) with double-inlet left ventricle and in 86% with double-inlet indeterminate ventricle.[53] Wang attributed the high incidence of double-inlet right ventricle in this study to the high prevalence of right atrial isomerism in the Chinese population and the known association between right isomerism and double-inlet or common-inlet right ventricle.[54,55]

Morphological considerations

At least 60–70% of all univentricular hearts are characterized morphologically by a dominant ventricle of left ventricular morphology.[2,8,22,23,30,31,33,40–49] There is usually a rudimentary right ventricle and the site of communication between these two chambers is a ventricular septal defect, called by some a bulboventricular foramen or outlet foramen (Figs 32-1 upper panel, 32-2).[27,28] The rudimentary right ventricle may be right-sided and anterior or left-sided and anterior.[47] All patterns of ventriculoarterial connection have been observed, but the most common is that of transposition of the great arteries or ven-

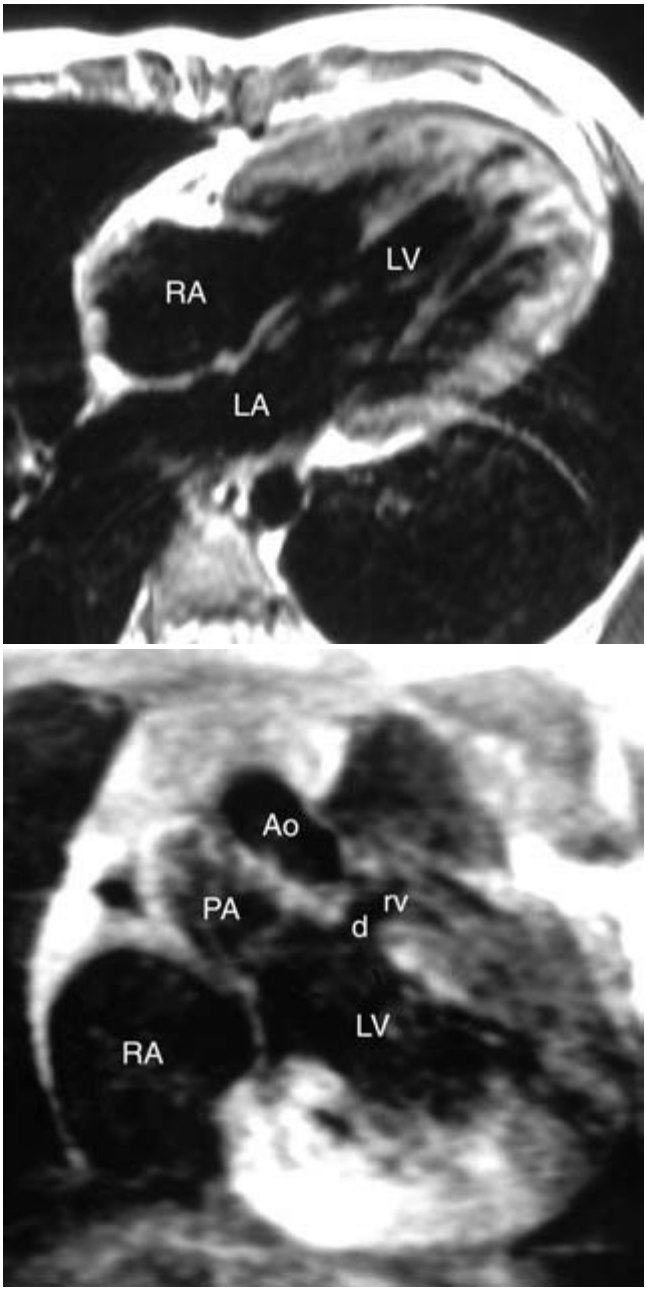

Fig. 32-2 Double-inlet left ventricle of left-hand topology with discordant ventriculoarterial connection. **A**. Axial MR image shows both right atrium (RA) and left atrium (LA) connected to the left ventricle (LV). **B**. Coronal MR image demonstrates the rudimentary right ventricle (rv) located at the superior and left corner of the left ventricle. The ventricular septal defect (d), which is a part of the subaortic outflow tract, is very restrictive. Ao, ascending aorta; PA, pulmonary artery.

triculoarterial discordance.[2,8,22,23,30,31,33,40–49] The most common pattern of internal organization of the ventricle conforms to a left-hand pattern, documented in from 60% to 70% of those with a dominant left ventricle.[2,8,22,23,30,31,33,40–49] The double-inlet left ventricle with left-sided rudimentary right ventricle and concordant ventriculoarterial connections is uncommon, and abnormalities of the left-sided atrioventricular valve are frequent in this setting.[56,57] The Holmes heart with a right-sided rudimentary right ventricle and normal ventriculoarterial connections is more common.[57–61] The second most frequent form of single ventricle is one of right ventricular morphology (Figs 32-1 middle panel, 32-2). A rudimentary left ventricle is usually present along the inferior, posterior or diaphragmatic surface of the ventricular segment. In its "purest" form, a rudimentary left ventricle is absent.[25,26] The single right ventricle is seen most commonly, but not exclusively, in patients with visceroatrial heterotaxy, particularly those with asplenia/right isomerism[53–55] (Fig. 32-3). The least common form of single ventricle is a ventricle of indeterminate morphology (Fig. 32-1 lower panel).[2,30–33,41,45,50,51] The type of atrioventricular connection may be that of a double-inlet, absent right or absent left atrioventricular connection. Virtually any abnormality of the systemic or pulmonary veins, atrial septum or atrial appendage (juxtaposition), form and function of the atrioventricular valves, pulmonary artery, aortic arch (laterality and/or obstruction), etc., may complicate the situation.

Change in form and function of hearts with one dominant ventricle

The change in form and function of "one ventricle" hearts has fascinated many of us for a long time. Any number of studies have addressed the changing nature of hearts with a univentricular atrioventricular connection.[62–79] These phenomena are of course applicable to hearts with a double-inlet or an absent right or absent left atrioventricular connection as well. Indeed, there is probably more information about progressive pulmonary outflow tract obstruction in patients with classic tricuspid atresia and concordant ventriculoarterial connections, and conversely there is more information about the development of systemic outflow tract obstruction in those patients whose aorta originates from a rudimentary right ventricle and pulmonary artery from the dominant left ventricle. Furthermore, hearts with an absent left atrioventricular connection or an obstructive one with an atrial septum that is intact or nearly so, are more likely to be candidates for the development of left atrial hypertension, and the deleterious consequence on pulmonary vascular morphology and hemodynamics. These changing phenomenon include:

- progressive systemic outflow tract obstruction
- progressive change in ventricular function/hypertrophy
- progressive atrioventricular valve regurgitation
- progressive left atrial hypertension
- progressive pulmonary outflow tract obstruction
- progressive deterioration in atrioventricular conduction
- development of pulmonary vascular obstruction
- development of aortopulmonary collateral blood flow.

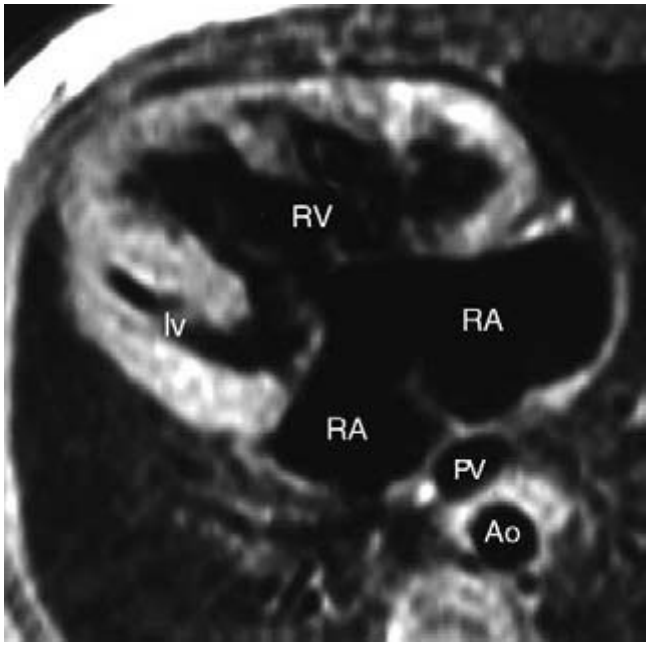

Fig. 32-3 Double-inlet right ventricle in a patient with right isomerism. Axial MR image shows that the whole left-sided right atrium (RA) and more than half of the right-sided right atrium are connected to the anteriorly located main chamber of right ventricular morphology (RV). The rudimentary left ventricle (lv) is located rightward and posterior to the right ventricle. Ao, descending aorta; PV, anomalous pulmonary venous confluence.

Progressive systemic outflow tract obstruction

Systemic outflow tract obstruction has been amply documented in patients with a single ventricle malformation. Subaortic stenosis or atresia may be present at birth, and in some of these patients the systemic circulation is duct-dependent.[45,48,80–88] There is also a substantial literature showing that systemic outflow tract obstruction may be acquired as well.[62,64–66,72,77–79,89–125] The most frequent setting for subaortic stenosis is found in the heart with a univentricular atrioventricular connection of left ventricular type, rudimentary right ventricle and transposition of the great arteries. The aorta originates above the rudimentary right ventricle and blood reaches the aorta and systemic circulation through the bulboventricular foramen or ventricular septal defect. Amongst hearts with a univentricular atrioventricular connection of left ventricular type and a rudimentary right ventricle with a discordant ventriculoarterial connection, the ventricular septal defect tends to be large and neither actually nor potentially restrictive when there is naturally-occurring important pulmonary outflow tract obstruction.[14,47,66,86,96,98,100,111,125] Conversely, in the absence of naturally-occurring pulmonary stenosis, the ventricular septal defect tends to be smaller than the aortic root diameter, and the substrate for subaortic stenosis will be present (Fig. 32-2).[14,47,66,86,96,98,100,111,120,125] These morphological observations should not be surprising considering the reciprocal relationship between systemic and pulmonary blood flow pathways in hearts with complex intracardiac disturbances. There are, of course, exceptions to this reciprocal relationship, and in some patients with naturally-occurring pulmonary outflow tract obstruction subaortic stenosis either will be evident or, over time, will develop. In those patients with a single left ventricle malformation, rudimentary right ventricle, transposed great arteries and an obstructive anomaly of the aortic arch, the ventricular septal defect is likely already restrictive, or certainly smaller than the aortic root, and thus likely to show further reduction in

size.[14,47,66,86,96,98,100,111,125] The patient with a univentricular atrioventricular connection of right ventricular type may also present with or develop subaortic stenosis.[86,125] In this situation the aortic outflow tract is narrowed, similar to the systemic outflow tract in the Taussig–Bing form of double-outlet right ventricle (see Chapter 28). The aortic outflow tract is wedged between the right-sided ventriculoinfundibular fold and the infundibular septum.[86,96,125]

Somerville and her colleagues were the first to report in August 1974 the phenomenon that subaortic stenosis may be acquired in the patient with a "common" ventricle.[64] Both patients reported by these authors had undergone pulmonary artery banding, and before the banding procedure no pressure gradient was measured at cardiac catheterization between the dominant ventricle and the aorta.[64] They wondered whether reduction in size of the bulboventricular foramen was "encouraged" by banding.[64] In 1976 we reported 4 patients who developed subaortic stenosis after pulmonary arterial banding for a "common" ventricle.[65] All 4 patients were found to have a univentricular atrioventricular connection of left ventricular type, a rudimentary right ventricle and transposition of the great arteries. Subaortic stenosis secondary to a restrictive bulboventricular foramen was diagnosed after the pulmonary artery banding. We suggested in 1976 that two factors likely contributed to the development of subaortic stenosis in these patients: (1) the ventricular septal defect or bulboventricular foramen was initially smaller than the aortic root, and thus already predisposed to spontaneous diminution in size; (2) pulmonary artery banding promoted myocardial hypertrophy and this likely contributed to further reduction in size of the ventricular septal defect subsequent to a reduction in pulmonary blood flow.[65] We commented as well that these patients demonstrated at necropsy very severe myocardial hypertrophy that virtually obliterated the functional cavity of the dominant left ventricle.[65] In 1984, we next reported 17 patients with subaortic stenosis complicating a single ventricle malformation.[98] All the patients in this report had a dominant left ventricle, a rudimentary right ventricle and transposed great arteries. In 15 of the 17 patients, the development of subaortic stenosis occurred following pulmonary artery banding, indeed a recurrent theme in these patients. The median duration from the banding procedure until the recognition of subaortic stenosis was 2.3 years. We extended these observations in 1986 by analyzing the courses of 43 patients seen between 1970 and 1985 at the Toronto Hospital for Sick Children with a univentricular heart palliated by pulmonary artery banding.[66] Thirty-two of the 43 patients (74%) had a single left ventricle, a rudimentary right ventricle, and transposed great arteries.[66] For the entire group, subaortic stenosis was diagnosed in 31 patients (72%) after pulmonary artery banding.[66] The mean age at banding was 0.21 years and the mean age at diagnosis of subaortic stenosis was 2.52 years. Rao who has published extensively about the fate of the ventricular septal defect in tricuspid atresia[73,75,76] has written that "it is the intrinsic nature of the ventricular septal defect rather than pulmonary artery banding that is responsible for spontaneous defect closure."[93] Donofrio and her colleagues have offered yet another explanation for the development of subaortic stenosis in these patients.[126] They suggested that early changes in ventricular septal defect size and ventricular geometry in single left ventricle occurs after volume-unloading surgery, namely the bidirectional cavopulmonary shunt. This finding has been confirmed by van Son and his colleagues.[127] This group documented that volume unloading of the single left ventricle resulted in instantaneous contraction of left ventricular size, an increase in left ventricular posterior wall thickness, a decrease of the median bulboventricular foramen area index, and development of a median gradient of 60 mmHg across the bulboventricular foramen.[127] Chin and his colleagues have also demonstrated changes in ventricular geometry and volumes early after the Fontan operation.[128] The views of Donofrio[126] and van Son[127] and their respective colleagues do not exclude the role of pulmonary artery banding as we have proposed in the genesis of subaortic stenosis.[13,14,65,66,96,98,100,125] In fact the views are complementary. Pulmonary artery banding does not result in dramatic instantaneous volume-unloading of the ventricle. But as we wrote some years ago reduction of pulmonary blood flow, myocardial hypertrophy secondary to the pulmonary artery band and increased ventricular afterload, together with the natural predisposition for spontaneous diminution in size of the ventricular septal defect all act in concert to promote systemic outflow tract obstruction.[65,66,86,96,98,100,111,120,125] Although some felt that a pressure gradient between the dominant left ventricle and aorta was necessary to make the diagnosis of systemic outflow tract obstruction, in a number of publications we showed that this was not the case.[66,86,96,98,100,125] The end result of a banded pulmonary trunk and a restrictive ventricular septal defect is relentless myocardial hypertrophy and ischemia.

The ventricular septal defect or bulboventricular foramen is so strategic in these patients as the "guardian" of the systemic outflow tract that it has received considerable attention from the morphologist and from the various imaging modalities. Anderson and his colleagues have shown with clarity the course of the specialized conduction tissue in the double-inlet left ventricle and the so-called safe areas for resection.[102,129,130] We have published extensively on the topography and morphology of the rudimentary right ventricle in the patient with a dominant left ventricle and have documented those sites and the mechanisms that can obstruct the systemic outflow pathway.[47,125] There is less emphasis today on angiocardiographic imaging[86,125,131–138] and more reliance on cross-sectional echocardiographic imaging.[139–141] There has been some interest as well in *en face* imaging or three-dimensional reconstruction of the ventricular septal defect from cross-sectional echocardiography in those univentricular hearts predisposed to subaortic stenosis (Fig. 32-4).[141A,141B,142] Magnetic resonance imaging has also been used in the assessment of the single ventricle through the various stages leading to the Fontan[143–146] and to evaluate Fontan pathway flow dynamics.[138] There is also some data comparing the roles of cross-sectional echocardiography and MR imaging.[147]

Progressive change in ventricular hypertrophy and function

Our early observations about subaortic stenosis did not occur in isolation. There was increasing experience in the late 1970s and into the 1980s with the Fontan operation, various modifications in technique, and expanded indications for this operation. Many examined risk factors for poor outcome of the Fontan operation, forcing continued scrutiny of the original criteria set forth by Choussat and his colleagues.[2,12–16,66,71,72,77–79,89,95–114,116–125] It became apparent that ventricular hypertrophy was identified as a risk factor for poor

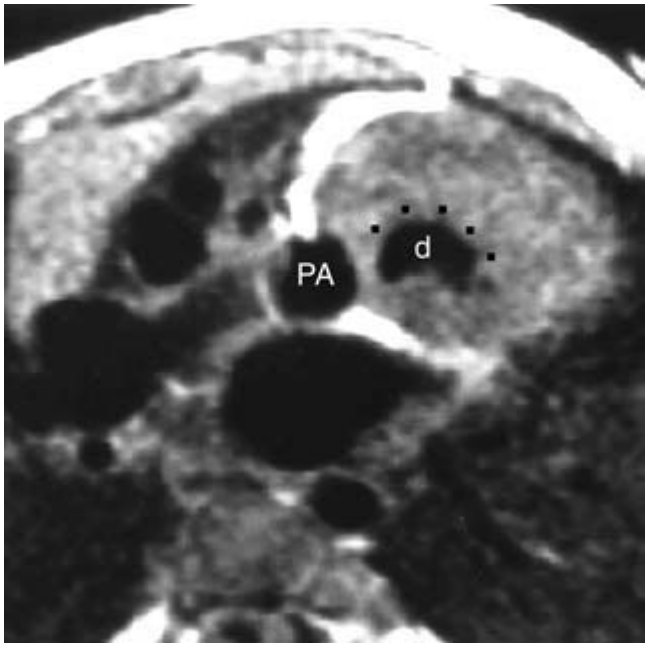

Fig. 32-4 *En face* imaging of the ventricular septal defect in double-inlet left ventricle with discordant ventriculoarterial connection. The cut-through section of the ventricular septal defect demonstrates a cashew-nut shaped defect (d). The expected course of conduction tissue is marked with dotted line. PA, pulmonary artery.

outcome at a Fontan operation, even when all other criteria were met.[2,12–16,66,71,72,77–79,89,95–114,116–125] One of the consistent features in those patients dying at Fontan or requiring early Fontan-takedown was the relationship between pulmonary artery banding and severe myocardial hypertrophy.[13–16,66,71,72,77–79,89,95–114,116–125]

Kirklin and his colleagues in 1986 provided data indicating that ventricular hypertrophy was a risk factor for death after Fontan's operation, and that hypertrophy of the main ventricular chamber may be an inevitable consequence of aging.[118] Seliem and his colleagues addressed in 1989 the relation between preoperative left ventricular mass and outcome of the Fontan procedure for patients with tricuspid atresia.[16] Their data demonstrated that the less satisfactory postoperative clinical outcome may be related to impaired diastolic function associated with inappropriately hypertrophied left ventricular myocardium. Those with a good clinical outcome had a left ventricular muscle mass (g/m^2) of 92 ± 31, while those with a poor outcome had a left ventricular muscle mass of 146 ± 61 (*P* value < 0.001). Thus at least in part the management of the neonate is to avoid those procedures that disproportionately increase the ventricular mass. Data from this institution published by Caspi and his colleagues in 1990 also showed that myocardial hypertrophy contributed to a poor outcome at the Fontan operation.[148] These observations were extended by Akagi in Toronto and Vogel in Munich, both in 1992, and their respective colleagues.[14,15]

The Mayo Clinic has had a very large experience with the Fontan operation. Barber and his colleagues from the Mayo Clinic reported in 1984 the outcomes of their institutional repair of double-inlet left ventricle with obstructed anterior outlet chamber, an experience from 1973 through 1983.[89] Of the 18 patients reported in this paper, 10 patients (56%) died early and there was 1 late death. Thirteen of the 18 patients (72%) had undergone previous pulmonary artery banding. They next reported the results of a staged approach to subaortic stenosis in hearts with a univentricular connection to a dominant left ventricle and an anterior subaortic chamber.[103] Of the 32 patients operated on between 1984 and 1989, the overall mortality decreased to 16%.[103] We reported in 1990 our findings in 37 patients who died from our cohort of 245 patients undergoing the Fontan from 1976 to 1988.[148] During this time our institutional mortality for the Fontan procedure was 15%, but was 40% in those with subaortic stenosis.[148] With increasing awareness of the hazard posed by systemic outflow tract obstruction, many surgical maneuvers were employed to treat subaortic stenosis. These included:

- creation of an aortopulmonary window proximal to the pulmonary artery band*[31,98]
- interposition of a vascular tube graft between the main pulmonary trunk proximal to the pulmonary artery band and descending thoracic aorta*[96,98]
- interposition of an apical left ventricle-to-descending aorta conduit*[98,98A,B]
- arterial switch option with/without pulmonary artery banding*[105,110,149]
- a Norwood (Damus–Kaye–Stansel) operation plus a systemic-to-pulmonary shunt in the neonate and young infant[97,99,109,150–152]
- surgical enlargement of the restrictive vsd plus a bidirectional cavopulmonary shunt[103,114,122]
- Damus–Kaye–Stansel operation plus a bidirectional cavopulmonary shunt[105,106,110]
- arterial switch and modified Fontan*[101]
- Damus–Kaye–Stansel operation plus modified Fontan.[103,114,122,153–155]

Those procedures followed by an asterisk have been abandoned, or nearly so. There is some evidence that there is an advantage to early relief of systemic outflow tract obstruction in univentricular hearts.[104] Ilbawi and his colleagues have shown that early relief of subaortic stenosis (in the neonatal period) is associated with a lower ventricular muscle mass compared to those operated in childhood, and similarly the mass/volume ratio was more favorable in those treated earlier.[104] There is less agreement as to which procedure affords better and sustained palliation at the lowest risk. For the neonate and young infant with obviously severe restriction at the ventricular septal defect, often with an obstructive anomaly of the aortic arch, most would perform a Norwood-like operation with a systemic-to-pulmonary artery shunt, converting to a bidirectional cavopulmonary shunt or hemi-Fontan within the first 6 months or so (Fig. 32-5). While the data about the relationship between pulmonary artery banding, progressive subaortic stenosis and the inevitable consequence of myocardial hypertrophy are compelling, most of these observations were published in the era before routine staging maneuvers to the Fontan were introduced. Indeed, from our many publications, it was often > 2 years from the time of the initial banding procedure to the clinical recognition and diagnosis of subaortic stenosis.[14,66,98,100,111,120] Today many perform the Fontan as early or even earlier than 2 years of age, with staging within the first 4–6 months. Thus there are still some who continue to palliate patients at risk for subaortic stenosis with pulmonary artery banding, acknowledging that these will require early staging with a bidirectional cavopulmonary shunt and either surgical

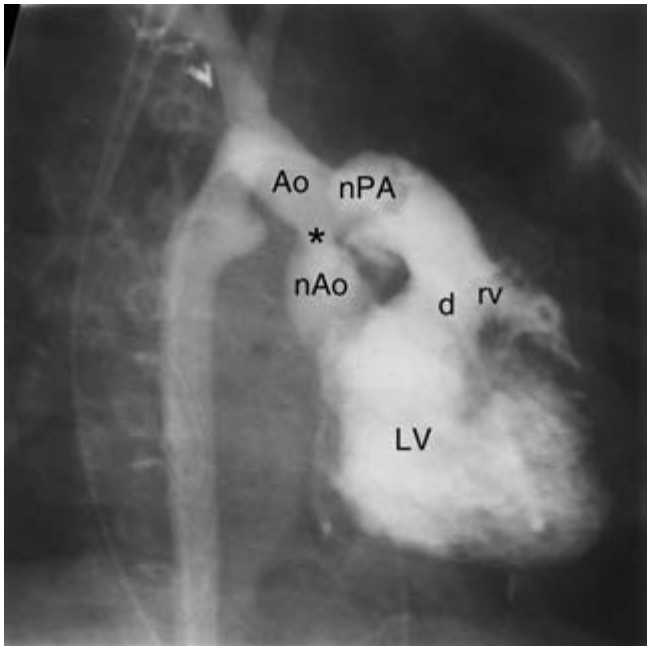

Fig. 32-5 Damus–Kaye–Stansel operation. The patient had double-inlet left ventricle (LV) with concordant ventriculoarterial connection. The native pulmonary artery (nPA) was anastomosed to the aorta (Ao). The native aorta (nAo) developed mild stenosis (asterisk). d, ventricular septal defect; rv, right ventricle.

enlargement of the ventricular septal defect, or a Damus–Kaye–Stansel pulmonary-to-ascending aortic anastomosis (Fig. 32-5).[107,121,123,124,156] When subaortic stenosis is recognized late (i.e. when Fontan surgery is contemplated), a Damus–Fontan procedure can be carried out or the ventricular septal defect can be enlarged at the time of the modified Fontan procedure. Indeed, a Damus–Kaye–Stansel procedure has been performed for systemic outflow tract obstruction recognized after a modified Fontan procedure had been performed,[157,158] although most have tended to enlarge a restrictive ventricular septal defect.[159–161] A number of studies have addressed the fate of the pulmonary valve in the systemic circulation (see Chapters 25B and 31). The most common conditions for the pulmonary valve to function in the systemic circulation are the arterial switch operation for transposition of the great arteries and the Norwood–Fontan continuum for the hypoplastic left heart syndrome.[162,163] Long-term banding of the pulmonary trunk, especially when the band is quite close to the pulmonary valve can lead to morphological changes in the pulmonary valve and pulmonary regurgitation.[164] There are clinical observations indicating that neonatal pulmonary artery banding with subsequent conversion to a Damus–Kaye–Stansel and either a bidirectional cavopulmonary shunt or modified Fontan within a year does not importantly compromise the function of the pulmonary valve.[165,166] Clearly we continue to urge caution[100] in the application of pulmonary artery banding in the treatment of these patients as do others.[116,117,117A]

Some years ago there seemed to be some enthusiasm for the arterial switch option in these patients.[110,149,167–169] However, it was often difficult to control the amount of the pulmonary blood flow, which despite a restrictive ventricular septal defect, tended to be excessive. A number of patients who underwent a palliative arterial switch operation required pulmonary artery banding. Some after the palliative switch became too hypoxic, and required a shunt to augment pulmonary blood flow. We only infrequently used this approach and with our improving results with a Norwood strategy have used the Norwood option with a systemic-to-pulmonary artery shunt.[170] From a survey of the contemporary literature, there seems to be less interest now in the palliative arterial switch option than a decade ago.[170] The assessment of ventricular function in patients considered for Fontan surgery and those factors influencing contractility are discussed in Chapter 36. In the history of the surgical treatment of systemic outflow tract obstruction in the patient with a "single" ventricle, Yacoub and hs colleagues were amongst the earliest, if in fact not the earliest to use a proximal pulmonary artery–aortic anastomosis as palliation.[154] His publication in 1976 overlapped with those of Damus and Kaye and Stansel in 1975, although Damus had conceived of the operation in 1972.[154A] It seems that none of these authors was aware of the others' contributions (see also Chapter 25B).

Progressive atrioventricular valve regurgitation

It is not uncommon for patients with single ventricle morphology to develop progressively severe atrioventricular valve regurgitation.[54,171–178] Considerable scrutiny has been paid to the form and function of the atrioventricular valve(s) in patients with a functional single ventricle. Regurgitation has its basis in both anatomical and functional issues. This occurrence is not ventricular-type specific, but is perhaps more common in those patients with a single right ventricle and a common atrioventricular valve.[54] This association is particularly frequent in patients with right isomerism (see Chapter 33).[179] Some years ago we reported the natural and modified history of 76 patients with a common atrioventricular valve guarding a double-inlet atrioventricular connection, and the dominant ventricle was of right ventricular morphology in 42. Abnormal atrioventricular valve function was detected in 46% of the patients at the time of initial presentation.[54] In this series from Toronto patients with a double-inlet ventricle guarded by a common atrioventricular valve had a high early mortality with 37% dying in the neonatal period.[54] Kawahira and colleagues from the National Cardiovascular Center in Osaka found in their study that of 31 patients with a double-inlet right ventricle, right isomerism was identified in 26% and normal atrial arrangements in 61%.[179] In the 93 patients with a common atrioventricular valve guarding a dominant right ventricle, right isomerism was found in 96% of the patients.[179] Before the Fontan procedure, regurgitation of one or both atrioventricular valves in those with a double-inlet right ventricle occurred in 10%, and in 30% of those with a common-inlet right ventricle.[179] Moak and Gersony have studied progressive atrioventricular valve regurgitation in patients with single ventricle.[172] Of 80 patients with single ventricle reviewed by these authors, 8 developed moderate-to-severe atrioventricular valve regurgitation, and in 7 of the 8 patients ventricular function was preserved. Six of the patients had a common atrioventricular orifice and 2 had an absent left atrioventricular connection.[172] They specifically noted that no patient in this small series had two distinct atrioventricular valves.[172] Ventricular unloading may have a salutary effect on the severity of atrioventricular valve regurgitation.[173] It is unlikely that severe atrioventricular valve regurgitation would be greatly improved solely by the construction of a bidirectional cavopulmonary shunt.[173] Imai and his colleagues have had a

large experience with repair of atrioventricular valve regurgitation at the time of a modified Fontan procedure and have not had to replace the regurgitant atrioventricular valve.[174,175] This experience in conserving the atrioventricular valve differs from that of Mahle and his colleagues who reported the results of atrioventricular valve replacement in 17 patients with single ventricle between January 1984 and August 2000.[176] The types of prosthetic valve included: St Jude's valve in 14, Bjork–Shiley in 1, Hall–Kaster in 1, and Carpentier–Edwards in 1. The valve size ranged from 17 to 33 mm. The median age at valve replacement was 3.0 years (range 7 days to 17.3 years). Of the 16 subjects with normal atrioventricular conduction preoperatively, 7 (44%) developed postoperative complete heart block. The hospital mortality was 29%, but decreased significantly from 56% in 1984–93 to no deaths from 1994 to 2000 ($P = 0.03$). Younger age (< 2 years) at operation was also a risk factor for hospital mortality ($P = 0.03$). There were 4 late deaths in this series and 1 patient underwent heart transplantation. Of the surviving patients, none has required replacement of the prosthetic valve. No patient has had a cerebrovascular accident subsequent to atrioventricular valve replacement. Functional status is New York Heart Association functional class I in 5, class II in 1, and Class III in 1. In this experience, the development of postoperative complete heart block was common.

Progressive left atrial hypertension

Left atrial hypertension is particularly common in those patients with an absent, imperforate, or severely obstructive left atrioventricular valve connection and a restrictive interatrial communication.[180–187] This situation may occur when there is naturally-occurring pulmonary stenosis; or when there is no morphologic substrate for pulmonary stenosis. In the former situation, left atrial hypertension may compromise the function of a surgically created systemic-to-pulmonary artery anastomosis.[184] In those patients with no morphologic substrate for pulmonary outflow tract obstruction, left atrial hypertension and pulmonary venous obstruction may blunt the development of pulmonary vascular obstruction. Indeed, striking changes in a patient's hemodynamics may occur following atrial septectomy (balloon; blade; or surgical). In this regard, while blade septostomy may provide immediate relief of left atrial hypertension, such relief is usually not longstanding.[182] There is no doubt that severe pulmonary venous hypertension, especially when longstanding, impacts on the pulmonary vascular bed. Relief of the obstruction may allow advantageous remodeling of the pulmonary circulation. There is little information in these types of complex malformations as to how long it takes to remodel the pulmonary circulation. The construction of a bidirectional cavopulmonary shunt or Fontan circulation is usually unforgiving if there is any substantial impedance to pulmonary blood flow. Thus it is always wise to delay cavopulmonary surgery for a period of time until vascular remodeling occurs. The development of left atrial hypertension should be anticipated in any patient with severe stenosis or atresia of the systemic atrioventricular valve, and thus sequential assessments of the status of the atrial septum are essential in these patients.[180,182,183]

Progressive pulmonary outflow tract obstruction

When there is the substrate for pulmonary outflow tract obstruction, one should anticipate worsening of the obstruction over time.[188] Thus in the Holmes heart, in patients with tricuspid atresia and concordant ventriculoarterial connections, in any heart malformation with a dominant left ventricle and rudimentary right ventricle and concordant ventriculoarterial connections, there is the potential for pulmonary outflow tract obstruction.[57,62,73–76,125,188,189] The development of pulmonary outflow tract obstruction depends on the initial size of the ventricular septal defect, the nature of the pulmonary valve and infundibulum and whether or not there is true anatomic obstruction of the branch pulmonary arteries. If the ventricular septal defect is initially large and non-restrictive, it is unlikely that diminution in size of the defect will occur and thus spontaneous improvement should not be anticipated. But the morphological bases for pulmonary outflow tract obstruction are diverse and even when the pulmonary trunk originates above the dominant left ventricle, the presence of a subpulmonary infundibulum may provide the substrate for pulmonary outflow tract obstruction. In the patient with a complex cardiac malformation, progressive cyanosis and hypoxemia are not invariably related to progressive pulmonary outflow tract obstruction. It may be related to one or more confounding features including disadvantageous intracardiac streaming especially when there is little mixing at atrial level.[56,125,133,171,190] Progressive left atrial hypertension and/or progressive pulmonary venous obstruction, etc., may also result in worsening hypoxemia. Pulmonary vascular obstruction may also contribute to a deterioration in oxygenation, but this process is slow and insidious. The management of the patient with severe reduction in pulmonary blood flow is to create a surgical systemic-to-pulmonary artery shunt, or less commonly to stent the arterial duct and then perform an early bidirectional cavopulmonary shunt. The pulmonary arteries can easily be distorted by a systemic-to-pulmonary artery anastomosis[191–193] or by ductal constriction.[194–196] Even though the central shunt is rarely used today, some patients may still develop pulmonary artery hypertension secondary to a systemic-to-pulmonary artery shunt.[193] It is important both to maximize mixing at atrial level, thus obviating disadvantageous streaming, and to reduce the potential for left atrial hypertension that the atrial septum be widely open.[171] Thus we favor balloon atrial septostomy in most patients with single ventricle physiology whose atrial septum is actually or potentially restrictive.

Progressive deterioration in atrioventricular conduction

There is only sparse information on the incidence of spontaneous complete heart block in patients with a univentricular heart. As in the patient with double-discordance, one would anticipate a higher incidence of atrioventricular conduction delay in hearts with a dominant left ventricle and rudimentary right ventricle whose internal organization conforms to a left-hand pattern of internal organization. Spontaneous onset complete heart block occurs at a rate of about 2% per year in patients with double discordance.[197–201] Fyler states that *c.* 12% of patients with single ventricle develop complete heart block.[202] Ammash and Warnes reported the survival into adulthood of 13 patients with unoperated single ventricle. Only 1 patient had complete heart block.[203] In the series of 83 patients with unoperated univentricular heart reported by Moodie and his colleagues from the Mayo Clinic, 2 patients presented in complete heart block, but no patient during the period

of follow-up developed complete heart block.[68] These numbers suggest that spontaneous onset of complete heart block is less common in patients with single left ventricle with a left-hand pattern of internal organization than in patients with double-discordance. Alboliras *et al.* reported in 1985 the results of the modified Fontan operation in patients without preoperative sinus rhythm. Of 297 patients undergoing the Fontan operation, 6 had complete heart block, and most had spontaneous preoperative onset of complete heart block.[203A]

Development of pulmonary vascular obstruction

Patients with an unprotected pulmonary vascular bed are at risk to develop pulmonary vascular disease. Such disadvantageous pulmonary vascular remodeling may occur in the first year of life. Many patients with an unprotected pulmonary vascular bed also have an obstructive anomaly of the aortic arch, and this combination is particularly serious, with most such afflicted patients dying in infancy.[48,77] Of the 13 patients with single ventricle surviving into adulthood reported by Ammash and Warnes, 9 had pulmonary stenosis, and 4 had pulmonary artery hypertension.[203] A number of other patients surviving into adulthood have been reported, some with pulmonary artery hypertension and pulmonary vascular obstruction, others with pulmonary stenosis.[204–208] Of 109 adults with Eisenmenger syndrome seen at the University of Toronto Congenital Cardiac Centre for Adults, 11 were found to have univentricular hearts.[209] When patients with complex anatomy are considered (i.e. univentricular hearts, complex transposition, common arterial trunk, etc.), the mean age at death was 28.2 ± 7.9 years. Niwa and colleagues from UCLA studied the outcomes of adult patients with univentricular heart and Eisenmenger syndrome.[210] They identified 16 patients with a univentricular heart ranging in age from 18 to 44 years (mean 30.6 ± 8.4 years). The 5-year actuarial survival rate for patients with a univentricular heart after the initial visit was only 34%. Hemoptysis recurred in 6 patients, and calcification of the pulmonary arterial wall was seen on computerized tomography.[210] During the course of follow-up, 9 patients died at a mean age of 31 ± 6.6 years. Eight of the 9 deceased patients had a univentricular heart of left ventricular morphology, ejection fraction < 30%, moderate to severe pulmonary and atrioventricular valve regurgitation and mild-to-moderate aortic regurgitation.[210] Since the nature of the pulmonary vascular bed is so important to a successful Fontan outcome, there has been obvious interest in the lung biopsy findings and indication for management and outcome.[211–213] Lung biopsy *per se*, once advocated, is now infrequently used in decision-making regarding suitability for the Fontan.[214]

Development of aortopulmonary collateral blood flow

The development of aortopulmonary collateral blood flow has been discussed in several papers[215–219] and elsewhere in this volume (see Chapter 40). Such collateral vessel formation may form in response to previous thoracotomy(ies). Furthermore as shown by Starnes and her colleagues. vascular endothelial growth factor and basic fibroblast growth factor are both increased in children with cyanotic congenital heart disease, possibly suggesting that the widespread formation of collateral vessels is mediated by these growth factors.[220] The incidence of the development, sites of, and various points of connection of systemic venous collateralization are discussed in Chapters 35 and 37.[221–228]

Outcome analysis

The anatomy of a double-inlet left ventricle and other forms of single ventricle pathology lend themselves to fetal echocardiography. The fetal four-chamber view is ideally suited for the recognition of those forms of congenital heart disease where the interventricular septum does not extend to the crux of the heart.[229–231] We have commented elsewhere on the fetal recognition and outcomes of fetuses with tricuspid atresia, hypoplastic left heart syndrome and those complex malformations associated with heterotaxia. Hornberger stated that of the 39 cases in the Allen and Sharland series of double-inlet ventricle, termination of pregnancy took place in 25.[232] There was one intrauterine death and two neonatal deaths, and eleven survived the neonatal period.[232] The prospective Bohemia Survival Study identified 67 children with double-inlet left ventricle.[17] In the first week of life the mean survival curve reached 77.6% and declined until the sixth month of life when the survival rate was 41.8%. The value for the first year of life was 38.8% and at 10 years the average survival curve had dropped to 35.6%, remaining at this level until 15 years of age.[17] Samanek has also reported on the probability of natural survival in patients with single ventricle.[233] Thirty-six per cent survived the first year, and the survival rate at 2 years of age was 33%, dropping slightly at 5 and 10 years to 31%.[233] We commented earlier on the natural survival of patients with double-inlet ventricle to adulthood, most with pulmonary vascular disease and Eisenmenger's syndrome. Survival into the sixth decade without intervention has been reported.[205] Moodie and his colleagues addressed the long-term follow-up of 83 patients with unoperated univentricular heart.[68] This study was already biased as most of the patients were older than 4 years of age.[68] They catalogued the types of univentricular hearts into those with an outlet chamber (type A) or type C, those without an outlet chamber (presumably either a ventricle of right ventricular or indeterminate morphology). For those with type A univentricular heart, 50% were dead 14 years after diagnosis, a death rate of 4.8% per year. By 16 years after diagnosis only 30% were still alive. The outcome for those patients with type C single ventricle was worse, with 50% dead 4 years after diagnosis. The presence of pulmonary stenosis did not seem to affect the overall survival in this series, again clearly biased towards the child. Hager and his colleagues have recently reported on a 62-year-old woman with double-inlet left ventricle, ventriculoarterial discordance and naturally-occuring pulmonary stenosis who at age 59 years developed atrial fibrillation.[68A] A catheter study was performed when she was 62 years and this showed a Qp/Qs of 2.3/1, a mean pulmonary artery pressure of 38 mmHg and the pulmonary vascular resistance was 3 Wood units.m^2. She did not undergo any sugery at that time. This group also tabulated 9 other patients with double-inlet left ventricle and ventriculoarterial discordance surviving from 57 to 62 years of age without surgical intervention. Of the 10 patients including the subject of this report, 6 had native pulmonary outflow tract obstruction, and 4 had pulmonary hypertension and presumably an unprotected pulmonary vascular bed.[68A] Moodie and his colleagues have also reported the long-term follow-up after palliative operations of patients with univentricular hearts.[69] In 1984 they published data on 84 patients aged 6 days to 25 years, mean age 10 years.

The mean follow-up period was 5 years. Of the 84 patients, 33 died and 51 were alive at the time of the report. The survivors were 1.5–41 years, mean 15 years. Using the same classification as in the earlier paper,[69] 5 years after diagnosis 70% of those with type A and 54% of those with type C univentricular heart were alive.[69]

Before the introduction of ventricular septation and then the Fontan operation, patients with single ventricle physiology were candidates for palliation. Palliation took the form of systemic-to-pulmonary artery shunt; pulmonary artery banding with/without repair of an obstructive anomaly of the aortic arch; and/or atrial septostomy/septectomy. Taussig documented in 1976 her long-time observations of the Blalock–Taussig shunt in patients with levocardia and single ventricle.[70] She reported the 20- to 28-year follow-up of 24 patients of the 1037 cyanotic patients operated on between January 1, 1945 and January 1951.[70] Eighteen patients survived the surgery and 1 was lost to follow-up. Eight survived for > 20 years after the initial operation and 6 for > 25 years after the initial operation. Seven patients required a second operation and 4 required a third palliative shunt. Progressive cardiac enlargement was common, indicating both chronic volume loading of the single ventricle and impaired function.[70] Three patients had infective endocarditis and 2 multiple episodes. One patient died with a brain abcess and a second patient died with purulent meningitis.[70] Three women and 4 men married.

Tremeau and colleagues have studied the outcomes of the three main palliative surgical procedures in patients with single ventricle: systemic-to-pulmonary shunt, pulmonary artery banding, repair of the aortic arch (usually associated with pulmonary banding).[234] One hundred and nineteen (63%) of the 185 patients hospitalized between January 1, 1970 and December 12, 1991 in the paediatric cardiology unit of the Cardiac Hospital of Lyon with a diagnosis of single ventricle, underwent one of these three procedures as the initial treatment. The survival of the 22 patients who underwent pulmonary artery banding of 90 ± 6%, 85 ± 8%, 85 ± 8% at 1, 5 and 10 years respectively was significantly better than that of the patients undergoing systemic-to-pulmonary shunt (63 ± 6%, 53 ± 6% and 49 ± 6% at 1, 5 and 10 years, respectively). On the other hand, repair of an obstruction of the aortic arch in the patient with single ventricle physiology had a poor prognosis with survival of only 23 ± 11%, 16 ± 11% and 16 ± 11% and 1, 5 and 10 years, respectively.[234] Dooley and his colleagues reporting the 5-year experience of the New England Regional Infant Cardiac Program stated that 11 of 20 patients (55%) with single ventricle survived pulmonary artery banding.[235] There is little long-term information on the outcomes of patients that have undergone atrial septostomy/septectomy in isolation, although Kirklin and Barratt-Boyes[2] suggest that Redo and his colleagues were likely the first to demonstrate the beneficial effect of a Blalock–Hanlon atrial septectomy in the patient with mitral atresia.[236]

Aeba and coworkers have addressed those factors correlating with outcomes of patients with single ventricle physiology.[237] Between 1961 and 1995, 158 patients with single-ventricle physiology, including tricuspid atresia and hypoplastic left heart syndrome, underwent 260 surgical interventions. The follow-up was 99% complete. The mean (SEM) actuarial survival rates at 1, 5, 10, and 20 years following birth were 70.3 ± 3.6%, 56.3 ± 4.0%, 48.8 ± 4.2%, and 40.9 ± 4.7%, respectively. Definitive palliation was attempted in 38 patients (univentricular in 35 and biventricular in 3). Multivariate analysis identified systemic ventricular outflow tract obstruction, mitral atresia, situs ambiguus, and pulmonary vein drainage tract obstruction as independent prognostic factors for early death. Visceral heterotaxy was the only independent risk factor for lack of application or failure (death or take-down within 30 days of operation) of univentricular or biventricular repair.

Franklin and his colleagues published a series of papers in 1991 addressing the outcomes of patients presenting in infancy with double-inlet ventricle at the Great Ormond Street Hospital for Sick Children.[77–79] The first paper addressed survival without definitive repair;[77] the second paper reported the results of palliative operations;[78] and the third in the series the outcome and potential for definitive repair.[79] This group reported on survival before definitive operation of 191 infants with double-inlet ventricle presenting before 1 year of age from 1973 to 1988, with a median follow-up of 8.5 years.[77] Overall survival including all surgically treated patients was 57% at 1 year, 40% at 5 years, and 35% at 10 years. When the patients were withdrawn (censored) as alive at the time of their definitive operation, the survival rate was 43% at 5 years and 42% at 10 years. Their analysis showed that the hazard rate before the definitive operation decreased dramatically over the first year of life, but persisted at a lower rate throughout the follow-up.[77] A univariate analysis showed that right isomerism, a common atrioventricular orifice, a single-outlet ventriculoarterial connection, obstruction of the systemic outflow at any level, extracardiac anomalous pulmonary venous connections or severe acidosis when first seen were all risk factors for death without definitive surgery.[77] In contrast, the presence of pulmonary valve and/or subpulmonary stenosis and a balanced pulmonary blood flow conveyed a much better outcome. Patients with a double-inlet left ventricle and discordant ventriculoarterial connections with either balanced or low pulmonary blood flow had predicted probabilities of survival of 96% and 90% at 1 year and 91% and 79% at 10 years, respectively.[77] Franklin and his colleagues showed a number of survival curves depicting those with high pulmonary blood flow with/without systemic outflow tract obstruction. For those with a double-inlet left ventricle, discordant ventriculoarterial connections and a high and unobstructed pulmonary blood flow the predicted survival at 1 year and 10 years was 79% and 60%, respectively. The predicted 1-year and 10-year survival for those with unobstructed pulmonary blood flow but also systemic outflow tract obstruction was considerably worse at 36% and 11%, respectively. An even more dismal outlook was found in those patients with right isomerism and double-inlet and double-outlet right ventricle, a common atrioventricular orifice, reduced pulmonary blood flow and extracardiac anomalous pulmonary venous connections, with 1-year and 10-year survivals of 3% and 0%, respectively.

Their second paper addressed the outcomes of 154 palliative operations performed in 121 patients.[78] Survival after either a systemic-to-pulmonary arterial shunt ($n = 57$) or banding of the pulmonary trunk ($n = 35$) was comparable, with 84% and 77% at 1 year, and 62% and 45% at 5 years, respectively.[78] Survival was worse for those who required repair of aortic arch obstruction and pulmonary artery banding ($n = 18$) with survival at 1 and 5 years of 44% and 22%, respectively. Palliative surgery, overall, in this era had a deleterious effect on immediate survival, but in those surviving medium-term outcome was improved, especially for those undergoing a systemic-to-

pulmonary artery shunt. By contrast, after banding of the pulmonary trunk, with or without additional repair of an obstructive anomaly of the aortic arch, medium-term risk was not altered.[78] This lack of benefit was attributed by Franklin and his colleagues to the development of subaortic stenosis in many of these patients, especially those who also required reconstruction of the aortic arch.[78] The third paper addressed outcome and potential for definitive repair of the 191 infants with double-inlet ventricle.[79] They emphasized that management in infancy should be aimed at maintaining the potential for later Fontan surgery.[79] At presentation 136 patients (71%) were potential candidates for a Fontan procedure, but by 2 years of age only 78 patients (57%) were alive and still considered suitable candidates. This attrition was attributed to death after presentation with low cardiac output and at palliative operation. In addition the adverse events of late sudden death and the development of new features precluding a Fontan operation all served to reduce the cohort with potential for the Fontan operation.[79] Patients who required no operation or those requiring only a systemic-to-pulmonary artery shunt fared better than those who required banding of the pulmonary trunk with/without repair of an obstructive anomaly of the aortic arch. Interestingly, they identified only 43 patients from the entire cohort of 191 infants with double-inlet ventricle (23%) who had morphological features additionally compatible with future ventricular septation.[79]

Ventricular septation was the initial method used to partition the single ventricle.[1,2] The surgical history of ventricular septation has been reviewed by Kirklin and Barratt-Boyes.[2] Of the types of single ventricle considered for septation, the double-inlet left ventricle with left-sided rudimentary right ventricle and transposition of the great arteries is seemingly the best candidate as the left atrium, left-sided atrioventricular valve and aorta are all lateralized to the left. Some have surgically partitioned the dominant left ventricle of the Holmes heart as well.[2–8] The form and function of the atrioventricular valves is of paramount importance in ventricular septation. Important atrioventricular valve hypoplasia, straddling of the tension apparatus into the rudimentary right ventricle, crossing or intertwining of chordal apparatus, or sharing of a papillary muscle between both atrioventricular valves could all confound ventricular septation.[1–8,177,178] McKay and her colleagues reported in 1982 the results of septation in 16 patients with univentricular heart of the left ventricular type, two atrioventricular valves, a left anterior subaortic outlet chamber, and transposition of the great arteries.[5] There were 7 hospital deaths (44%; CL 29–60%), 6 from low cardiac output, including each of 5 patients with outlet foramen obstruction. In the subset of 11 patients with unobstructed outlet foramen, there were only 2 deaths, both in patients with small ventricular size. Multivariate analysis in the group of 16 patients indicates that small ventricular size and the presence of outlet foramen obstruction were incremental risk factors for hospital death.[5] In 1984 Ebert reported the outcomes of staged partitioning of single ventricle in 5 patients.[238] The first stage involved the placement of a small patch in the apex and a second patch between the atrioventricular and semilunar valves. A center section was left open, as if there were ventricular septal defect. A pulmonary band was placed at this time if one had not been previously placed. The second stage of the repair, consisting of closure of the ventricular septal defect, was performed 6–18 months after the first procedure. All 5 patients survived staged-partitioning and none sustained complete heart block. One patient subsequently developed pulmonary stenosis, and a right ventricle–pulmonary artery conduit was placed. Naito and colleagues have reported the successful outcome of the staged approach of ventricular septation in a young infant.[239] While this approach did generate some interest,[240] there is relatively little if any more published experience with this approach.

Kurosawa and his colleagues reported in 1990 the results of septation in 12 patients with double- (11 patients) or common inlet (1 patient) left ventricle, left anterior rudimentary right ventricle and transposition.[241] The average age of these patients was 9 years, ranging from 1 to 24 years. Nine of these 12 patients had undergone previous pulmonary artery banding and 1 of these also required repair of a thoracic coarctation.[241] At the time of the septation procedure, 3 patients required enlargement of a restrictive ventricular septal defect. Complete heart block was present in 1 patient before septation and developed in one patient after septation.[241] There was 1 operative death (8.3%). This modest experience did not find a restrictive ventricular septal defect to be an incremental risk factor for death, but did find that an increased left ventricular wall mass portended a poor outcome.[241] Shimazaki and his colleagues and others had earlier suggested that the left ventricular end-diastolic volume of the single left ventricle should be at least 200% of a normal left ventricular end-diastolic volume to achieve a successful septation.[242–244] Four of the 5 patients in Kurosawa's series with a left ventricular end-diastolic volume of the single left ventricle < 200% of normal survived, with the only death in the patient with the smallest volume, 168% of normal.[241] This experience with ventricular septation was extended in 1997 to 23 patients with 2 early (9.5%) and 3 late deaths (14.5%).[245] Non-survivors of ventricular septation were significantly older at the time of operation (14.0 ± 6.0 vs. 7.0 ± 54.4 years; $P < 0.05$). The nonsurvivors also had a greater left ventricular mass (383% ± 100% vs. 206% ± 57% of normal predicted value; $P < 0.005$), and greater left ventricular mass to left ventricular end-diastolic volume ratio (1.84% ± 1.18% vs. 0.77% ± 0.17 of normal predicted value; $P < 0.005$). Univariate logistic regression analysis revealed age at operation ($P < 0.05$) and mass/end-diastolic volume ratio ($P < 0.05$) were significant risk factors for death after septation.[245] The multivariate regression analysis showed that age at operation positively influenced increased mass/end-diastolic volume ratio ($P < 0.001$). Thus as Kirklin *et al.* had suggested earlier in reference to outcome analysis of the Fontan procedure ventricular hypertrophy had a tendency to progress with age[118] and was a risk factor for ventricular septation in Nagashima's *et al.*'s experience.[245] In view of these findings they recommend that if septation is the surgical choice that it be considered early before progression of ventricular hypertrophy;[245] they did not state how early. Although patients with and without pulmonary stenosis have been septated, the better long-term outcomes have been in those patients who have not required a ventricle-to-pulmonary artery conduit.[2,4,5,8,239] The absence of a ventricular-to-pulmonary artery conduit facilitates more functional ventricle and this likely contributes to the better outcome. Margossian and colleagues have recently revisited the issue of ventricular septation, reporting in 2002 their experience with septation of 11 patients with single ventricle.[245A] Eight of the 11 patients survived with 2 early and 1 late death. Six of the patients underwent one-stage septation and 5 planned two-stage. Seven of the 8 survivors have undergone complete septation, 5 as single stage and 2 as two stages. One patient sustained

complete heart block and another patient had significant residual ventricular septal defects.

We will discuss in Chapter 36 the original and modified criteria used to predict a successful outcome for a Fontan-type operation. The Mayo Clinic has provided compelling data that unfavorable early and late outcomes are directly related to the number of preoperative risk factors.[246] The lower the number of risk factors, the better the outcome, and the converse as well.[246,247] Staging to the modified Fontan with a bidirectional cavopulmonary shunt is certainly one factor that has led to improved outcomes of the entire potential Fontan cohort (see Chapter 35). At this staging, one can address surgical or duct-related stenosis of the pulmonary artery, atrioventricular valve regurgitation, and systemic outflow tract obstruction, all factors that can adversely affect the outcome of the modified Fontan operation. There are some data on the repair of the regurgitant atrioventricular valve, and the improvement anticipated by volume unloading surgery.[172–176] Significant atrioventricular valve regurgitation can contribute to ventricular hypertrophy, and thus adversely affect the outcome of the Fontan operation.

The cascade of information about the morphological bases for subaortic stenosis and the surgical maneuvers to deal with this complication have been dealt with earlier in this chapter. Suffice-it-to-say, surgical results to treat subaortic stenosis have continued to improve. There have been numerous reports of the various surgical procedures used to treat subaortic stenosis with/without aortic arch obstruction in the neonate with single ventricle physiology. Although some cardiologists in the 1980s questioned the wisdom of Norwood palliation for the hypoplastic left heart syndrome, Mayer indicated that from this experience we as a "community" have gained considerable experience applicable to many forms of left heart obstructive lesions.[248] Whether one uses a modified Norwood procedure as the initial therapy, the Damus–Kaye–Stansel procedure at the time of staging with a bidirectional cavopulmonary shunt, or ventricular septal defect enlargement, etc., the concern about subaortic stenosis has been largely obviated. Some advocate initial palliation with a modified Norwood approach or Damus–Kaye–Stansel procedure.[151,155,249] Those who use this approach feel there is less re-obstruction of the ventricular septal defect, less heart block, and less damage to the myocardium from the resection of tissue.[151,155,249] However, the use of the Damus–Kaye–Stansel procedure risks distortion of the semilunar valve and increased insufficiency of the semilunar valve.[250] We also reported a higher than anticipated incidence of heart block after the Damus–Kaye–Stansel procedure.[155] Knowledge about the course of the specialized conduction tissue in the double-inlet left ventricle and the so-called safe area for muscular resection has reduced, but not eliminated the risk of surgical complete heart block (Fig. 32-4).[102,129,130,251] In addition, when the incision was made in the rudimentary right ventricle, it was important to avoid disruption of the delimiting coronary arteries.[125,252,253]

Ross and his colleagues reported in 1994 the results of direct relief of the subaortic stenosis in 16 patients with univentricular atrioventricular connection and discordant ventriculoarterial connections.[253] Fifteen of the 16 patients had undergone prior pulmonary artery banding, and 6 had required repair of a coarctation and one patient underwent repair of a type A interruption.[253] All the patients underwent enlargement of the ventricular septal defect via a transventricular approach. There were 4 early and two late deaths, with an actuarial survival of 50% at 7 years.[253] Three of the deaths were related to iatrogenic damage to the aortic valve resulting in severe aortic regurgitation.[253] Two patients sustained complete heart block requiring permanent pacemakers. No patient developed a ventricular aneurysm at the site of the ventriculotomy that was closed with Impra.[253] Pass and his colleagues from the Babies and Children's Hospital of New York reported in 2001 their results of bulboventricular foramen resection in 9 children operated on from June 1990 to June 1999.[254] The patients ranged in age from 1 month to 27 years, with a median age at surgery of 16.5 years. Most of the patients underwent enlargement of the restrictive ventricular septal defect via the aortic root, although several patients also underwent resection via the right atrium and atrioventricular valve.[254] There was one perioperative death in a 3 year old boy who died after bulboventricular foramen resection combined with a Fontan operation. The late death occurred in an infant who underwent a partial septation and bulboventricular foramen resection, dying 5 months after the surgery of fungal sepsis.[254] Brawn and his colleagues reported their experience with a primary Damus procedure for the univentricular heart with systemic outflow tract obstruction.[151] This approach was used in 24 consecutive patients whose median age at operation was 6 days with a median weight of 3.4 kg. They used as well an aortopulmonary shunt 3.5 mm in diameter. There were 9 early deaths (37.5%), and 10 of the 15 survivors had undergone a bidirectional cavopulmonary shunt with one death. One patient required patch angioplasty of the aortic arch and innominate artery with revision of the aortopulmonary shunt. The results of the univariate analysis of the potential risk factors stratified by outcome revealed that presence or absence of transposition, presence of aortic atresia and chronological rank number of the operation were risk factors for death.[151] McElhinney and his colleagues reported in 1997 their approach of a modified Damus–Kaye–Stansel procedure that had been performed in 14 neonates and seven infants with single ventricle and subaortic stenosis, including 15 with arch obstruction.[249] Diagnoses were double-inlet left ventricle (n = 12), tricuspid atresia (n = 2), and other forms of hypoplastic ventricle with subaortic obstruction (n = 7). Three patients underwent concurrent bidirectional Glenn shunt. In the most recent seven patients with arch obstruction, arch repair was achieved with an end-to-side anastomosis of the descending aorta to the ascending aorta with continuous upper body perfusion. One early death occurred among the 14 neonates (7%) and three among the infants, for an early mortality of 19%. At a median follow-up of 33 months, there were no late deaths or neurologic complications. Nine patients underwent subsequent bidirectional Glenn anastomosis, including three who had Fontan completion and one who later underwent conversion to a partial biventricular repair. One patient required a transplant for cardiomyopathy of unknown etiology. The remaining 12 patients were considered good candidates for Fontan completion. No patient has recurrent arch obstruction. Four patients have mild (n = 1) or trivial (n = 3) semilunar valvular regurgitation. They concluded that: the modified Damus–Kaye–Stansel procedure is an effective primary palliation for single ventricle and subaortic stenosis, with or without arch obstruction.[249]

Mosca and his colleagues also using a modified Norwood approach in their initial management of this difficult group of patients have had outstanding results.[152] They reported in 1997 the outcomes in 38 patients with either tricuspid atresia or a double-inlet left ventricle and ventriculoarterial discordance operated between January 1987 and December 1996. The mean

age was 15 days, and their mean weight was 3.4 kg. Aortic arch anomalies were present in 92% of the patients. There were 3 early deaths (7.8%) and 5 late deaths (13.1%). The actuarial survival rates at 1 month, 1 year, and 5 years were 89%, 82%, and 71%, respectively. Follow-up was complete in all children at a mean interval of 30 ± 9 months. None of the patients had significant neoaortic valve insufficiency, and only 1 patient required therapy for residual aortic arch obstruction. Nine patients (30% of the survivors) have undergone the hemi-Fontan procedure, and 18 patients (60%) successfully have undergone the Fontan procedure.

Jensen and his colleagues at the University of California at Los Angeles (UCLA) reported in 1996 the outcomes of pulmonary artery banding in patients with single ventricle at risk for subaortic obstruction.[121] Their patient cohort included 26 patients operated on within 6 months of age between January 1984 and December 1994 at mean age of 2.1 ± 1.8 months. The patients included those with either a double-inlet left ventricle or tricuspid atresia, with transposition of the great arteries in both.[121] Associated aortic arch abnormalities were present in 8 patients (31%). Nineteen patients (73%) underwent further surgery with a Damus–Kaye–Stansel procedure or ventricular septal defect enlargement for a significant subaortic gradient or a morphologically small ventricular septal defect, alone or in conjunction with a bidirectional cavopulmonary shunt or modified Fontan. The cumulative mortality for the entire cohort was 19%. Odim and his colleagues at UCLA continued these observations in 1999, focusing on a staged surgical approach in neonates with aortic obstruction and single ventricle physiology.[124] They reported the outcomes of 15 neonates with single ventricle physiology and either coarctation or interruption of the aortic arch.[124] Again, the surgical strategy was that of initial pulmonary artery banding and repair of the aortic arch obstruction. The median age at operation was 6 days with a median weight of 3.3 kg. There were no early deaths, but 1 late death after the initial palliation. Of the 14 survivors, 8 underwent a bidirectional cavopulmonary anastomosis at a median age of 9.75 months, and 7 infants underwent a Damus–Kaye–Stansel procedure for subaortic stenosis at a median age of 4 months. Thirteen of the 15 patients are alive (87%), and 6 have proceeded to a Fontan procedure. A single failing Fontan required takedown to a bidirectional cavopulmonary anastomosis and central aortopulmonary shunt.[124] Webber and his colleagues have also advocated pulmonary artery banding in the treatment of double-inlet left ventricle with transposition and aortic arch obstruction.[107,123] They reported in 1995 their results with this approach in 17 patients at a median age of 1.4 weeks.[123] Sixteen patients had coarctation and one interruption. Four of the infants had important subaortic stenosis on admission. There was 1 early death after banding and aortic arch reconstruction, and all but 1 developed subaortic stenosis. In these 15, subaortic stenosis was treated with a Damus–Kaye–Stansel operation with 2 early deaths and 1 late death.[123] Of the 13 surviving patients, 12 underwent either a bidirectional cavopulmonary shunt or Fontan. This group uses the approach of pulmonary artery banding and repair of the aortic arch in neonates who do not have severe subaortic stenosis on admission.[123] Lan and colleagues have just reported the results from UCLA of a staged surgical approach to neonates with single left ventricle and moderate size bulboventricular foramen.[124A] This study examined the outcomes of neonates with either double-inlet ventricle or tricuspid atresia with transposed great arteries who had a bulboventricular foramen between 1 and 2 cm^2/m^2. Their institutional results of initial palliation with pulmonary artery banding with/without repair of aortic arch obstruction were excellent and these patients went on to early bidirectional cavopulmonary shunt and a Damus–Kaye–Stansel connection without mortality, similar to the comparison group with an initially larger bulboventricular foramen. These authors did find what they described as a mild bulboventricular foramen gradient (18 ± 10 mmHg) by cardiac catheterization by a mean age of 7 months (before the bidirectional cavopulmonary shunt and Damus–Kaye–Stansel connection). Although the authors state this did not impact on left ventricular wall thickness, since the pulmonary outflow tract remained patent, this gradient is not insignificant.[96,98,100] Daenen and colleagues have also shown gratifying results using a similar staged surgical approach, beginning with banding followed by second-stage palliation at a mean age of 9 months. The cohort consisted of 25 neonates with a univentricular heart, transposed great arteries, subaortic obstruction and pulmonary artery hypertension, with coarctation in 14. The early stages of palliation had no associated mortality.[124B] Furthermore patients from Toronto and the Mayo Clinic who experienced important systemic outflow tract obstruction and ventricular hypertrophy following pulmonary artery banding were treated in a different era and as such the pulmonary artery band was left in place usually for 2 years or longer.[65,66,89,96,98,100,103]

Daebritz and her colleagues from the Children's Hospital in Boston compared the Norwood stage I operation for hypoplastic left heart syndrome and other complex malformations with ductus-dependent systemic circulation.[255] The outcomes of 194 patients undergoing a Norwood stage I palliation between 1990 and 1998 were reviewed. Malformations in 131 patients were classified as hypoplastic left heart syndrome and 63 patients had other lesions. These included hypoplastic left ventricle with ventricular septal defect (n = 18), unbalanced complete atrioventricular canal (n = 9), complex double-outlet right ventricle (n = 14), double-inlet left ventricle (n = 11), tricuspid atresia with transposition of the great arteries (n = 6), and others (n = 5), including heterotaxia. The operative (< 30 days) and 1-year survivals were lower for patients with hypoplastic left heart syndrome than for those with other lesions (63.4% vs. 81%, P = .008, and 51.2% vs. 71.4%, P = 0.02, respectively). The presence of a non-hypoplastic left ventricle (n = 27) was associated with higher operative and 1-year survivals (96.3% vs. 64.7%, P = 0.002; 88.9% vs. 52.7%, P < 0.001). A restrictive atrial septal defect and prematurity tended to increase mortality across both groups. Cox proportional hazards regression indicated that a single right ventricle was the most important independent predictor of death (P < 0.001). Operative mortality for all patients undergoing the stage I procedure decreased from 38.5% (1990–94) to 21.4% after 1994 (P = 0.02). On the basis of these results they concluded that the survival of patients with malformations other than hypoplastic left heart syndrome after the Norwood procedure is better than for those with hypoplastic left heart syndrome. Furthermore, staged palliation is valid surgical therapy in these patients, with good results in intermediate follow-up.[255] Bradley and his colleagues have eschewed pulmonary artery banding in the management of the infant with single ventricle and excessive pulmonary blood flow, rather employing the strategy of pulmonary artery division and a shunt.[255A] From January 1996 to June 2001, 22 patients were operated at a median age of 22 days, with no operative and only

one late death (Fig. 32-6). Thirteen of the 22 patients (59%) had an associated aortic coarctation.

Jahangiri and coworkers reported in 2001 the long-term results of relief of subaortic stenosis in univentricular atrioventricular connection with discordant ventriculoarterial connections.[122] Twenty-four patients underwent enlargement of ventricular septal defect between 1985 and 1998 at a median age of 3.2 years (range 3 weeks to 14 years). Ten patients were younger than 1 year. Eighteen had undergone previous banding of the pulmonary trunk, 9 of whom also required repair of coarctation of the aorta. The median subaortic gradient before enlargement was 46 mmHg. Twenty-three patients had a patch to enlarge the rudimentary right ventricle. Five patients (21%) died in the early postoperative period. The overall survival at 1 and 3 years was 73%, and at 5 and 10 years was 68% and 60%, respectively. Complete heart block requiring insertion of a pacemaker occurred in 2 patients (8%). A Fontan operation was performed in 10 patients, 5 underwent a bidirectional Glenn procedure, and 2 required cardiac transplantation. Follow-up was complete in all survivors at a median time of 6.7 years (range, 8 months to 13 years). From the earlier part of the series, 3 patients experienced aortic insufficiency and 2 had recurrent obstruction. Factors adversely affecting survival were younger than 1 year at operation and presence of obstruction within the aortic arch. Their experience shows that, in patients with univentricular atrioventricular connection to a dominant left ventricle and subaortic stenosis, enlargement of the ventricular septal defect provides satisfactory relief of obstruction except in those younger than 1 year of age, and those who have associated obstruction in the aortic arch. Cerillo and colleagues have also recently reported their satisfactory experience with pulmonary artery banding and enlargement of a restrictive ventricular septal defect.[122A]

We have used during the last three decades a variety of procedures to treat subaortic stenosis in the patient with a univentricular atrioventricular connection.[14,65,66,96,98,100,125,171,256] With our long interest in this condition, we have had a "low threshold" for treating potential subaortic obstruction in these patients at the initial palliative operation, or at the time of staging. Our current initial management of the neonate and young infant with severe systemic outflow tract obstruction has evolved to a Norwood/Damus–Kaye–Stansel approach. In our recent experience, the mortality for the modified stage-one Norwood procedure is in the range of 10%; the second stage had a mortality of 2.5%, with no mortality in the last 60 procedures, and there is a 4% mortality at the time of the modified Fontan procedure.[170] While subaortic stenosis has been and can be dealt with at the time of the modified Fontan procedure, we prefer to deal with it earlier in the surgical algorithm, allowing time for ventricular remodeling and regression of hypertrophy. Systemic outflow tract obstruction can occur after the modified Fontan procedure, tends to progress, and the results for surgical treatment of this post-Fontan subaortic stenosis are good[159–161] (see Chapter 37). It is likely that the substrate for systemic outflow tract obstruction was present before the Fontan and that further ventricular unloading unmasked it.[128] Our own experience with ventricular septation has been very limited, and we have not septated a patient with a univentricular heart in more than two decades. The Mayo Clinic has evolved away from septation,[4] and the University of Alabama has not reported any recent experience with this procedure. Nearly two decades ago, Stefanelli and his colleagues reported the outcomes of the 147 operations carried out in 116 patients with single ventricle between 1967 and July 1982.[257] Confining comments just to the 36 patients who underwent ventricular septation between 1967 and November 1, 1983, 13 (36%) died in the hospital. Of the 13 patients considered to have the ideal morphology for ventricular septation and without the need for atrioventricular valve replacement of a valved extracardiac conduit, there were no hospital deaths and a late survival rate of 77%.[257] In this early experience 88% of the patients at risk for complete heart block did in fact develop complete heart block.[257] The more recent data from Kurosawa and Nagashima and their colleagues from 1990 and 1997 respectively shows less hospital mortality and is thus more encouraging, but compared to the Fontan experience, their numbers of ventricular septation patients are still very small.[241,245] Finally, Cochrane has asked in terms of the management of the univentricular connection: "are we improving?"[258] With one exception we are improving: the management of the patient with a single ventricle and obstructed total anomalous pulmonary venous connections continues to be disappointing.[259–263] Indeed, this may qualify as the "worst disease," not aortic atresia[264] (see also Chapter 33).

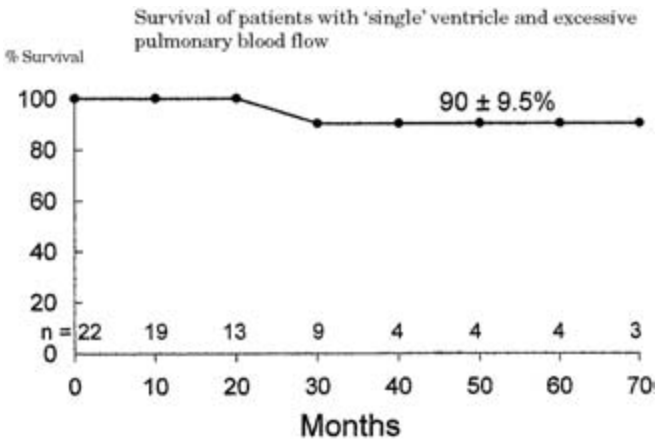

Fig. 32-6 Kaplan–Meier curve depicting survival in a group of infants with single ventricle and excessive pulmonary blood flow treated by pulmonary artery division and a shunt. (From Bradley *et al.*[255A] with permission.)

Double-inlet ventricle issues can be summarized as follows.

- Double-inlet ventricle embraces striking morphological heterogeneity.
- Liveborn prevalence is likely to be reduced by termination of pregnancy.
- The "natural" history is poor without intervention.
- Some particular groups do worse than others including those with isomerism and obstructed total anomalous pulmonary venous connections or those with discordant ventriculoarterial connections and an obstructive anomaly of the aortic arch.
- With the introduction of the Fontan principle in 1968, strategies are employed to protect the integrity of the pulmonary vascular bed and myocardium.
- Patients with double-inlet ventricle and other malformed hearts not amenable to biventricular repair are scrutinized in the context of satisfying the "10 commandments" of Choussat *et al.* to optimize later Fontan outcome.[12]
- Distortions of the pulmonary arteries secondary to an arterial shunt may be addressed at the time of staging maneuvers.

- Myocardial hypertrophy is a risk factor for poor Fontan outcome.
- Systemic outflow obstruction is causal to myocardial hypertrophy.
- Volume unloading surgery, long-standing pulmonary artery banding, and the size of the VSD in patients with double-inlet left ventricle and transposition of the great arteries are important factors in the genesis of systemic outflow tract obstruction.
- Strategies are and must be employed to minimize myocardial hypertrophy acknowledging that numerous factors contribute to systemic outflow tract obstruction:
  - short-term banding followed by staging and intervention to treat systemic outflow tract obstruction;
  - primary palliation with Norwood–Damus type connection.
- There has been some recent interest in ventricular septation.
  - Myocardial hypertrophy is a risk factor for poor outcome of ventricular septation.

All references can be found at the end of the book. See pp. 784–92 for Chapter 32.

The Natural and Modified History of Congenital Heart Disease
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Aijaz Hashmi, Robert M. Freedom, and Shi-Joon Yoo

The Syndrome of Isomeric Right Atrial Appendages and Visceroatrial Heterotaxy, Often Associated with Congenital Asplenia

It was just half a century ago when Bjorn I. Ivemark, then a young pathologist from Sweden, obtained funding from the Rockefeller Foundation to spend a year at the Children's Hospital in Boston studying a group of very complex cardiac malformations associated with agenesis of the spleen. His wonderful observations about this association were published in 1955 as supplement 104 of Vol. 44 in *Acta Paediatrica*, and his name is deservedly linked forever as "Ivemark's syndrome" with this constellation of anomalies.[1] It was clear from his and others' descriptions of the heart, lungs, and abdominal organs that common to patients with complex congenital heart disease and frequently asplenia was visceral heterotaxy, or abnormal symmetry (Figs 33-1 to 33-3).[2–16] As pointed out by Dr Stella Van Praagh, visceral heterotaxy (from the Greek *heteros*, meaning other, and *taxis*, meaning order) is a syndrome characterized by inconsistency of the situs of the thoracic and abdominal viscera.[15] Often there is preservation of the normal early pattern of liver symmetry and some of the systemic veins.[1–7] Visceral heterotaxy is usually associated with congenital heart disease, pulmonary symmetry, especially bronchial symmetry, splenic abnormalities, including asplenia or polysplenia (although rarely a normal spleen, a bilobed or multilobed spleen, or multiple little splenuli), and some degree of a similar shape of the atrial appendages.[17–21] By convention, some began to characterize these hearts by the nature of the splenic abnormality, referring to patients with congenital heart disease and a splenic abnormality as having the asplenia or polysplenia syndrome. Those features pointing to one or the other syndrome are well-known and have been reviewed in detail elsewhere.[16] As discussed in detail in the subsequent chapter and elsewhere, some prefer to designate these syndromes, not by the nature of the splenic abnormality which may be inconsistent, but rather by the appearance of the atrial appendages, referring rather to the syndromes of right and left isomerism.[22–31] Asplenia tends to occur in those hearts with right isomerism and polysplenia in those hearts with left isomerism. The concept of isomerism in this situation is not precise, but the similarity in appearance of the atrial appendages and the disposition of the pectinate muscles to the atrioventricular orifice suggests bilateral right appendages or bilateral left appendage morphology.[31] Furthermore those who advocate the use of isomerism in this situation state that since one cannot define the atrial anatomy as clearly solitus or inversus, the designation of isomerism, right or left, is appropriate. Some vigorously disagree with this concept, considering it erroneous.[15,28,32] And thus both nosologies are entrenched in the literature. Most patients with visceral heterotaxy have some degree of malrotation with non-fixation as well. The midline symmetrical liver in the patient with cyanotic congenital heart disease was once considered a sign of inoperability because of the often complex cardiac malformations encountered in this syndrome.[4,5,33]

Incidence and patterns of inheritance

The syndromes of right and left atrial isomerism are uncommon in the occidental population. From increasing fetal surveillance and parental counseling, the trend is to a lower liveborn than fetal prevalence. Data from the New England Regional Infant Cardiac Program (NERICP) indicated that 95 of 2251 liveborn infants had congenital heart malformations associated with visceral heterotaxia.[34] More than half of the infants identified by the NERICP with heterotaxy died before their first birthday, and 74% of the babies with levocardia and asplenia or polysplenia died. The Baltimore–Washington Infant Study surveyed 4390 infants with congenital heart disease between 1981 and 1989.[35] Ninety-nine or 2% were identified with heterotaxy, but the breakdown between right and left isomerism was not provided. We identified 91 patients with right atrial isomerism between 1970 and 1996.[36] These accounted for about 2.2% of all the new patients with congenital heart disease seen during that period, about half that of left isomerism. Lin and coworkers identified 58 cases of heterotaxy from a cohort of 201 084 births in the ongoing Active Malformation Surveillance Program at the Brigham and Women's Hospital.[37] Although most cases of heterotaxy in this series were sporadic events, an associated condition was present in about one-fourth of the cases. Not all of these conditions would be considered causative etiologies. Interestingly, three cases were associated with maternal diabetes, but based on this small series alone, maternal insulin-dependent diabetes cannot be viewed as a risk factor for heterotaxy. However, they suggested that the specific association of diabetes with polysplenia with/without left atrial isomerism is noteworthy, and adds weight to animal and epidemiologic case–control data.[38–40]

Ruscazio and his colleagues have reviewed the hereditary patterns of visceral situs abnormalities.[41] From clinical experience, it seems that while most instances of asplenia/right atrial isomerism occur as sporadic events, there are numerous examples of familial occurrence in siblings, suggesting an autosomal recessive pattern of inheritance.[41–48] Furthermore there are a number of sibships with clustering of asplenia and polysplenia syndromes, and one sibship with asplenia in one child and isolated total anomalous pulmonary venous connections in the second child.[48] The familial aggregation of the asplenia and

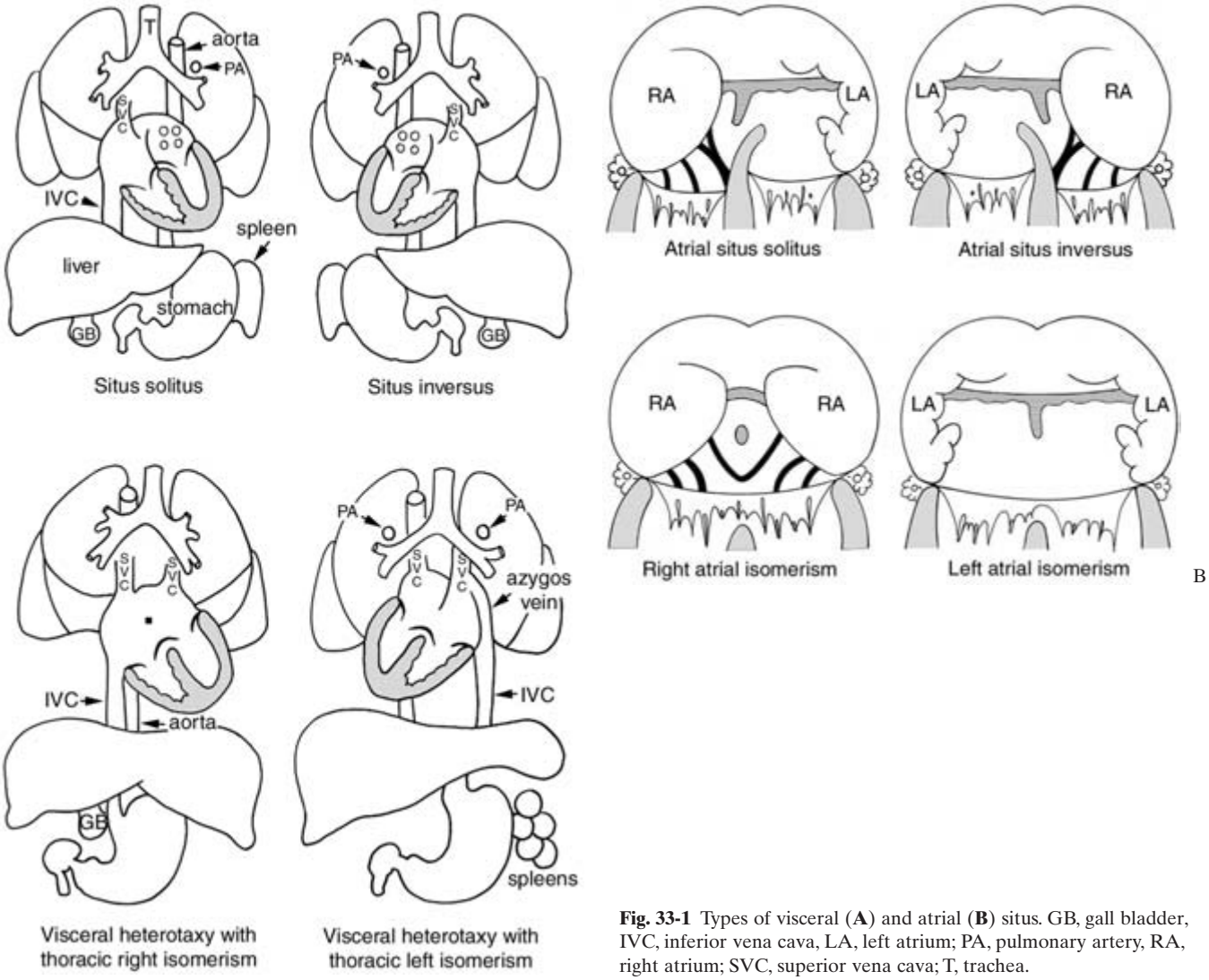

Fig. 33-1 Types of visceral (**A**) and atrial (**B**) situs. GB, gall bladder, IVC, inferior vena cava, LA, left atrium; PA, pulmonary artery, RA, right atrium; SVC, superior vena cava; T, trachea.

polysplenia syndromes in siblings suggests that these syndromes may share common etiologic and morphogenetic factors. Kuehl and Loffredo analyzing data from the Baltimore–Washington Infant study found that a history of maternal diabetes is strongly associated with cardiac disorders of sidedness.[42] Others have found recurrent involvement of chromosome region 6q21 in heterotaxy.[43]

The types of heart malformations identified in patients with right atrial isomerism

The types of congenital heart malformations identified in patients with the right isomerism/asplenia syndrome have received considerable attention since Ivemark's benchmark contribution.[1–3,6–16,19,22,23,26,28,29,31,36,41,49–55] There is considerable overlap of these malformations with patients with left isomerism/polysplenia (Table 33-1).

Indeed, there is not a specific cardiological marker for the patient with right vs. left isomerism. The appearance of the atrial appendages as bilaterally right or bilaterally left and disposition of the pectinate muscles allows one to assign or suggest asplenia and right isomerism or polysplenia and left isomerism.[24,31] But these markers may be difficult to recognize in the clinical situation. In any compilation of hearts with right isomerism, azygos continuation of the inferior vena cava is distinctly uncommon,[15,41] and conversely, probably > 90% of patients with left isomerism tend to have this venous anomaly.[16] Yet an occasional patient with asplenia will have this particular venous anomaly.[41] The abdominal juxtaposition of the aorta and inferior vena cava is highly predictive of visceral heterotaxy and has been acknowledged as typical of patients with asplenia/right isomerism.[56] However, this vascular malposition has been observed in the patient with left isomerism/polysplenia as well.[16]

Hearts with left isomerism tend to be biventricular and those with right isomerism univentricular[57] (see also Chapter 34). Both tend to have complex forms of an atrioventricular septal defect and common atrioventricular orifice. A common atrium is particularly common in patients with asplenia/right isomerism. The ventricular morphology in patients with right isomerism is frequently a univentricular atrioventricular connection of right ventricular morphology. The ventriculoarterial connections in hearts with asplenia/right isomerism are overwhelmingly abnormal, often approaching 90–95%, with double-outlet right ventricle frequently seen, and evidence of bilateral muscular infundibulum.[16,36] The discordant ventriculoarterial connections are distinctly less common than double-

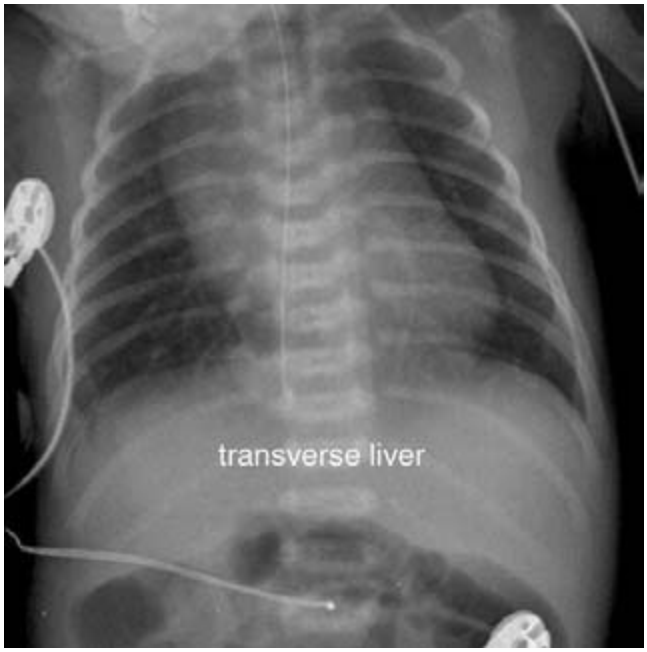

Fig. 33-2 Plain chest radiogram from a patient with right isomerism shows transverse liver.

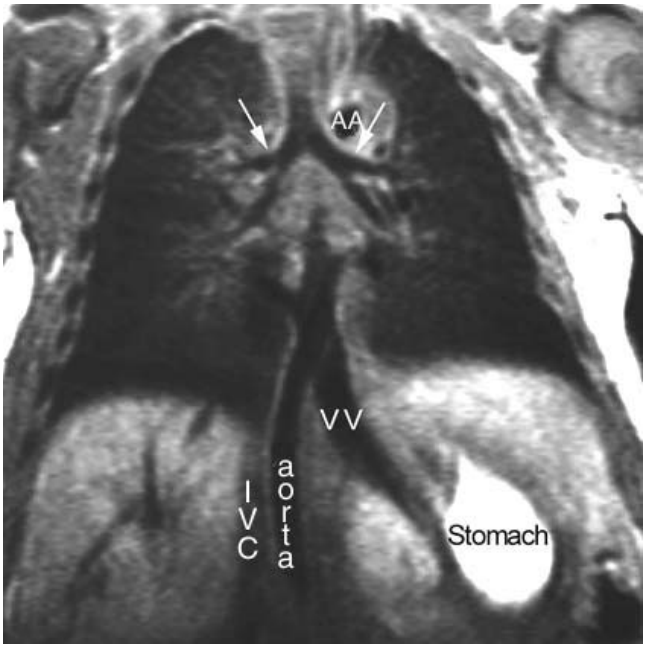

Fig. 33-3 Symmetric bronchial branching in right isomerism. T1-weighted MR image in a coronal plane demonstrates bilaterally short main bronchi (arrows). Neither right nor left pulmonary artery is seen above the bronchi. The aorta and inferior vena cava (IVC) are juxtaposed on the same side of the spine. There is infracardiac type of total anomalous pulmonary venous connection through a vertical vein (VV). AA, aortic arch.

outlet right ventricle in patients with right isomerism. Complex forms of pulmonary stenosis or atresia are very common in patients with right isomerism, although this occurs in the patient with left isomerism as well.[16,36] Systemic ventricular outflow tract obstruction ± coarctation is certainly more common in the patient with left isomerism, but once again, complex forms of aortic atresia have been seen in patients with asplenia/right isomerism.[29,36,53–55] Anomalies of systemic venous connections are common to both groups, especially bilateral superior caval veins. Again from the report of Van Praagh and her colleagues, 71% of patients with asplenia had bilateral superior caval veins, as did nearly half the patients with polysplenia.[15] Nearly 90% of patients with right isomerism have an absent coronary sinus septum with complete unroofing of the coronary sinus. This is less common in the patient with polysplenia/left isomerism.[15] Hepatic vein connection directly to the atrium is particularly common in patients with left isomerism and at one time this finding was considered diagnostic of left isomerism/polysplenia. However, this finding has been noted in an occasional patient

Table 33–1 Common congenital cardiac defects in right and left isomerism

Defect	Right isomerism	Left isomerism
Bilateral superior venae cavae	45%	45%
Bilateral systemic venous drainage	70%	60%
Absence of coronary sinus	~ 100%	~ 60%
Interruption of the inferior vena cava	< 2.5%	80%
Juxtaposition of the aorta and inferior vena cava	~ 90%	Uncommon
Extracardiac type of total anomalous pulmonary venous connection with/without obstruction	50%, with obstruction in 50%	Rare
Pulmonary venous connection to ipsilateral atria	4%	45%
Atrioventricular septal defect	90%	50%
Atrial septum	Functionally common atrium in 50%	Usually better formed, intact in ~ 20%
Atrioventricular connection	Univentricular in 70%	Biventricular in ~ 75%
Ventriculoarterial connection	Concordant only in 4%	Concordant in ~ 70%
Pulmonary atresia or stenosis	80%	30%
Left sided obstructive lesion	< 5%	~ 30%
Heart block/bradycardia	Rare	~ 70%

(From Phoon & Neill,[6] Anderson *et al.*,[19] Hashmi *et al.*,[36] Phoon & Neill,[51] Gilljam *et al.*,[57] Peoples *et al.*[57A] and Uemara *et al.*[57B] with permission.)

with right isomerism, again reflecting the overlap between the isomerism/splenic syndromes.[15] Rarely, an hepatic vein may connect to the coronary sinus or to the left-sided atrium. If this is not recognized before a Fontan procedure and dealt with, then postoperatively these patients may become progressively cyanotic because of hepatic veno-venous shunting (see Chapter 37). Anomalies of pulmonary veins are common in all patients with heterotaxy, but total anomalous pulmonary venous connections, especially with obstruction, occur considerably more frequently in patients with right isomerism.[15,16,36,49–52] In the series reported by Van Praagh and colleagues, nearly two-thirds of patients with asplenia had total anomalous pulmonary venous connections, mostly to a systemic vein (Fig. 33-4).[15] About 60% of patients with polysplenia in their series had normal pulmonary venous connections. Because of the retention of primitive embryonic symmetry in the heterotaxy syndromes, it is not surprising that bilateral sinoatrial nodes have been recognized in patients with asplenia/right isomerism.[9–11]

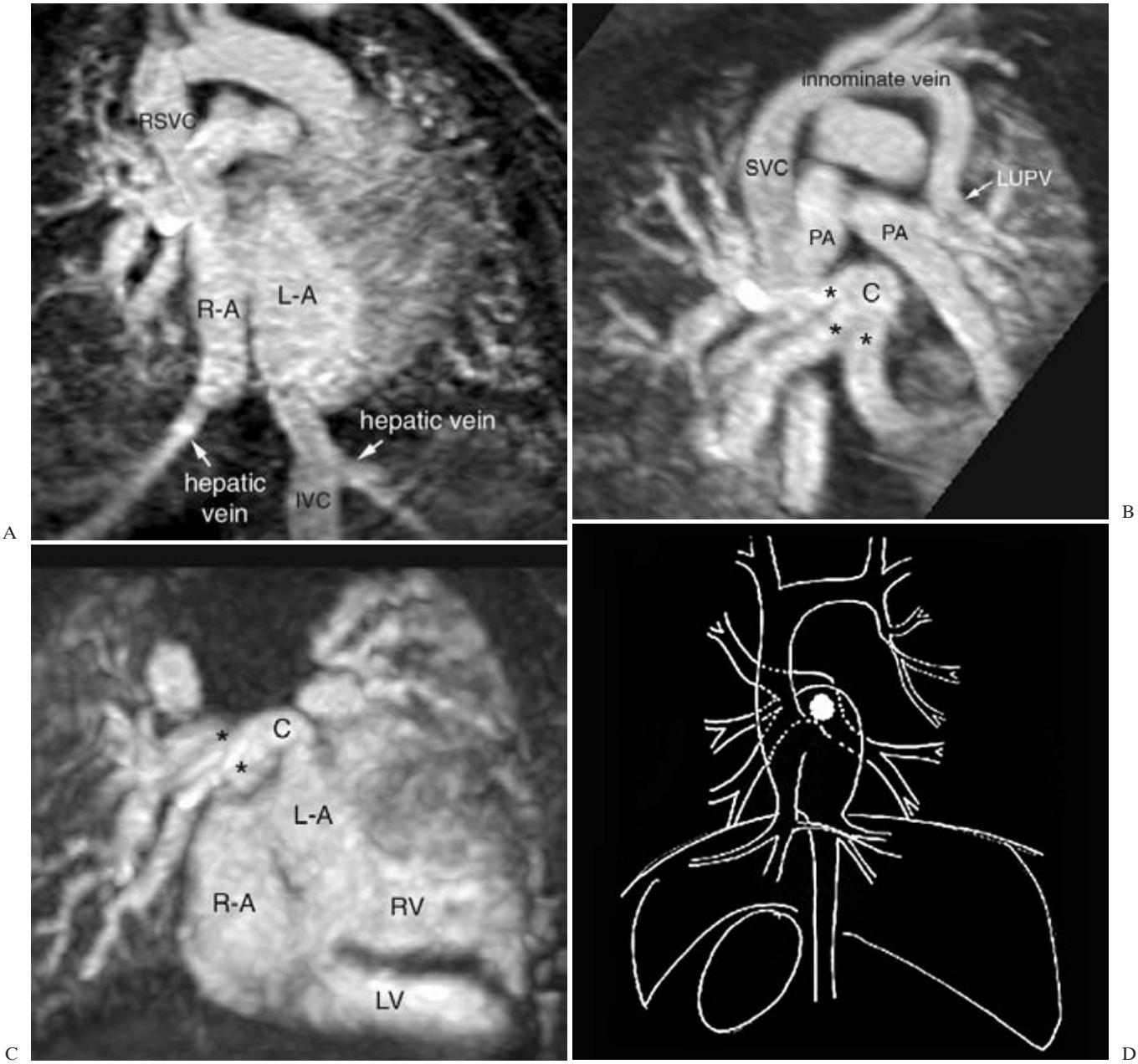

Fig. 33-4 Complex systemic and pulmonary venous anatomy in a patient with right isomerism. Contrast-enhanced MR angiograms show the right superior vena cava (RSVC) and a hepatic vein connected to the right-sided atrium (R-A) and the inferior vena cava (IVC) draining another hepatic vein connected to the left-sided atrium (L-A) (**A**). The pulmonary veins draining the right lung and left lower lung (asterisks) form a narrow confluence (C) to connect to the left-sided atrium (**B**, **C**). The left upper pulmonary vein (LUPV) is connected to the innominate vein (**B**). Composite diagram shown in **D** provided for surgical planning. LV, left ventricle; PA, pulmonary artery; RV, right ventricle. (Reprinted from Valsangiacomo *et al*., Contrast-enhanced MR angiography of pulmonary venous abnormalities in children, *Pediatr Radiol* 2003; **33**: 92–8, Fig. 3, Copyright (2003), with permission from Springer-Verlag.)

The paired sinus nodes and paired atrioventricular nodes are connected by a sling of conduction tissue, thus forming the substrate for an AV re-entrant tachycardia.[9–11,58,59]

Extracardiac abnormalities

Considerable attention has been focused over the years on the extracardiac anomalies in patients with heterotaxy syndromes as these contribute to the morbidity and mortality (Table 33-2).[60–66]

Both groupings have a predisposition to the retention of primitive embryonal symmetry. This is reflected in bronchopulmonary symmetry, hepatic symmetry, non-fixation of the intestines with the potential for malrotation. One of the more common extracardiac feature that most jeopardizes the patient with left isomerism is extrahepatic biliary atresia (see Chapter 34). This complication is extremely uncommon in the patient with right isomerism/asplenia. As we pointed out many years ago and as confirmed by the observations of Phoon and Ticho *et al.*, these patients are at risk for major malformations of gastrointestinal, genitourinary, skeletal, and nervous systems.[6,61] Ticho and his colleagues have stressed the high incidence of midline-associated defects in patients with heterotaxy.[61] These authors suggest that the midline plays an important role in establishing left–right asymmetry. It was also of interest that a midline anomaly was twice as likely to be detected on a complete post-mortem than from clinical observations alone. These findings have been confirmed by others as well.[64]

Patients with asplenia are at risk for overwhelming infection, and thus in any patient with a suggestion of heterotaxy, it is paramount that the presence or absence of a spleen be defined and its function ascertained.[12,21] Any number of investigations have been used in the investigation of splenic status and function, including examination of peripheral blood for Howell–Jolly bodies or pitted erythrocytes, radionuclide splenic scans, ultrasound, magnetic resonance imaging, and abdominal CT scans. Phoon in an exhaustive review of splenic issues in syndromes of isomerism published in 1997 suggests that of all the examinations that have been used in the investigation of splenic status and function, examination of peripheral blood for Howell–Jolly bodies or pitted erythrocytes coupled with ultrasonography is probably the set of tests with the highest sensitivity and convenience.[21] He suggests management of the asplenic patient includes standard and timely immunizations and recommends as well polyvalent pneumococcal and meningococcal vaccines. Daily antimicrobial prophylaxis is also necessary and usually consists of oral penicillin, amoxicillin, or trimethoprim-sulfamethoxazole. This prophylaxis is aimed particularly toward prevention of pneumococcal disease, and is most important in those patients < 2 years of age who have not yet received pneumococcal vaccine. There is not consensus when such prophylaxis can or should be discontinued, and most suggest it be continued into adulthood.

Predisposition to supraventricular tachycardia in patients with right isomerism

The bilateral sinoatrial and atrioventricular nodes which are joined together by a sling of conduction tissue form the ideal substrate for a re-entry type of tachycardia.[9–11,58] Wu and colleagues identified between 1987 and 1996 a total of 101 patients (61 male and 40 female) and 4 fetuses with right isomerism.[59] The median follow-up duration was 38 months, ranging from 0.2 to 270 months. Supraventricular tachycardia was documented in 25 patients (24%) and 1 fetus (25%). The median age at onset was 4 years of age, ranging from prenatal detection to 14 years of age. Actuarial Kaplan–Meier analysis revealed the probability of being free from tachycardia was 67% and 50% at 6 and 10 years, respectively. They found that patients with two ventricles were more likely to develop tachycardia than those with a univentricular heart. The type of ventricular loop, ventricular morphology and position of the cardiac apex were not significant predictors for the occurrence of the supraventricular tachycardia. The tachycardia may compromise the borderline hemodynamics of these patients, especially if they have not undergone complete univentricular palliation. The experience of Wu and colleagues indicates that these patients are good candidates for radiofrequency ablation if they do not respond to medical therapy.[59] Cheung and colleagues have also studied the cardiac rhythm and symptomatic arrhythmias in 110 patients with right isomerism.[59A] They found that all patients but one had normal sinus rhythm with intact atrioventricular connection. Nine-five (87%) had a single P-wave morphology. Fifteen of 85 patients (18%) developed symptomatic cardiac arrhythmias, including 11 with supraventricular tachycardia, 1 patient each with atrial tachycardia, atrial flutter, ventricular tachycardia and congenital complete heart block.[59A] The arrhythmia occurred before surgery in 4 patients, early after surgery in 5 patients and late after surgery in 6 patients. Of the 32 fatalities, in only 1 was it attributable to arrhythmia.[59A] Freedom from arrhythmia at 1, 5, 10, 15, and 20 years was 93%, 86%, 80%, 73%, and 48%, respectively. This group could not identify any risk factor for symptomatic arrhythmia.[59A]

Outcome analysis

There is considerable information about the prenatal diagnosis of patients with asplenia and polysplenia syndrome, using a variety of markers.[67–78] These markers include the association of an atrioventricular septal defect with other complex cardiac

Table 33-2 Extracardiac anomalies in right and left isomerisms

Right isomerism	Left isomerism
Intestinal malrotation virtually in all	Intestinal malrotation virtually in all
Partial thoracic stomach (hiatal hernia) in ~ 25%	Biliary atresia and/or hypoplastic or absent gallbladder in 20%
Very heterogeneous anomalies	Urinary anomalies in 17% encountered
	Duodenal atresia in 7%

(From Van Mierop *et al.*,[11] Hashmi *et al.*,[36] Phoon & Neill,[51] and Gilljam *et al.*[57] with permission.)

malformations, from careful analysis of the spatial relationships between the abdominal aorta and inferior vena cava, non-visualization of the splenic artery, recognition of abnormalities of the fetal central veins and umbilicoportal system, and from recognition of an abnormal right fetal cardiac axis, among others.[67–78] Data provided from a combined experience of 121 cases of isomerism detected during fetal life indicated that left isomerism was detected twice as often as right isomerism.[75] In terms of outcome, 52% of parents elected to interrupt the pregnancy, 10% resulted in a spontaneous intrauterine death, and 13% died after birth. Nineteen per cent of the total were currently surviving. The authors state that the survival rate in continuing pregnancies was 40%.[75] Lin and colleagues recently reported the outcomes of 25 fetuses with right isomerism.[78] Of 25 fetuses with right isomerism, 6 pregnancies were terminated and 10 fetuses were lost to follow-up. Nine patients with right isomerism were delivered, with 5 deaths in infancy.[78]

There is substantial clinical documentation about the poor prognosis in those patients identified with right atrial isomerism.[33,36,51] While prolonged survival has been observed to adulthood in an occasional patient with right isomerism either without surgical intervention or with a shunt only, this is very uncommon.[79,80,80A] Obviously such prolonged survival without surgical intervention requires a balanced circulation. Franklin and his colleagues identified 191 infants with double-inlet ventricle presenting in infancy and studied survival before definitive operations.[81] Thirty-four of these patients had right atrial isomerism, with a 2-year survival of 17 ± 6% and a 5-year survival of 14 ± 6%. The Baltimore–Washington Infant Study identified 71 patients with Ivemark syndrome[35] and Kartagener's syndrome[35] (see Chapter 41E) and they found a 1-year survival of 41%. Unfortunately, the authors provide little specific information about these patients.

A number of reports have detailed the various surgical strategies applied to these patients.[82–104] The majority of patients with right atrial isomerism are candidates only for single ventricle palliation.[36] For some of these patients the results of the various staging maneuvers, the bidirectional cavopulmonary shunt, or Fontan outcomes have clearly improved over the years. In addition, an occasional patient is a candidate for a biventricular repair, often requiring some form of intraventricular tunnel and extracardiac conduit, etc. Biventricular repair has been accomplished in some patients, even those who required unifocalization.[90–92,99] There have been some ingenious procedures to repair/replace a severely regurgitant atrioventricular valve in these patients as well.[92] The common atrioventricular orifice in many of these hearts departs considerably from what is appreciated in standard biventricular hearts, and the observations of Uemura and his colleagues are particularly relevant.[105,106] But most reports of Fontan outcome in patients with right isomerism address the fate only of those undergoing Fontan palliation.[85,94] Fontan results continue to improve in patients with heterotaxy, but most large clinical experiences still show a higher mortality in patients with heterotaxy than those without heterotaxy.[103,104,107,108] We have commented earlier on the prevalence of obstructed total anomalous pulmonary venous connections in patients with right isomerism. There is also some evidence that the pulmonary veins in this condition may be intrinsically small, further confounding surgical management.[49,50,109,110]

The majority of patients with right atrial isomerism have severe reduction in pulmonary blood flow and thus palliation must attempt to augment pulmonary blood flow. A minority of patients will have excessive pulmonary blood flow, and pulmonary artery banding will be required. Unfortunately, in so many of these patients as well, bilaterally obstructed total anomalous pulmonary venous connections complicate the situation and this must be addressed at the time of initial palliation (Fig. 33-2). Defining the adequate amount of pulmonary blood flow has been difficult. Data from several centers indicate that the combination of anomalies (reduced pulmonary blood flow and obstructed pulmonary venous connections) in the neonate conveys a dismal outlook.[36,84,86–88,95,96–98,102] Sadiq and his colleagues have reviewed the experience of the United Kingdom's Birmingham Children's Hospital with the management and outcome of infants and children with right atrial isomerism.[87] They reviewed the outcomes of 20 consecutive children with right atrial isomerism and complex congenital heart disease requiring surgical intervention from 1987 to 1993. The patients were divided into two groups, 11 patients requiring intervention in the first month of life (mean age 5 days), and the remainder who required surgery after the first month of life (mean age 6.8 months). Seven of the 11 patients in the first group had obstructed total anomalous pulmonary venous connections, and 10 of the 11 had pulmonary atresia. There were 7 early deaths including the 5 patients who required both a systemic-to-pulmonary artery shunt and simultaneous repair of obstructed pulmonary veins. The long-term survival in this group was 18%. Amongst the second group, pulmonary venous obstruction was found in 2 patients and 4 had pulmonary atresia. There were no early deaths, with 1 late sudden death and 1 death at a second palliative procedure. The long-term survival rate for this group was 78%. Gaynor and his colleagues have reported on the long-term outcome of 73 infants with single ventricle and total anomalous pulmonary venous connections treated between 1984 and 1997.[95] Overall survival was 45% at 6 months of age, 37% at 1 year of age, and 19% at 5 years. Twelve patients died before surgery. Of the 61 patients undergoing surgery, survival was 54% at 6 months of age, 44% at one year of age, and 23% at 5 years. The heterotaxy syndrome was present in 52 patients. For the entire cohort, survival was worse for those with obstructed total anomalous pulmonary venous connections than for those without obstruction ($P = 0.02$). Like the experience of Sadiq, repair of total anomalous pulmonary venous connection at the time of the initial operation was associated with worse survival ($P = 0.02$). Cheung and colleagues reported on the outcomes of a large cohort of infants with right atrial isomerism, also showing that those with obstructed pulmonary venous connections had a far worse outcome than those with normal connections.[95A] Their review comprised 116 patients seen between January 1980 and December 2000. No interventions were planned in 31 patients (27%), all of whom died. The overall mean survival at 1 month, 1, 5, 10, and 15 years was 80%, 65%, 51%, 43%, and 34%, respectively. The significant independent risk factors for survival were pulmonary venous obstruction and a main ventricular chamber of single ventricle morphology.[95A]

We reviewed several years ago the management and outcomes of all 91 patients with right atrial isomerism seen to that time at the Toronto Hospital for Sick Children from 1970 to 1996.[36] Eighty-nine per cent presented within the first month of life, and 62% at birth. Fifty-four were males (58%) and this is consistent with the male dominance in this syndrome. Cardiac anomalies included a common atrioventricular septal defect in 81%, ventricular hypoplasia or "single" ventricle in 73%, abnormal ventriculoarterial connection in 96%, pulmonary outflow

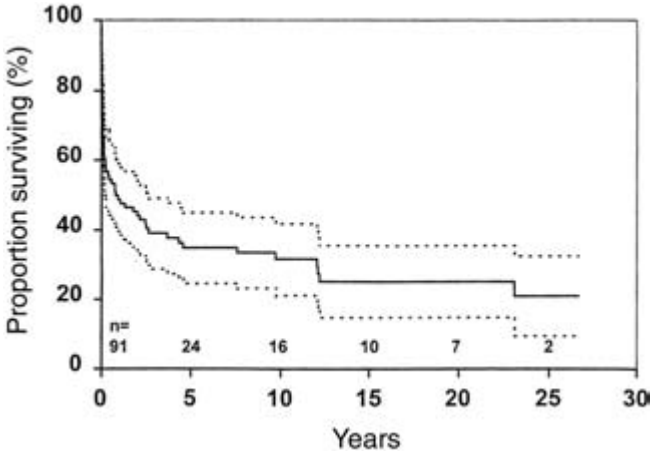

Fig. 33-5 Kaplan–Meier survival estimates of overall survival of 91 patients with right atrial isomerism. The overall mortality was 60%. Dashed lines, 95% CL. (Reprinted from Hashmi, *et al*.,[36] Copyright (1998), with permission from The American College of Cardiology Foundation.)

tract stenosis or atresia in 84%, and anomalous pulmonary venous connections in 87%. The pulmonary venous connections were obstructed in 30%. The overall mortality was 69%. No interventions were planned or performed in 24%, 95% of whom died. The mortality rate for patients requiring their first cardiovascular operation in the neonatal period was 75% vs. 51% for those with later first operations ($P < 0.05$). The surgical mortality for those undergoing pulmonary vein repair ± a systemic-to-pulmonary artery shunt in the first month of life was 95%. Overall estimates of survival were 71% at 1 month, 49% at 1 year, and 35% at 5 years (Fig. 33-5). Independent risk factors for decreased time to death included the absence of pulmonary outflow tract obstruction, presence of severe atrioventricular valve regurgitation, and obstructed pulmonary veins. The majority of the patients were candidates for single-ventricle palliation. However only 22% had completion of their Fontan connection, with a surgical mortality of 21%. Our Fontan mortality was considerably higher for these patients in the earlier era than in the past 10 years, similar to reports from the Mayo Clinic and elsewhere. We have recently reviewed our more recent institutional experience with the outcomes of the Fontan operation in children with atrial isomerism and heterotaxy.[103] Between January 1993 and April 2000, 30 patients underwent a total cavopulmonary connection for atrial isomerism and heterotaxy at a mean age of 5.3 ± 3.6 years. Nineteen had right and 11 left atrial isomerism.[103] There were 4 hospital deaths. Kaplan–Meier survival at 1 month was 86% (95% CL, 75% to 97%) and at 1 and 5 years 83% (95% CL, 70% to 96%). Others have also reported excellent outcomes for small numbers of patients with asplenia syndrome undergoing total cavopulmonary connection [103A,103B] (see also Chapters 35 and 36). Stamm and his colleagues reviewing the Fontan experience of 135 patients with the heterotaxy syndrome (93 with right isomerism and 42 with left isomerism) at the Boston Children's Hospital reported a surgical mortality of 19% before 1991; 3% since 1991 and in this large experience no patient died after 1993.[103B] The "denominator" of this study is unclear, and it would be of interest to know how many patients with heterotaxy died before any surgery was carried out, during or before any staging procedure, and how many were excluded from Fontan surgery. Esophageal varices have been observed in some of these patients, and massive hemorrhage has been seen.[111 112]

Finally, despite the complexity of systemic and pulmonary venous connections in these patients, previous cavopulmonary connection, palliation and dextrocardia, a number of these patients have undergone successful cardiac transplantation.[113–115] Larsen and colleagues have reported the results of cardiac transplantation in 29 patients with visceral heterotaxy.[116] The median age of cardiac transplantation was 3.1 years, and 20 patients had undergone some form of cardiac surgery before cardiac transplantation. The actuarial graft survival at 30 days, 1, 5, and 10 years was 100%, 86%, 68%, and 50% respectively. For those surviving Fontan palliation, one can anticipate a variety of late complications (see Chapter 37). Perhaps particular to this group of patients is the long-term function of the systemic, morphologically right ventricle, and the form and function of the common atrioventricular valve.[117]

All references can be found at the end of the book. See pp. 792–5 for Chapter 33.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Thomas Gilljam, Robert M. Freedom, and Shi-Joon Yoo

The Syndrome of Isomeric Left Atrial Appendages, Often Associated with Polysplenia

In the previous chapter we defined a group of patients in whom it is seemingly difficult, if not impossible, to assign visceral situs because the abdominal viscera are not lateralized, or at least incompletely lateralized[1–13] (see Chapter 33). These patients additionally share in common splenic abnormalities, often complex congenital heart disease, and extracardiac anomalies. In this chapter we will examine those patients who have been identified with so-called left atrial isomerism, acknowledging that many but not all of these particular patients have polysplenia (Figs 34-1 to 31-3). Indeed, polysplenia was the terminology first used to identify and group such patients. It was Moller and his colleagues in 1967 who first fully documented the polysplenia syndrome.[1] Considerable data summarized by Becker and Anderson support their view that cardiac malformations and designation should not be based on the type of splenic malformation because splenic status is often a poor marker of cardiac morphology.[2] This view departs considerably from convention because the terms asplenia and polysplenia have become so entrenched for the designation of certain complex forms of congenital heart disease. Most patients with polysplenia have normal splenic function, but polysplenia carries an impact beyond the functionality of the splenic tissue itself, the potential for splenic torsion,[3–5] the association with extrahepatic biliary atresia,[6–15] malrotation and the short pancreas (see Chapter 33, Table 2).[16–22] Up to 25% of babies with biliary atresia bear associated malformations that most often cluster in the polysplenia syndrome.[8,9] Vazquez and his colleagues found that the anomalies associated with polysplenia/biliary atresia did not jeopardise those surgical maneuvers promoting biliary drainage.[8] Thus while one may infer or suggest the status of the spleen on the basis of the particular constellation of cardiac anomalies, clearly each patient must be evaluated for his or her particular splenic status and cardiac anomaly.[23] What unites patients with asplenia/right isomerism and polysplenia/left isomersim is visceroatrial heterotaxy and congenital heart malformations, usually more severe in the former group (see Chapter 33).

Incidence

Data from the New England Regional Infant Cardiac Program (NERICP) indicated that 95 of 2251 infants had congenital heart malformations associated with visceral heterotaxia.[24] More than half of the infants identified by the NERICP with heterotaxy died before their first birthday, and 74% of the babies with levocardia and asplenia or polysplenia died. Through 1975 at the Toronto Hospital for Sick Children we had recognized 52 patients with asplenia or polysplenia.[26] Thus the prevalence at live birth is very uncommon.[25,27,28] We have extended our observations about asplenia/right isomerism with the publications from Hashmi[29] and Gilljam and colleagues.[30] Over a 28-year period we identified 163 patients with left atrial isomerism at the Toronto Hospital for Sick Children. This population accounted for 0.4% of all new patients seen at our institution over this period.[30]

There are some data addressing the genetics of defects in laterality/atrial isomerism. Clinical data on recurrence of atrial isomerism show that only about 5% of siblings are affected.[31–37] This is considerably lower than the experimental work of Layton and Manasek would suggest.[38] Their data support the concept that situs inversus or ambiguus is due to an autosomal recessive trait with reduced penetrance. Fetal loss could explain some of this discrepancy. Cesko and colleagues have described an autosomal-recessive inherited familial heterotaxy syndrome with two affected siblings – one of whom has situs inversus, and the other with polysplenia syndrome.[35] It is also of interest that there is a tendency for right isomerism to affect males, and for left atrial isomerism to affect females. In our report of left isomerism, 63% were female. These findings indicate that there is an increased risk of inheriting atrial isomerism, and that genetic counseling is indicated after the birth of an affected child. There is also the suggestion that heterotaxia occurs as an outcome of maternal diabetes, but the population on which this hypothesis is based is quite small.[39–42]

The types of heart malformations identified in patients with left atrial isomerism

Anderson and his colleagues[43] have provided a thoughtful summary of the types of heart malformations associated with these syndromes, and provided a comprehensive literature review as well. They state: "The essence of the cardiac malformation is atrial isomerism. This does not mean that the hearts have two normal right atria (each receiving a superior caval vein, an inferior caval vein and coronary sinus) or two normal left atria (each receiving four pulmonary veins). Description of atrial isomerism simply means that there is duplication of those parts of the atrial chambers that exhibit the characteristic anatomical features of rightness or leftness".[43] Van Praagh and his colleagues take those to task for what they consider inappropriate usage of the term "isomerism," furthermore indicating that the atria in such patients are indeed lateralized despite a superficial appearance of atrial symmetry.[44–46]

Any number of studies have catalogued the types of heart

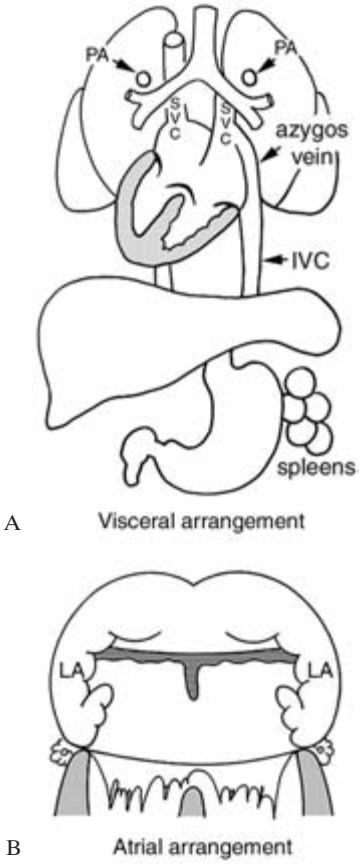

Fig. 34-1 Visceral (**A**) and atrial (**B**) arrangement in left isomerism. Both lungs consist of two lungs with symmetrically long bronchi and the pulmonary arteries (PA) coursing backward above the main bronchi. The liver tends to be symmetrical and multiple spleens are present in most cases. Interruption of the inferior vena cava (IVC) with azygos continuation is common. Both atrial appendages show the morphology of the normal left atrial appendage. The pectinate muscles do not extend to the atrioventricular junction on both sides. SVC, superior vena cava.

malformations associated with the syndromes of disturbed lateralization, atrial isomerism and splenic abnormalities. There is considerable overlap in the complex heart malformations within these two syndromes (see Chapter 33 Table 33-1). Perhaps the most specific marker of the syndrome of left atrial isomerism (aside from bilaterally left atrial appendages) and often polysplenia is azygos continuation of the inferior caval vein (Fig. 34-3), a finding only rarely documented in right isomerism and asplenia.[1,26,37,45–47] Both syndromes demonstrate anomalies of systemic and pulmonary venous connections. Hearts with left atrial isomerism demonstrate a normal ventriculo-arterial junction in almost 70%, according to the extensive institutional review of Gilljam and literature review of Peoples and their colleagues.[30,48] Hearts tended to be overwhelmingly biventricular in hearts with left atrial isomerism, and conversely, among hearts with right atrial isomerism, the atrioventricular connection was univentricular, almost always to a double inlet ventricle via a common atrioventricular orifice. In both syndromes complex forms of atrioventricular septal defect are common. The cardiac apex could be in the left chest, the right, or in the midline. Amongst the patients with polysplenia, normal pulmonary venous connections predominated in the Van Praagh survey, followed by total anomalous pulmonary venous return to the morphologically right atrium.[45] Less common still was drainage of the right pulmonary veins to the right-sided atrium and left pulmonary veins to the left-sided atrium. In their analysis of systemic and pulmonary venous connections in patients with visceral heterotaxy, they found a consistent relationship between the presence of totally anomalous pulmonary venous connection to a systemic vein and an abnormal infundibulum, subaortic or bilateral.[45] Partial or total direct pulmonary venous connections to the right atrium has been attributed by Van Praagh and her colleagues to malposition of septum primum.[49] Of the 36 patients reported by these authors, 33 had visceroatrial heterotaxia.[49] Jenkins and her colleagues have found that individual pulmonary vein size at diagnosis is a strong independent predictor of survival in patients with totally anomalous pulmonary venous connections.[53] The outlook for surgery for patients with single ventricle pathology, pulmonary outflow tract obstruction and total anomalous pulmonary venous connections has been poor[29,50–52] (see also Chapter 37). The poor results have been attributed in part to defective development of the pulmonary veins.[53–55] Although this consideration is more germane for the patient with right atrial isomerism, these considerations will be important for some patients with left atrial isomerism.

Complex forms of atrioventricular septal defect are common to both syndromes, but systemic outflow tract obstruction is certainly more common in those patients with left atrial isomerism.[55A] Complex forms of pulmonary atresia are also seen in both syndromes, but these are more common in the group of patients with right isomerism. While for > 40 years we have been aware of azygos continuation of the inferior caval vein,[56] we have more recently documented the so-called persistent primitive hepatic venous plexus with underdevelopment of the infrahepatic inferior vena cava in patients with left atrial isomerism.[57–59] Rarely, the hepatic vein may connect to the coro-

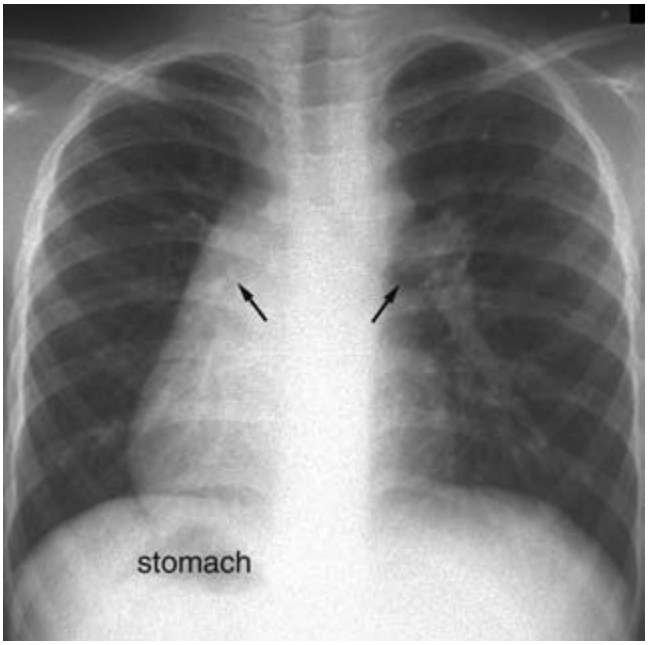

Fig. 34-2 Left isomeric bronchial branching. Frontal chest radiogram shows symmetrically long bronchi (arrows). The stomach bubble is seen below the right diaphragm and there is levocardia.

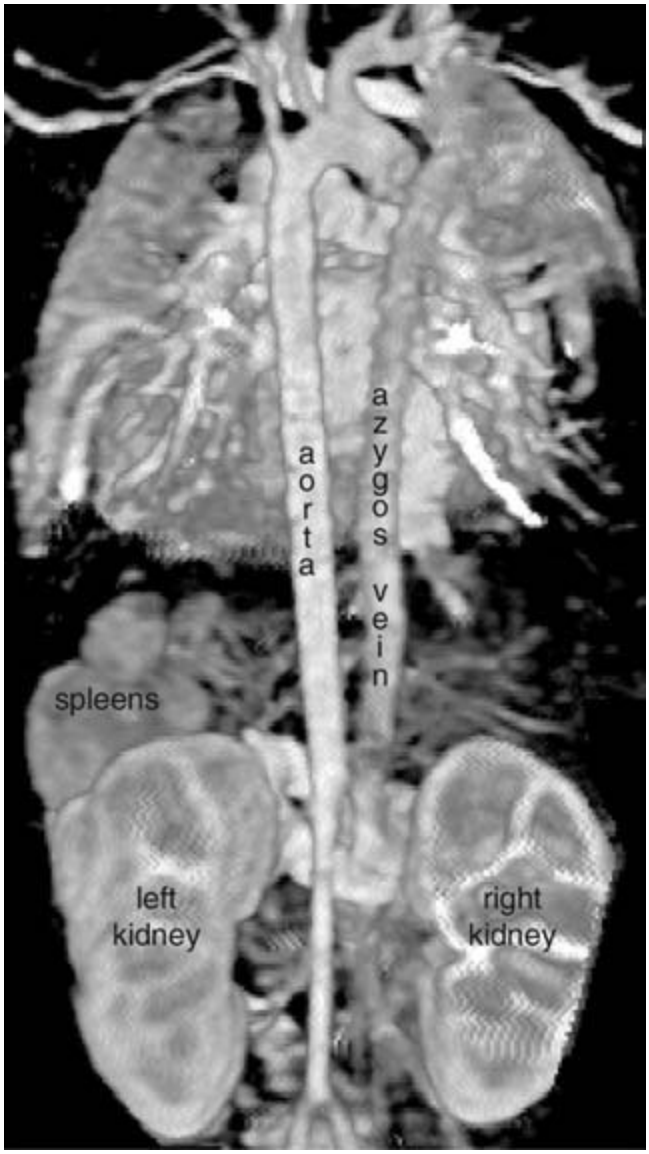

Fig. 34-3 Contrast-enhanced MR angiogram in coronal view seen from behind shows interrupted inferior vena cava with azygos venous continuation and polysplenia.

nary sinus or to the left-sided atrium. If this is not recognized before a Fontan procedure and dealt with, then postoperatively these patients may become progressively cyanotic because of hepatic venous–venous shunting (see Chapter 37). Hepatic vein connection to the coronary sinus or pulmonary venous atrium usually occurs in the setting of heterotaxy, particularly left isomerism/polysplenia, although this has been recorded in a patient with lateralized atria who developed pulmonary arteriovenous malformations. Interestingly, the pulmonary arteriovenous malformations resolved after the hepatic veins were diverted back to the right atrium.[60]

The angiographic and echocardiographic findings of this syndrome have been reviewed in detail elsewhere,[47,61–66] and there is now increasing experience with both computerized tomography and magnetic resonance imaging in patients with heterotaxia.[67–70]

Predisposition to atrial rhythm disturbances and congenital complete heart block

Intrinsic to hearts exhibiting left atrial isomerism is abnormal formation of the sinoatrial node, and thus it is not surprising that such patients may have a leftward and superior P-wave axis, so-called coronary sinus rhythm on their scalar electrocardiogram and may be prone to sick sinus rhythm.[71–74] An abnormal P-wave axis, leftward and superior, is found in about 50–75% of patients with left atrial isomerism, and complete heart block is far more common in patients with left isomerism than right isomerism.[72–74] Congenital complete heart block may exact its toll on the fetus with left atrial isomerism.[75] The morphology of congenital complete heart block in patients with left isomerism is discontinuity between the AV node and conduction axis.[71] Momma and his colleagues[73] reported the characteristics and natural history of abnormal atrial rhythms in left atrial isomerism. This group has had a long interest in the electrocardiograms of these patients and reviewed 450 tracings from 50 patients followed as long as 19 years. In 70%, the frontal P-wave axis was between –30° and –90°. Slow atrial rates below the second percentile were observed in 50%, and progressive slowing of the atrial rhythm was characteristic of these patients.

Extracardiac abnormalities

The extracardiac anomalies identified in the patient with left atrial isomerism have been fully characterized (see Chapter 33: Table 33-2).[1–23] These are often anomalies of midline-associated structures. The digestive tract abnormalities consist of malrotation of the intestine, preduodenal portal vein, gastric volvulus, esophageal hiatal, hernia and biliary atresia.[1–23] A short pancreas has also been observed as well as absence of the gall bladder. Important genitourinary, craniofacial, and musculoskeletal abnormalities have also been catalogued in these patients.[20–22,76]

Outcome analysis

We commented in the previous chapter on the prenatal recognition of patients with visceroatrial heterotaxia, and those specific markers that assist in this diagnosis. The fetal outlook is consistently poorer for those with left atrial isomerism and fetal complete heart block,[77] especially those developing first or second trimester heart block.[77,78] We have stated earlier that a form of atrioventricular septal defect is often present in patients with heterotaxy. This feature has been recognized in the prenatal detection of cardiac anomalies and the presence of associated cardiac anomalies worsens their outcome.[79–82] Interestingly while the fetal outcome is somewhat worse for patients with left isomerism compared with right isomerism, the reverse is true postnally.[29,30]

Franklin and his colleagues from Great Ormond Street Hospital for Sick Children in London have looked at the fate of patients with double-inlet ventricle presenting in infancy and who survived without definitive repair.[83] This retrospective review included 191 infants with double-inlet ventricle seen from 1973 to 1988. The actuarial survival rate before definitive repair for the entire cohort was 57% at 1 year, 43% at 5 years, and 42% at 10 years. Fourteen patients were recognized to have left isomerism and survival at 2 and 5 years was 65 ± 13% and 57 ± 13%, respectively, considerably better than for those with right atrial isomerism.

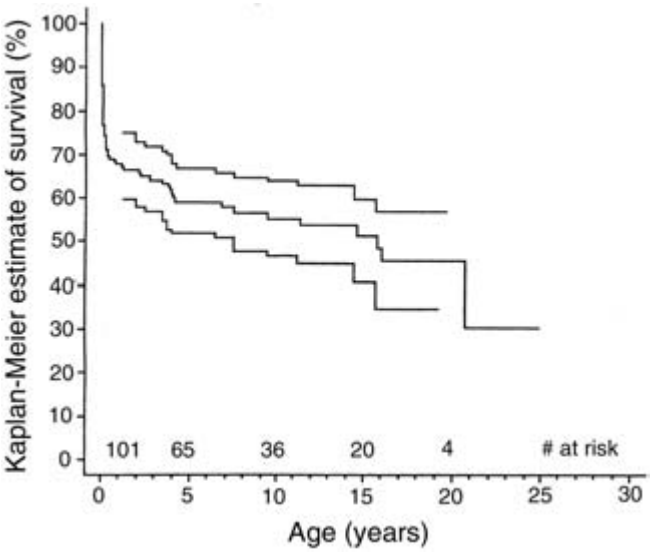

Fig. 34-4 Kaplan–Meier survival (central line) with 95% CL (outer lines) in 163 patients with left atrial isomerism. (Reprinted from Gilljam *et al.*,[30] Copyright (2000), with permission from The American College of Cardiology Foundation.)

There are a large number of reports of the outcomes of various surgical interventions for the patient with left atrial isomerism and heterotaxy. These reports detail the correction of anomalies of systemic and pulmonary venous connections; the Mustard or Senning repair for so-called isolated ventricular inversion (actually left isomerism with lateralized systemic and pulmonary veins); other forms of biventricular repair, and univentricular palliation.[84–92] In the first decade or so after univentricular palliation of the Fontan type was introduced, patients with atrial isomerism, right or left, were considered at higher risk for this form of palliation (see Chapter 36). The introduction of staging with a bidirectional cavopulmonary connection or hemiFontan has led to improved results as these maneuvers allow the surgeon to deal with important anomalies of systemic and pulmonary venous return. Important atrioventricular valve regurgitation has remained a difficult issue to manage, although there are some data indicating that volume unloading surgery may improve mild degrees of regurgitation. Imai and his colleagues have had a very large surgical experience repairing the regurgitant atrioventricular valve.[93] In their experience, Fontan mortality for patients without atrioventricular valve regurgitation was only 3%, but for those requiring atrioventricular valve surgery, Fontan mortality was higher at 12%. Actuarial survival for this latter group was 84% for years 5 through 10, and for those without atrioventricular valve regurgitation, survival at 10 years was 93%. It was the observation of this group that the cause of the regurgitation was mainly annular dilatation or prolapse of the leaflets. It is of interest that Imai's group addressed the atrioventricular valve regurgitation at the time of the Fontan, while others repair the valve at the time of staging and perhaps have a somewhat lower Fontan mortality. However, these reports all address the "tip of the iceberg"; that is, they address only those patients undergoing surgery (the numerator), not the outcome of the entire cohort of patients (the denominator).[30]

Gilljam and his colleagues from the Toronto Hospital for Sick Children reviewed the outcomes of all 163 patients with left atrial isomerism identified over a 28-year experience (1970–98).[30] These patients accounted for 0.4% of all new patients with congenital heart disease diagnosed at our institution during the study period. In 20 patients (12%), the diagnosis was made or suspected at fetal echocardiography. There were an additional 14 fetal cases who subsequently underwent termination of pregnancy or spontaneous fetal death. As in other reports, there is a preponderance of females (63%). Cardiac defects included interrupted inferior caval vein in 92%; anomalous pulmonary venous connections in 56%; atrioventricular septal defect in 49%; pulmonary stenosis or atresia in 28%; aortic coarctation in 16%; 10% severe systemic outflow tract obstruction and congenital complete heart block in 7%. Of 22 patients with a normal heart, 18% died of extracardiac anomalies. As one would expect, important extracardiac anomalies were identified in 58 patients or 36% of the entire cohort. Sixteen patients were found to have biliary atresia; 11 of these underwent a portojejunostomy and 4 of these went on to a liver transplant. The overall survival of the 163 patients was 80% at 1 month, 68% at 1 year, 59% at 5 years, 55 at 10 years, and 51% at 15 years (Fig. 34-4). During the study period, 20% of patients died shortly after birth or were not considered eligible for surgery due to the presence of complex cardiac malformations, associated anomalies, or severe prematurity. We divided the cohort into three groups: (1) patients with a structurally normal heart (or nearly so); (2) patients with balanced defects suitable for biventricular repair; (3) patients suitable only for univentricular palliation. There were 22 patients in the first group (13%); 71 in the second group (44%); and 70 patients in the third group (43%). Overall survival in group 1 was 82%; those with a biventricular heart (group 2) 66%; and for group 3, those suitable for univentricular palliation, 37% (Fig. 34-5). In multivariate analysis, three cardiac factors (complete atrioventricular block, single ventricle morphology, and coarctation of the aorta)

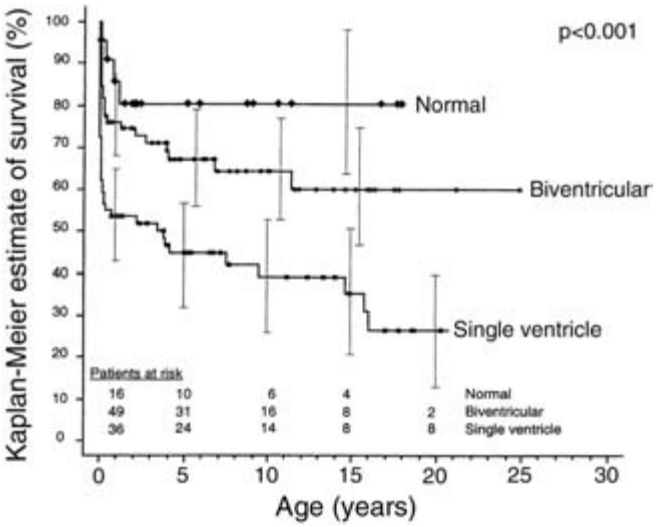

Fig. 34-5 Kaplan–Meier survival in 163 patients with left atrial isomerism and a normal heart ($n = 22$), a heart suitable for a biventricular repair ($n = 71$) and a heart suitable for single ventricle palliation ($n = 70$). Survivors are denoted by dots. Vertical bars represent 95% confidence limits. Differences between groups were analyzed using the log-rank and Wilcoxon tests. (Reprinted from Gilljam *et al.*,[30] Copyright (2000), with permission from The American College of Cardiology Foundation.)

were independently associated with increased mortality. In addition three extracardiac findings were associated with increased mortality, low birth weight, biliary atresia, and other important gastrointestinal malformations. Survival in the biliary atresia group was only 31%. With increasing experience and improving results with Norwood palliation, it is likely that results in the third group of patients should improve.[94] These patients will be subject to the panorama of complications that may jeopardize any survivor of Fontan palliation (see Chapter 37). Because many requiring single ventricle palliation have a common atrioventricular orifice and a functioning systemic ventricle of right ventricular morphology, the form and function of these two structures will be of considerable importance. The data published several years by Sinzobahamvya *et al.* and in 2001 by Azakie and his colleagues from Toronto demonstrate continued improving results in patients with left isomerism, and better results as well in patients with right isomerism surviving infancy.[91,95] Finally, some patients with left isomerism will have associated aortic atresia and these patients have been successfully palliated on a Norwood–Fontan tract.[96] The issue of the development of pulmonary arteriovenous malformations, their prevention and treatment will be fully discussed in Chapters 36 and 37. In this regard, the Kawashima operation and pulmonary arteriovenous malformations are also discussed in Chapter 37. A wonderful review of life and contributions of this surgical giant has recently been published.[97]

All references can be found at the end of the book. See pp. 795–7 for Chapter 34.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom, Shi-Joon Yoo, and W.G. Williams

The Cavopulmonary Shunt

The surgical odyssey leading to right heart bypass is indeed an international one. Trusler and his colleagues,[1] Konstantinov and Alexi-Meskishvili,[2,3] Karl and Stellin,[4] and Robicsek[5,6] have all reviewed in detail the cavopulmonary shunt and have defined with clarity the origins of this bold and imaginative contribution. In a letter from Konstantinov and Alexi-Meskishvili to the editor of the *Annals of Thoracic Surgery*[3] in response to Karl's and Stellin's "Early Italian contributions to cavopulmonary surgery,"[4] they write: "It is always interesting to see how the same idea evolves in different groups working independently and often unaware of each other's efforts. It was undoubtedly Carlo A. Carlon, professor of surgery at the University Medical School in Padua, who first described the concept of the cavopulmonary shunt."[3] Konstantinov and Alexi-Meskishvili in their own paper wrote: "It often occurs in medicine that a syndrome or operation is named not after those by whom it was first described, but rather after those who convinced the world. William Glenn, was not the first to introduce the concept of cavopulmonary anastomosis. He reported neither the first experimental study, nor the first clinically successful operation. However, it was an extensive study undertaken by the Yale University group and prolific writing of Glenn published in the most-read surgical journals that finally convinced the world. By virtue of experimental and clinical work, Glenn's name is generally attached to the operation. None the less, a remarkable pioneering contribution of many other surgeons, namely, Carlon, Francis Robicsek, Nikolai Galankin, Tigran Darbinian, Harris Schumacker, and Evengenii Meshalkin should be remembered, respected, and never regarded as just a historical curiosity."[2] Robicsek, with his long interest in cavopulmonary connections[5,6] and indeed as one of the pioneers of this innovative operation, has also reviewed in two wonderful papers, the first of which was published two decades ago, the history of this operation, and those in the United States, Italy, and the Soviet Union who pioneered this innovative procedure.[5,6] In terms of William Wallace Lumpkin Glenn, Sewell and Glenn began their experimental work on right heart bypass in 1950 and Glenn and his colleagues continued this work throughout most of the 1950s.[2,5,6–10] Glenn's first experimental work on the cavopulmonary shunt was published with Patino in 1954.[7] The first report of an experimental method of performing an anastomosis between the superior vena cava and the right pulmonary artery was presented by Carlon, Mondini and deMarchi in 1950 and published in English the following year.[11] Their surgical connection utilized the azygos vein. These authors speculated that this procedure might be helpful in certain cardiac malformations. Glenn reported in 1958 the clinical application of the cavopulmonary connection (Fig. 35-1).[10] Before the introduction of the Fontan procedure,[12] the classic cavopulmonary shunt or Glenn shunt to the right lung and blood supply from the heart and/or a systemic-to-pulmonary artery shunt to the contralateral lung provided a "balanced" circulation and offered reasonably good long-term palliation As pointed out by Yeh and his colleagues, the Fontan operation[12] changed the objective of the cavopulmonary connection to one of staging to the Fontan, thus reducing the risk of a subsequent Fontan.[13] Like the Blalock–Taussig shunt, the Potts or Waterston shunt, the Norwood operation, the Damus–Kaye–Stansel operation, the Jatene operation, the designation "Glenn shunt" is firmly entrenched in our vernacular. In view of the international multifocal contributions to the cavopulmonary connection, this operation should be more appropriately designated the Carlon, Robicsek, Galankin, Darbinian, Schumacker, Meshalkin, Glenn operation!

The classical cavopulmonary shunt: the Glenn operation

The classical Glenn anastomosis between the right pulmonary artery and the superior caval vein has provided excellent long-term palliation for many forms of complex congenital heart disease since its introduction in the 1950s.[14–23] The classical Glenn anastomosis is constructed between the end of the divided right pulmonary artery and the side of the superior caval vein, with ligation of the azygos vein (Fig. 35-1). The superior caval vein is also ligated between the anastomosis and the right atrium to divert all superior caval return into the right pulmonary artery. Necessary for a satisfactory outcome of this operation is low pulmonary vascular resistance and an acceptable-size right pulmonary artery.[1] It is also important to determine whether or not there is a left superior vena cava and bridging brachiocephalic vein. If a left superior caval vein is present in the absence of a bridging innominate vein, but not recognized preoperatively, the patient would not benefit as much from this procedure. If the brachiocephalic vein is of appreciable caliber, the left superior vena cava can be ligated. In the absence of a left brachiocephalic vein, the left superior vena cava could be judiciously ligated, while measuring the venous pressure proximal to the ligation. thus ensuring that a cerebral venous infarction does not result.[24] Rarely ligation of a left superior caval vein will result in a myocardial infarction.[25–31] This occurs in those patients with coronary sinus ostial atresia where the left superior caval vein provides the conduit for egress of coronary venous blood (Fig. 35-2B).[25–31]

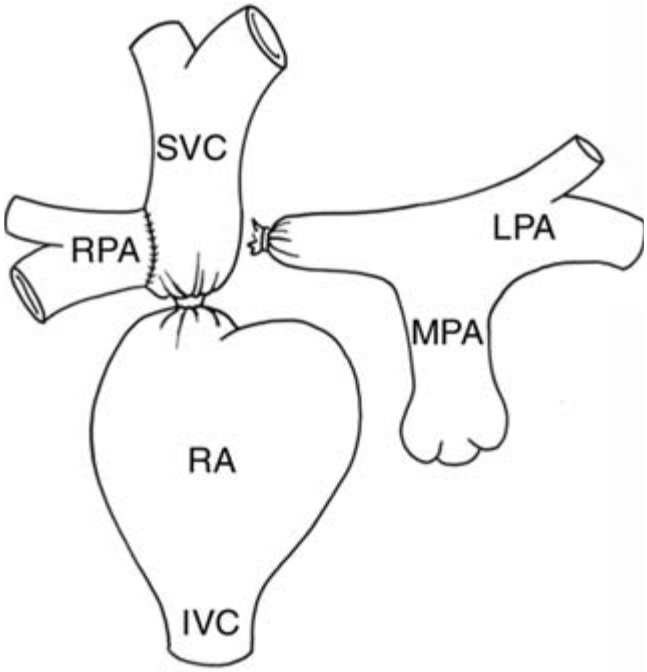
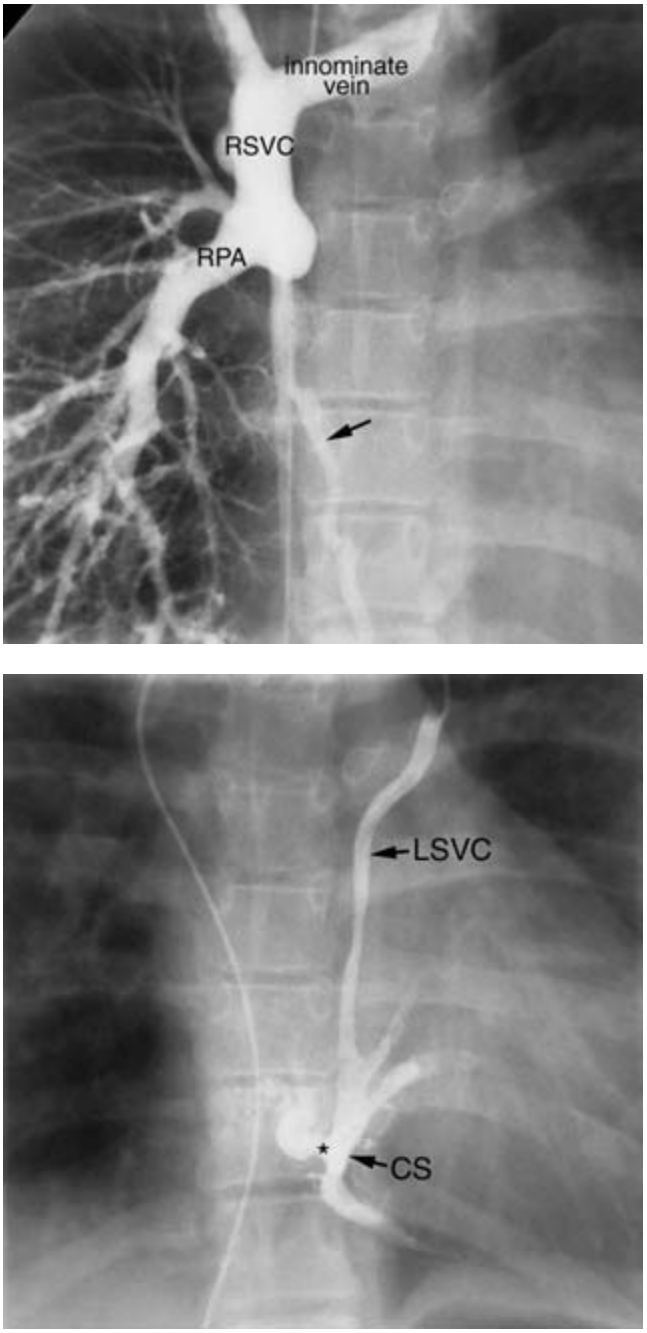


Fig. 35-1 Classical Glenn cavopulmonary anastomosis to the right lung. The superior vena cava (SVC) is connected to the divided right pulmonary artery (RPA) and the superior vena cava is ligated above its entrance into the right atrium (RA). IVC, inferior vena cava; LPA, left pulmonary artery; MPA, main pulmonary artery.

We reported in 1975, 1980, and 1982 our clinical experience with the classical Glenn anastomosis amongst other shunts.[23,32,33] In his Glenn lecture, Trusler and his colleagues reported on our entire Glenn experience to that time.[1] From 1961, the year of the first Glenn shunt performed in Toronto at the Hospital for Sick Children through 1988, 139 classical Glenn shunts were performed. Forty-five of these were performed for tricuspid atresia; 43 for single ventricle; 21 for complex transposition of the great arteries, 10 for pulmonary atresia and intact ventricular septum, and another 10 for miscellaneous conditions. The patients' ages ranged from 17 days to 17 years with a mean of 5.9 years. There were 8 early deaths in the series of 139 patients, seven in the first 39 patients and only one in the last 100. Patient survival rates were 84.9% at 5 years and 61.7% at 15 years. Shunt survival rates, from the time from creation of the shunt to the tie of the next palliative or reparative operation, were 61.1% and 31.8% at 5 and 10 years respectively. As one might anticipate after a classical Glenn anastomosis, decreased flow to the right upper lobe is apparent both from inspection of chest radiographs and from pulmonary perfusion scans.

A number of factors have been implicated in late deterioration of the functionality of the classical Glenn anastomosis as evidenced by increasing hypoxemia and polycythemia[34–42] (Table 35-1).

With growth of the patient, the upper-to-lower body ratio will change in a disadvantageous way, and this will lead to reduced benefit from this shunt.[43,44] That is why the cavopulmonary shunt is rarely used alone in the adult patient.[45,46] Isolation of the left pulmonary artery secondary to progressive closure of a ventricular septal defect or infundibular obstruction as in the patient with tricuspid atresia and normal ventriculoarterial connections previously palliated with a classical Glenn anastomosis is another anatomic reason responsible for late deterioration of the Glenn anastomosis.[1,19–23,34–42] Other reasons for late deterioration are diminished flow through the cavopulmonary connection caused by increased vascular resistance secondary to polycythemia and hyperviscosity. In some patients development of collateral venous circulation from the brachiocephalic vein or one of its tributaries bypassing the lungs and thus reducing



A

B

Fig. 35-2 Classical Glenn anastomosis. **A**. Injection into the innominate vein shows the connection of the right superior vena cava (RSVC) to the right pulmonary artery (RPA). The right upper lung is underperfused. A systemic venous collateral (arrow) diverts the blood flow into the inferior vena caval system. **B**. A small persistent left superior vena cava (LSVC) is catheterized. The coronary sinus (CS) shows ostial stenosis (asterisk). Inadvertent ligation of this channel may cause myocardial infarction.

Table 35-1 Mechanisms implicated in late failure of the Glenn anastomosis

Unfavourable upper/lower body ratio
Systemic venous collateralisation
Pulmonary arteriovenous malformations
Isolation of contralateral pulmonary artery
Recanalization of SVC–RA connection

SVC, superior caval vein; RA, right atrium.

the effective pulmonary blood flow will also contribute to progressive hypoxemia (Fig. 35-2).[1,19–23,34–42] Others have suggested the decreased perfusion to the right upper and middle lobes reflecting the dependent nature of flow to the right lung characteristic of the classical Glenn anastomosis (Figs 35-2, 35-3).[41] Occasionally the site of ligation of the superior caval vein at the right atrial junction may recanalize, thus reducing flow to the right lung (Fig. 35-3).[47] Perhaps the most egregious cause of late failure of the classical Glenn anastomosis is the development of pulmonary arteriovenous fistulae (see next section in this chapter). Our data suggest this complication could be as high as 21%, with the potential for an increasing hazard of this complication with longer duration of the cavopulmonary shunt.[1,41] The role of hepatic vein exclusion is discussed in detail in Chapter 37. Suffice it to say, experience with the Kawashima operation and the development of pulmonary arteriovenous malformations suggested hepatic venous exclusion from the pulmonary circulation as one etiology.[48–51] It is likely far more complex than that. Some have advocated "fenestrating" the Kawashima operation in young infants to optimize postoperative hemodynamics.[51A]

In the era before the Fontan operation, once failure of the classical Glenn anastomosis has occurred, palliation could take the form of a systemic-to-pulmonary arterial shunt to augment flow to the contralateral lung. Others have advocated augmenting flow through the classical Glenn anastomosis by creation of an axillary artery-to-vein (or basilic artery-to-vein) fistula.[52–54] We previously reported our experience with this procedure which provides reasonable palliation.[54] We have augmented flow through either a classical Glenn anastomosis or bidirectional cavopulmonary connection in those patients not considered candidates for Fontan's operation. This maneuver affords some palliation, but at a cost of ventricular loading.[54] One of the late complications of this maneuver is aneurysmal transformation of the superior caval vein.[42] We have also found that the creation of an axillary artery-to-vein fistula may be difficult to take down at the time of a subsequent cardiac transplant (personal communication, Dr John Coles). We will consider the etiologies of acquired pulmonary arteriovenous malformations in the setting of the classical Glenn and bidirectional cavopulmonary connection later in this chapter.

The bidirectional cavopulmonary shunt

Construction of a bidirectional cavopulmonary shunt without ligation of the proximal right pulmonary artery was first performed by Achille Mario Dogliotti of Turin, Italy in 1961[55] and independently in dogs by Haller and his colleagues in 1964 (Fig. 35-4).[56] Azzolina, Eufrate and Pensa reported their experience with this technique in the patient with tricuspid atresia

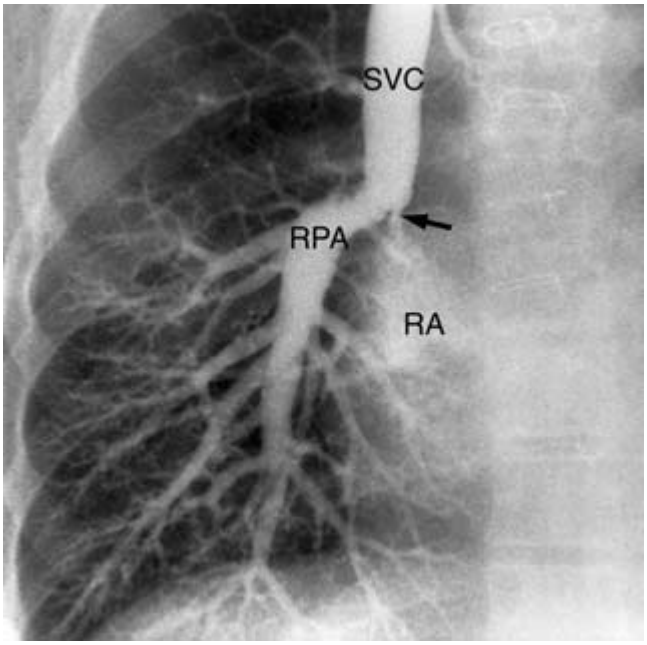


Fig. 35-3 Recanalization (arrow) of the ligated superior caval vein and underperfusion of the right upper lung after classical Glenn anastomosis. RA, right atrium; RPA, right pulmonary artery; SVC, superior vena cava.

in 1972.[57] There is now a large clinical experience with the bidirectional cavopulmonary connection.[58–99] This shunt utilizes an end-to-side anastomosis between the superior vena cava and the undivided right pulmonary artery. In those patients with a

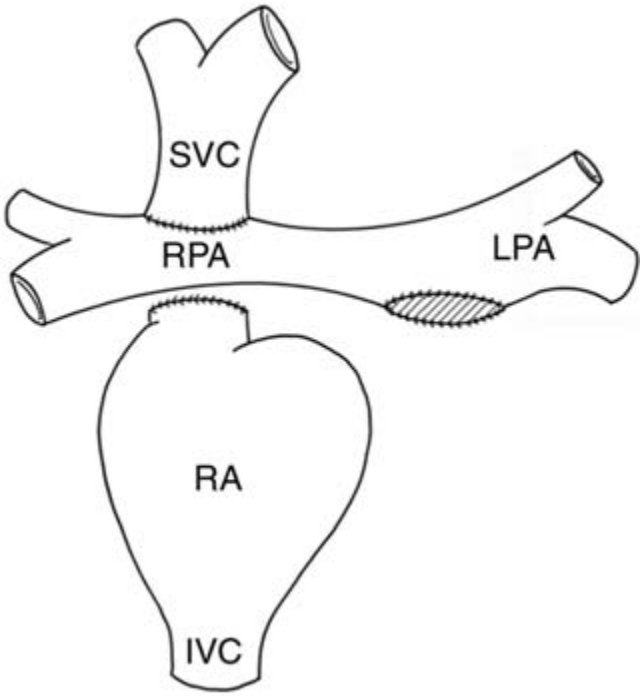


Fig. 35-4 Bidirectional cavopulmonary anastomosis. The superior vena cava (SVC) is divided and its cranial end is anastomosed to the incision in the right pulmonary artery (RPA). The cardiac end of the superior vena cava is oversewn. IVC, inferior vena cava; LPA, left pulmonary artery; RA, right atrium.

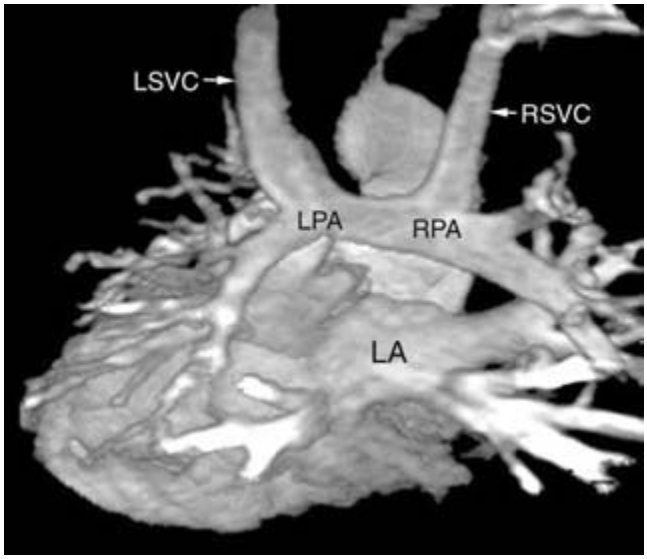


Fig. 35-5 Bilateral bidirectional cavopulmonary anastomoses. Contrast-enhanced MR angiogram seen from behind shows right and left superior venae cavae (RSVC and LSVC) connected to the right and left pulmonary arteries (RPA and LPA). LA, left atrium.

right and left superior vena cava but without a bridging brachiocephalic vein, it is necessary to perform bilateral bidirectional cavopulmonary connections (Fig. 35-5).[100] In the majority of patients undergoing a bidirectional cavopulmonary connection, flow from the heart into the pulmonary trunk is interrupted (so-called competitive blood flow), although this is not always the case as some patients are left with pulsatile forward flow (Fig. 35-6).[69,71,74–76,81–83] The bidirectional cavopulmonary connection has some advantages over the classical Glenn anastomosis, and is being applied to ever younger infants, some as young as a month of age.[59,61,62,66,73,77,78,91] The anastomosis is constructed in an end-to-side anastomosis thus allowing the caliber of the superior caval vein rather than the size of the ipsilateral pulmonary artery to define the size of the anastomosis. Secondly, the bidirectional cavopulmonary connection usually results in a higher oxygen saturation in young children reflecting the proportionately higher upper to lower body segment in younger children compared to older children.[64] In this regard, Salim and colleagues demonstrated that in healthy children superior vena caval flow rose from 49% of total cardiac output in the neonate to a maximum of 55% at 2.5 years, declining to the adult level of 35% by age 6.5 years.[44] As well, the bidirectional cavopulmonary connection provides flow to the contralateral lung without subjecting it to volume overloading and possibly pulmonary vascular obstructive disease from a systemic-to-pulmonary artery anastomosis to that lung, or inadequate growth and resultant hypoplasia from reduced flow. The bidirectional cavopulmonary anastomosis accomplishes these without volume-loading the ventricle, an important advantage for the patient with a univentricular atrioventricular connection.[1,58,59,63,64,67,69,77,78,84-89,92,98] Berman and Kimball found that a bidirectional cavopulmonary connection results in a significantly reduced ventricular preload and size while systolic ventricular performance is preserved.[101] This effect was more pronounced in those patients with single left ventricle morphology than in those with right ventricular morphology. Even with an additional source of pulmonary blood flow, a bidirectional cavopulmonary connection still volume unloads the single ventricle. Forbes and his colleagues looked at the influence of age at the time of the bidirectional cavopulmonary connection in ventricular unloading.[92] They found that the bidirectional cavopulmonary connection facilitates ventricular volume unloading and as well promotes regression of left ventricular mass in younger children, but was of questionable value in older children. As we discussed in considerable detail in Chapter 32, ventricular unloading has the potential for contributing to the development of systemic outflow tract obstruction in some patients with a double-inlet ventricle. The additional benefit of unloading the ventricle by construction of a bidirectional cavopulmonary connection is some improvement in the degree of atrioventricular valve regurgitation.[86–88] The final advantage to a bidirectional cavopulmonary connection is that the pulmonary arteries remain confluent, and this may prove important at the time of the Fontan procedure. Many have addressed the outcome of the bidirectional cavopulmonary shunt and the risk factors for early death, shunt failure, or necessity for bidirectional cavopulmonary shunt takedown. Among some of the risk factors identified with early mortality have been mean pulmonary artery pressure ≥ 18 mmHg, younger age at the time of surgery, abnormal pulmonary venous connections, heterotaxy, severe atrioventricular valve regurgitation. Alejos and colleagues have also suggested that right ventricular morphology is a risk factor for death or shunt failure.[72] Several years ago Reddy and his colleagues reviewed their institutional experience with the bidirectional cavopulmonary shunt.[77] Of the 120 bidirectional cavopulmonary connections performed in 120 patients from January 1990 to April 1996, 6 patients (4.9%) died in the early postoperative period and the overall early failure rate (death or takedown) was 8.1% (n = 10). By multivariate analysis, longer bypass time, age < 1 month, and higher pulmonary vascular resistance were significant risk factors for early shunt failure.[77] Including early and late mortality, actuarial survival rates at 1 and 2 years were 91% and 88%, respectively. Among the hospital survivors, the only

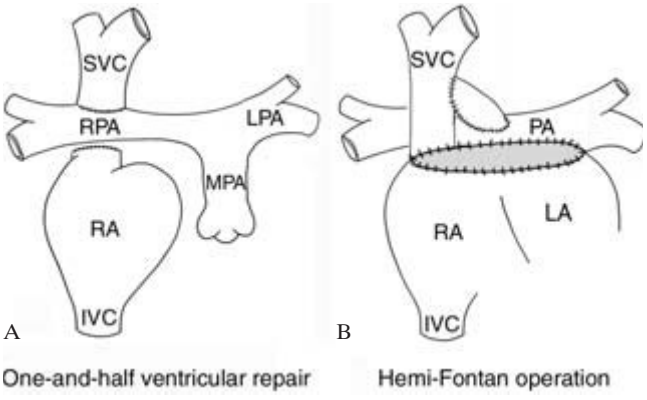
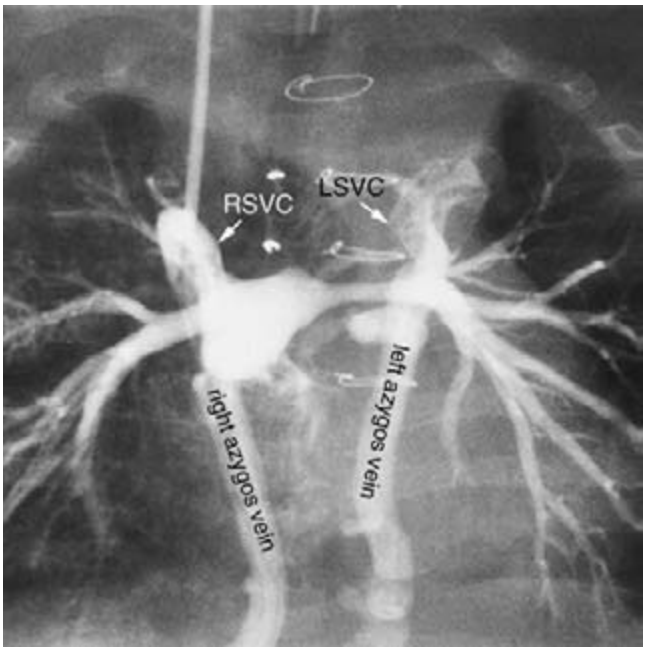


Fig. 35-6 Modifications of bidirectional cavopulmonary anastomosis. **A**. So-called one-and-half ventricle repair with pulsatile flow through the right ventricle into the main pulmonary artery (MPA). **B**. Hemi-Fontan operation. The roof of the right (RA) and left (LA) atria are anastomosed to a long incision on the inferior side of the confluent pulmonary arteries (PA). A large patch is interposed between this anastomosis and the right atrium (RA). IVC, inferior vena cava; LPA, left pulmonary artery; RPA, right pulmonary artery; SVC, superior vena cava.

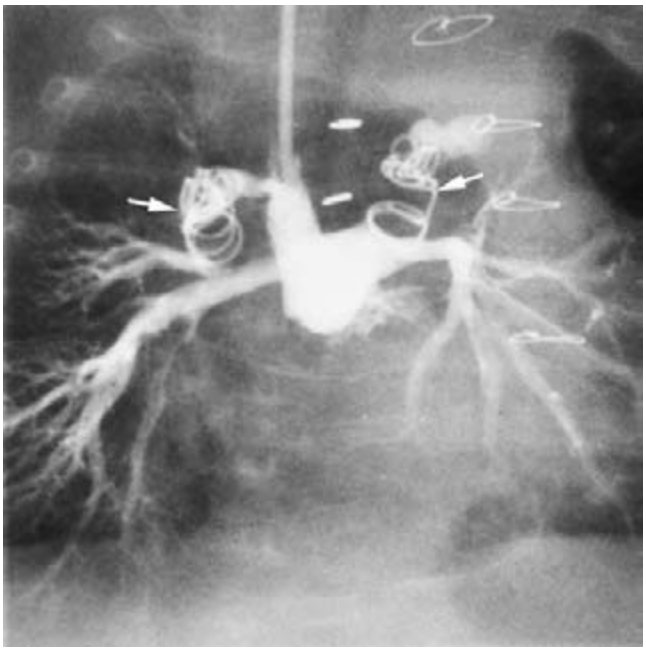
significant predictor of poorer survival by Cox regression was age < 2 months at the time of the initial cavopulmonary shunt.[77] Bradley and his colleagues found that elevated pulmonary vascular resistance was significantly associated with perioperative mortality.[91] An elevated pulmonary vascular resistance was associated with increased pulmonary artery pressure, decreased pulmonary blood flow, decreased effective pulmonary blood flow, and decreased aortic saturation.[91] Aeba and coworkers have studied those factors influencing arterial oxygenation early after the bidirectional cavopulmonary shunt in the absence of additional sources of pulmonary blood flow.[78] They found that there was a significant inverse relationship between the postoperative superior vena cava pressure and the arterial oxygen saturation. A low arterial oxygen saturation early after the bidirectional cavopulmonary shunt was a predictor of mortality or exclusion from univentricular repair within 24 months.[78] This group identified from multiple regression analysis that age < 8 months and ventricular volume overload predicted a lower arterial oxygen saturation after bidirectional cavopulmonary shunting.[78] We have also found that very rapidly after a bidirectional cavopulmonary connection, reopening of systemic venous collaterals can reduce effective pulmonary blood flow resulting in a concerning systemic arterial oxygen saturation (Figs 35-7 to 35-9).[42,102,103] Occasionally, the systemic venous collaterals develop to the left atrium or pulmonary vein as well as to the systemic veins (Figs 35-8, 35-10). Among these many studies no study has seemingly identified the same risk factors for early shunt failure. But most have identified higher pulmonary artery pressure and pulmonary vascular resistance as important predictors of shunt failure.

A number of studies have addressed growth of the right and left pulmonary arteries after a bidirectional cavopulmonary connection. Mendelsohn and his colleagues have studied the growth of the pulmonary arteries after a bidirectional cavopulmonary connection.[60] Serial angiographic and hemodynamic examinations before and 17.6 ± 1.6 months after bidirectional Glenn procedures were compared by these authors. At the follow-up study there was no significant change in diameter of the pulmonary artery ipsilateral to the bidirectional cavopulmonary shunt. Concerning, however, was the observation of a significant decrease in the diameter of the pulmonary artery contralateral to the bidirectional cavopulmonary shunt. There was also a 32% decrease in the Nakata index of total cross-sectional pulmonary artery area after the bidirectional Glenn procedure. In addition, total pulmonary blood flow and mean pulmonary artery pressure had decreased, but arterial oxygen saturation had increased at follow-up. The study of Slavik and associates indicates that the bidirectional cavopulmonary connection promotes growth of a small right pulmonary artery, but there is less evidence that it promotes growth of the small left pulmonary artery.[70] Reddy and his colleagues, using the indexed cross-sectional area of the lower lobe branch of the right and left pulmonary arteries, showed that pulmonary artery indices, including the lower lobe index, did not change significantly after bidirectional cavopulmonary shunt during medium-term follow-up and did not influence the Fontan outcome.[80] Penny and his colleagues measured pulmonary arterial size during cineangiography in 23 patients, 1.9 months before, and 14 months after bidirectional cavopulmonary connection. The measurements were standardized for body surface area using the method of Nakata and co-workers (pulmonary artery index). There was a significant reduction in pulmonary artery index after the bidirectional cavopulmonary connection, indicating that pulmonary arterial growth is impaired after the creation of a bidirectional cavopulmonary shunt.[104] They suggested this could be related to an absolute reduction in pulmonary arterial flow, and/or the loss of systolic expansion of the pulmonary artery.

Seliem and colleagues have studied lung perfusion patterns after the bidirectional cavopulmonary shunt.[97] They found sym-



A



B

Fig. 35-7 Florid systemic venous collaterals after bilateral bidirectional cavopulmonary anastomosis. **A**. Injection into the right superior vena cava (RSVC) shows retrograde filling of the dilated right azygos vein. The pulmonary arteries are small. There is retrograde filling of the left superior vena cava (LSVC) and left azygos vein. **B**. The collateral venous channels were occluded with coils (arrows).

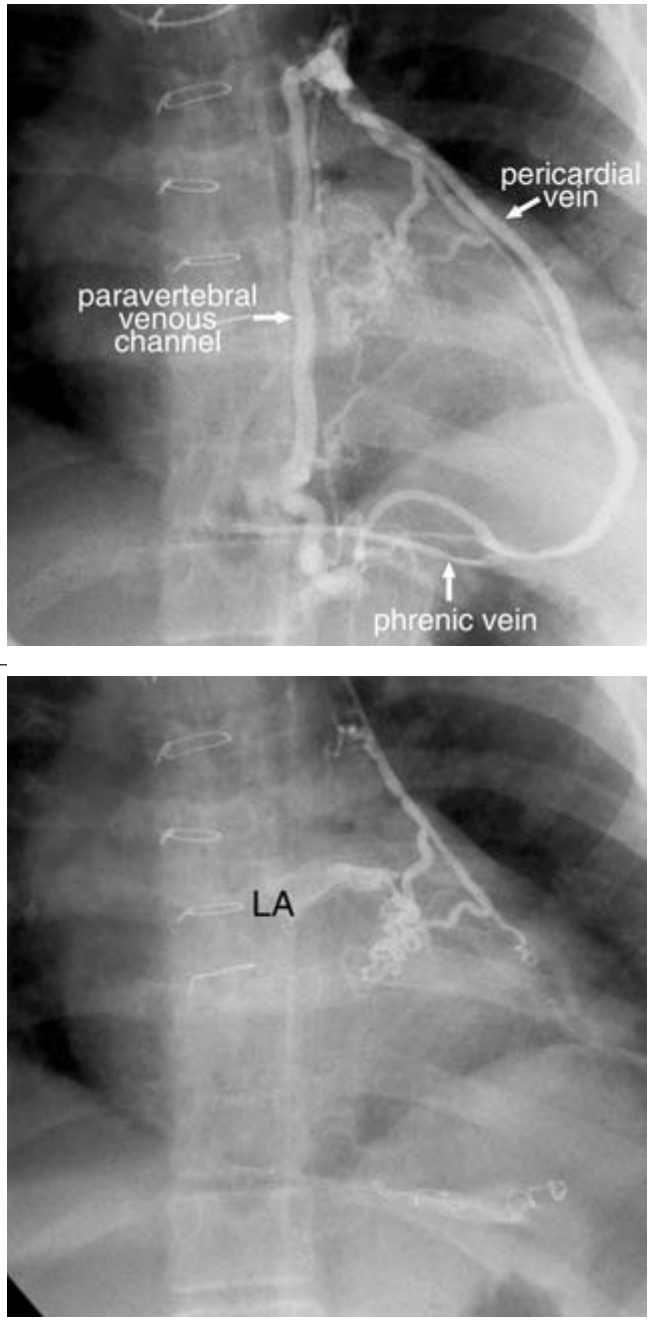


Fig. 35-8 Systemic venous collaterals to the systemic veins and left atrium. **A**. Selective injection into a collateral vein in the left upper mediastinum shows filling of the paravertebral channels and pericardial and phrenic veins. **B**. Injection into the channel after coil occlusion of the pericardial and phrenic veins shows filling of the left atrium (LA).

metrical pulmonary blood flow distribution in only 27% of the patients, and moderately to severely abnormal pulmonary blood flow distribution in 35%.[97] As one might expect in those patients with moderately to severely abnormal pulmonary blood flow distribution, the right lung almost always had greater perfusion than the left lung. Reich and colleagues have quantitated the pulmonary blood supply in patients with bidirectional cavopulmonary anastomosis and pulsatile pulmonary blood flow using radionuclide angiocardiography.[105] Patients with cavocaval collaterals prevented quantitative analysis and thus were excluded from analysis. They found that the bidirectional cavopulmonary anastomosis provided 42.3% of total pulmonary blood flow. From the total bidirectional cavopulmonary anastomosis flow, 67.2% was directed to the ipsilateral lung. This lung received only 16.5 (3.3%) of all the blood from sources of pulsatile blood flow. The blood flow to the lung at the side of the anastomosis accounted for 35.3 (1.7%) of the total pulmonary blood flow. Non-pulsatile flow from bidirectional cavopulmonary anastomosis is mainly directed to the ipsilateral lung, whereas pulsatile flow is directed to the contralateral lung. Total perfusion of the

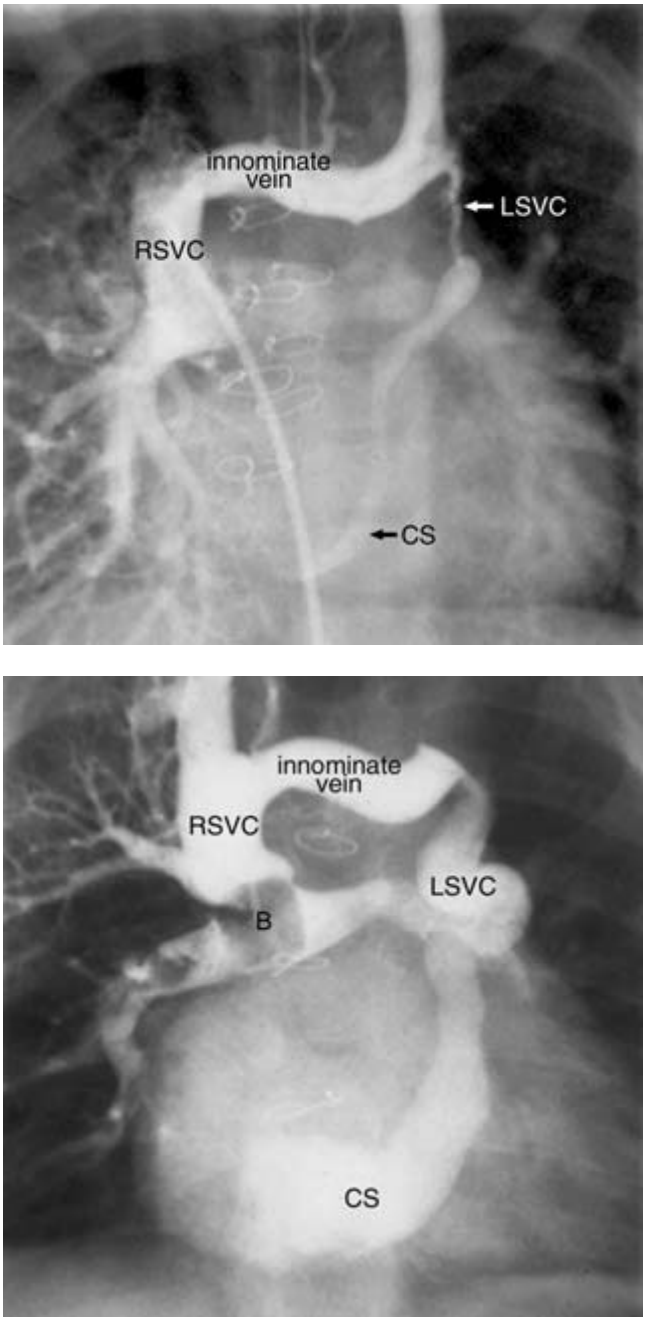


Fig. 35-9 Reopened left superior vena cava (LSVC) after bidirectional cavopulmonary anastomosis in two different patients. B, balloon; CS, coronary sinus; RSVC, right superior vena cava.

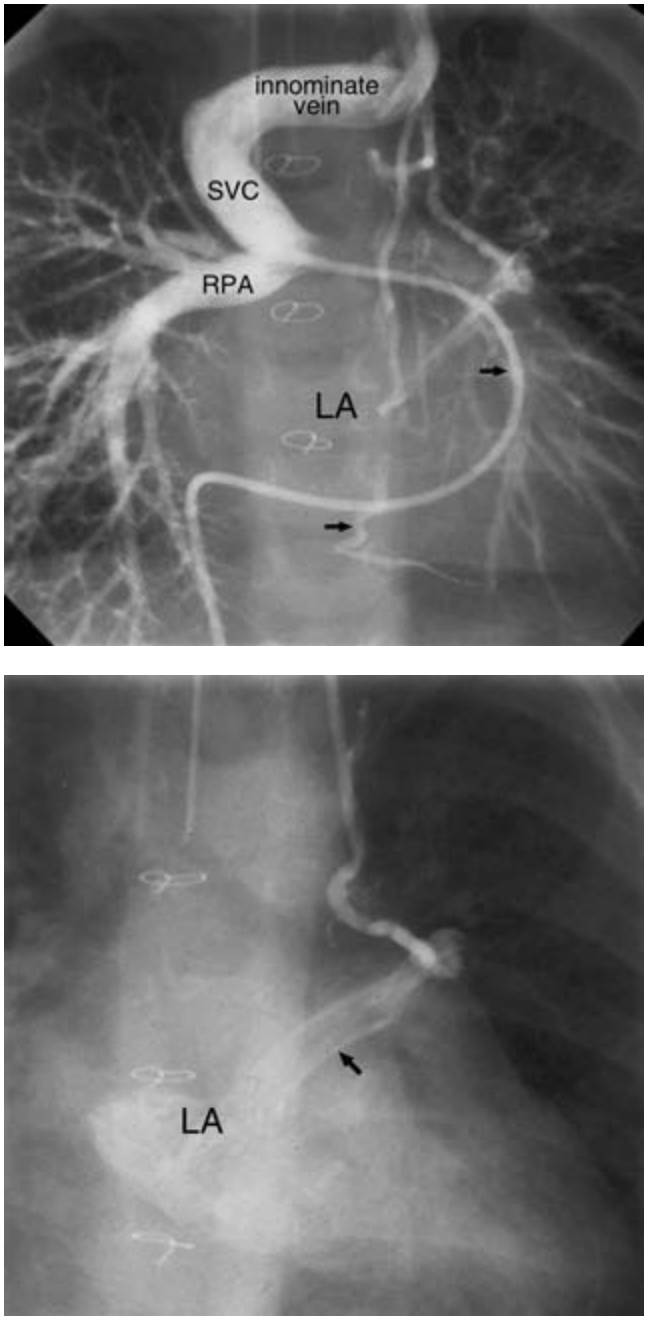


Fig. 35-10 Systemic venous collaterals draining into the left atrium in a patient with one-and-half ventricular repair. **A**. Injection into the innominate vein shows good anatomy of the bidirectional cavopulmonary anastomosis. The functional left pulmonary artery is not opacified because of forward flow through the main pulmonary artery. The catheter was introduced into the innominate vein through the right ventricular outflow tract. Two channels (arrows) drain into the left atrium (LA). **B**. Selective injection into the upper collateral channel shows a large tract (arrow) leading to the left atrium.

ipsilateral lung is less than the perfusion of the contralateral lung.[105]

The influence of competitive pulmonary blood flow on the bidirectional cavopulmonary shunt has been assessed in several centers.[69,71,74–76,78,81–83,106–110] The multi-institutional study of Webber and his colleagues showed that competitive flow is well tolerated in the short and medium term after bidirectional cavopulmonary shunt, with improvement in early, but not late, systemic arterial oxygen saturation.[74] These authors discuss the potential benefits of leaving some pulsatile flow including the prevention of development of pulmonary arteriovenous fistulae, the prevention of the development of systemic-to-pulmonary artery collaterals and as well the potential to enhance pulmonary arterial growth. The data of Mainwaring is more cautionary in the evaluation of the role of accessory blood flow, and they state that morbidity and mortality are increased in those patients with accessory blood flow.[75] The analysis of Frommelt and her colleagues indicates that an additional source of pulmonary blood flow in patients with a bidirectional cavopulmonary shunt usually results in higher oxygen saturations. However, the patients have higher central venous pressures, and they may be more at risk for late development of chylothorax.[76] Aneurysmal transformation of a left superior caval vein has also been reported as a complication of a pulsatile cavopulmonary connection.[71] As pointed out by Aeba and colleagues, it may be necessary to provide an additional source of pulmonary blood flow in those patients remaining hypoxemic after a bidirectional cavopulmonary shunt providing they have a low superior vena caval pressure.[78] Yamada and his colleagues have addressed the issue of bidirectional cavopulmonary shunt with additional source of pulmonary blood flow should be the definitive palliation for the functional single ventricular heart.[107] Their data do not support the clear superiority of long-term bidirectional cavopulmonary shunt over the construction of Fontan circulation for management of the functional single ventricular heart.[107] Miyaji found that the pulmonary artery area index showed a tendency to increase.[110] They also found that the mean number of risk factors for the Fontan procedure decreased significantly from 1.8 ± 1.1 to 0.7 ± 0.8 after the pulsatile bidirectional cavopulmonary shunt. A number of their patients initially considered too high risk for a Fontan went on to this definitive surgery after the pulsatile bidirectional cavopulmonary shunt.

We indicated earlier in this chapter that some patients without a brachiocephalic vein will require bilateral bidirectional cavopulmonary connections (Fig. 35-5). We have found that this is a risk factor for adverse outcome when compared to patients undergoing a unilateral bidirectional cavopulmonary shunt.[100] The overall outcome of 39 children requiring bilateral bidirectional cavopulmonary connections was compared to 274 children having a unilateral cavopulmonary anastomoses. Nine patients (23%) with bilateral superior venae cavae were found to have thrombus in the cavopulmonary circulation after the bilateral anastomoses (b-CPA) (Fig. 35-11). Postoperative mean arterial oxygen saturation was significantly lower in those who had thrombus ($69\% \pm 10\%$ vs. $82\% \pm 7\%$; $P < 0.01$). Thrombus formation was associated with mortality. The indexed superior venae cavae size was not a risk factor for thrombosis. In follow-up studies the connecting pulmonary artery segment between the two cavopulmonary anastomoses was smaller than the pulmonary arteries adjacent to the hilum. Survivors of a b-CPA were less frequently converted to a Fontan circulation at 5 years of follow-up (Kaplan–Meier 5-year estimates, 39% for b-CPA vs. 74% for u-CPA; $P = 0.02$). We concluded that bilateral superior vena cava-to-pulmonary artery anastomosis is associated with an increased risk of thrombus formation and unfavorable growth in the central pulmonary arteries. We speculated that

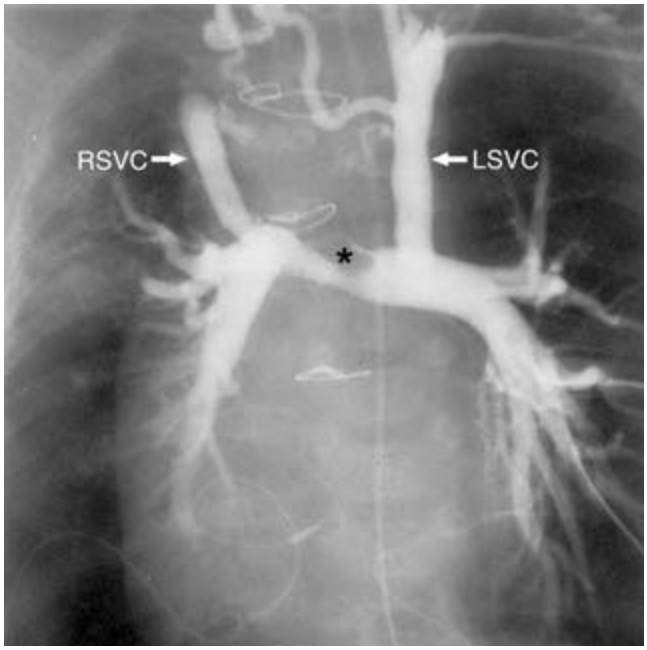


Fig. 35-11 Bilateral bidirectional cavopulmonary anastomoses. A thrombus (asterisk) is formed in the confluent part of the pulmonary artery. LSVC and RSVC, left and right superior vena cava, respectively.

anticoagulation therapy may be an important adjunct in children undergoing bilateral bidirectional cavopulmonary connections. The finding of increased tendency to shunt thrombosis after the bilateral bidirectional cavopulmonary shunts was also recognized by Forbes.[93] Thrombus can also develop as a complication of unilateral bidirectional cavopulmonary anastomosis (Fig. 35-12).

Systemic venous collateralization is very well documented after a bidirectional cavopulmonary shunt and this is likely to be progressive over time, reflecting the chronically elevated systemic venous pressures (Figs 35-7 to 35-9).[102,103,111–113] The development of these important collaterals leads to reduced flow to the lungs and a lower effective pulmonary blood flow, thus contributing to hypoxemia. We reported the incidence of systemic venous collaterals in 103 patients who had undergone a bidirectional cavopulmonary shunt.[111] Angiographically detectable systemic venous collaterals developed in 31% of the patients. The majority of these collateral vessels originated from the brachiocephalic vein or its junction with the superior vena cava, and many of these drained below the diaphragm. Collateral development was associated with an abnormal superior vena cava connection; increased mean pulmonary artery pressure and an increased mean pressure gradient between superior vena cava and right atrium. Similar findings have been reported by McElhinney and his colleagues who also found that in the patients who developed venous collateral channels, the mean transpulmonary pressure gradient early after the operation was higher, and the mean arterial oxygen saturation at follow-up was lower.[113] When necessary, such venous collaterals may be treated successfully with a variety of catheter-introduced devices or by video-assisted thoracoscopic surgery (Figs 35-7, 35-8).[42,114–116]

Systemic-to-pulmonary artery collateral vessels are well-known sequelae of cardiac surgery, particularly but not exclusively after a lateral thoracotomy (Fig. 35-13). McElhinney and his colleagues reviewed the angiographic and clinical data of 76 patients who had undergone a bidirectional cavopulmonary shunt between January 1990 and June 1996.[117] The median age at the bidirectional cavopulmonary shunt was 10 months and the median duration from the bidirectional cavopulmonary shunt to follow-up catheterization was 18 months. Arterial collateral vessels were detected in 59%. Those factors associated

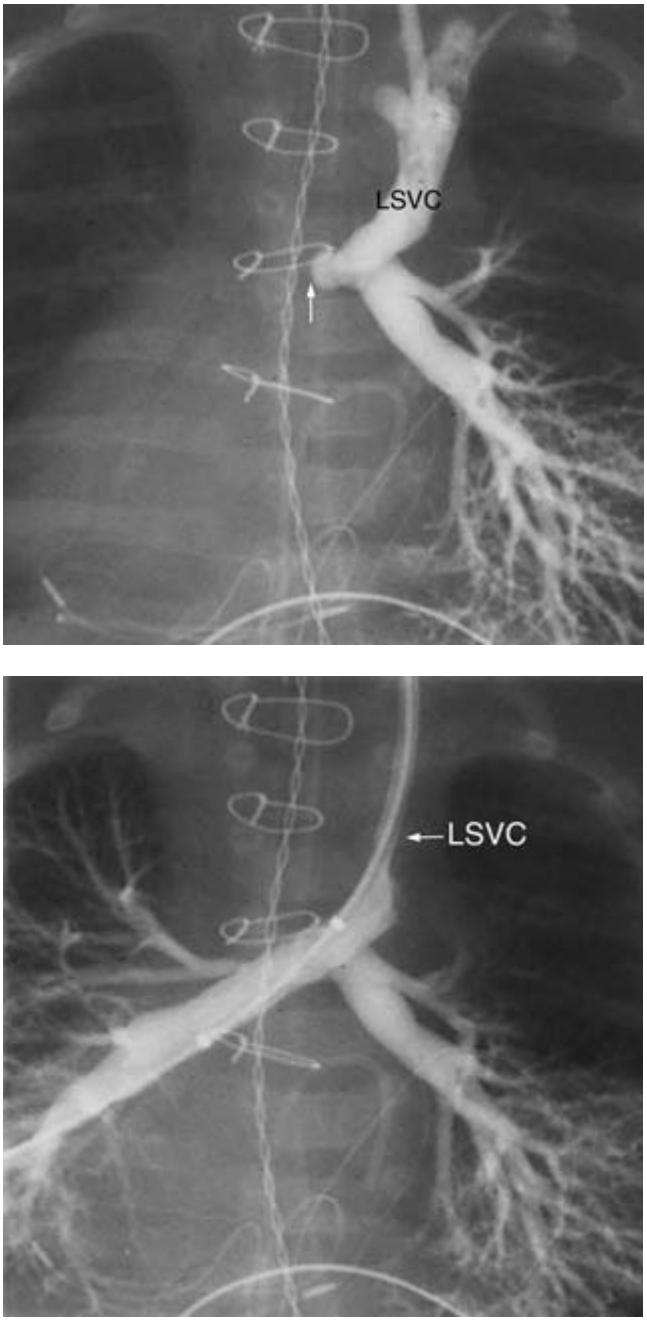


Fig. 35-12 Complete obstruction of the right pulmonary artery after left-side bidirectional cavopulmonary anastomosis in a patient with right isomerism. **A**. Injection into the left superior vena cava (LSVC) shows complete occlusion (arrow) of the functional right pulmonary artery due to thrombus formation within a narrowing segment. **B**. After removal of the thrombus thorough a catheter, the right pulmonary artery was dilated by placing a stent.

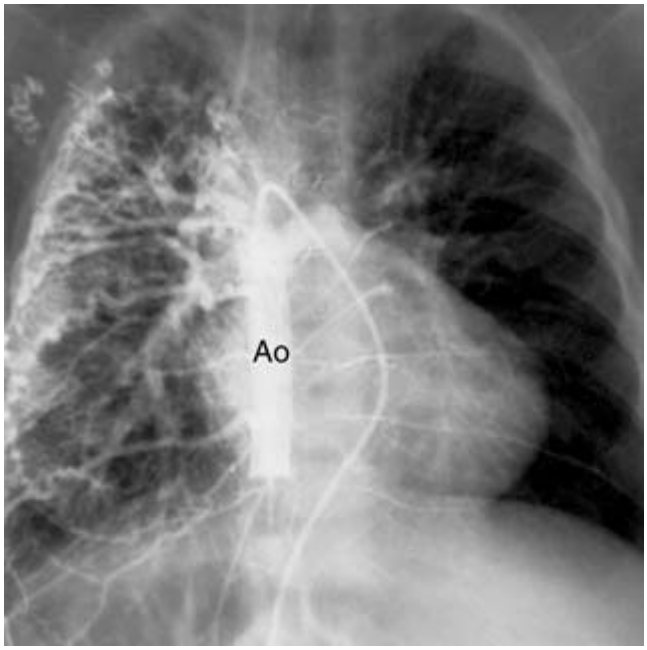


Fig. 35-13 Systemic artery-to-pulmonary arterial collaterals after bidirectional cavopulmonary anastomosis. A myriad of small channels has developed across the pleura and through the existing bronchial arteries. Ao, descending aorta.

with collateral development included a prior right-sided systemic-to-pulmonary arterial shunt; a lower pre-bidirectional cavopulmonary shunt end diastolic ventricular pressure; a lower pulmonary vascular resistance; and the use and duration of cardiopulmonary bypass during the construction of the bidirectional cavopulmonary shunt. The majority of these arterial collateral arteries originate from the subclavian arteries, internal mammary arteries, and/or the thyrocervical trunk. They are best imaged by direct selective injection of contrast into the subclavian and internal mammary arteries. An injection into the descending aorta with distal balloon occlusion is also helpful. Although the clinical significance of these collaterals is unclear, some have suggested that pre-Fontan interruption of the larger collaterals may reduce Fontan mortality and morbidity, especially prolonged effusions.[118–122]

Sinus node dysfunction is a well-known complication of atrial surgery for transposition of the great arteries, and has been documented after the Blalock–Hanlon atrial septectomy, and the Mustard or Senning repair (see Chapter 25A). This dysfunction has been attributed to injury to the sinus node and to its artery. It is not surprising, therefore, to document sinus node dysfunction after a systematically staged Fontan procedure.[123–125] The morbidity and mortality of total cavopulmonary connection (modified Fontan procedure) may be decreased in many patients with single ventricle in whom the risk of surgery is high by performing the operations in a staged fashion.[125] Each operative intervention, however, exposes the sinoatrial node region to risk of injury, and it is likely that a staged approach could increase the risk of altered sinoatrial node function in these patients. Manning and his colleagues have addressed the impact of a stgaed approach to the Fontan on sinus node function.[125] Of 324 patients undergoing a Fontan operation, 227 had a Fontan operation without a prior cavopulmonary shunt (group 1) and 97 had a cavopulmonary shunt before a Fontan operation (group 2). They classified arrhythmias as altered sinoatrial node function, supraventricular tachycardia, or atrioventricular block. The prevalence of both transient (resolving before hospital discharge) and fixed (persisting until hospital discharge) altered sinoatrial node function was similar for the two groups after cavopulmonary shunt or primary Fontan despite a heterogeneous patient population (group 1: 10.6%/4.4%; group 2: 10.3%/3.1%; $P = 0.28$). Conversion from cavopulmonary shunt to Fontan in group 2 resulted in a higher prevalence of altered sinoatrial node function in the early postoperative period (transient: 23.7%; fixed: 23.7%; $P < 0.001$) and on follow-up (group 1: 7.7%; group 2: 16.7%; $P < 0.02$). In group 2, 40 of 82 patients without arrhythmia after first intervention (cavopulmonary shunt) had an arrhythmia after the second intervention (Fontan) (49%); of 14 with an arrhythmia after the first operation, 10 (71%) had one at the second intervention ($P < 0.01$). In conclusion, a multistaged operative pathway to Fontan reconstruction is associated with a higher early risk of altered sinoatrial node function. The occurrence of altered sinoatrial node function after cavopulmonary shunt is itself a risk factor for arrhythmia after the Fontan operation. In this regard, there is little information on the incidence of sinus node dysfunction after the classical Glenn anastomosis. Indeed, sinus node dysfunction was not mentioned by Trusler in his excellent Glenn lecture about the cavo-pulmonary shunt.

The Pediatric Cardiac Care Consortium consisting of nearly 40 participating centers have reported their data on outcome of the cavopulmonary connection. Since 1984 and through 1994, data were obtained on a total of 36 855 operations. Of these, 5447 were performed in neonates; 9566 on infants; 20 260 on children; and 1582 on adults. From 1985 to 1993, 567 Glenn shunts, bidirectional cavopulmonary shunts and hemi-Fontans were performed in patients aged between 29 days and 32 years (median 2.0 years) and with a median weight of 10.2 kg. These operations represented 2% of all the operations carried out by the consortium over this time interval. The principal diagnoses were single ventricle in 29%, tricuspid atresia in 23%; hypoplastic left heart syndrome in 9%; pulmonary atresia and intact ventricular septum 8%; mitral atresia in 6%; and complex pulmonary stenosis or atresia in 6%. The overall mortality for this experience was 8.8%, with the mortality slightly higher in infants at 11.3% compared to children 7.8% and adults 8.3%. Mortality was higher in the neonates and in those with a somewhat lower body weight. Mortality was lower for those with tricuspid atresia or mitral atresia when compared to those with the hypoplastic left heart syndrome. Interestingly, in the consortium data, heterotaxia had no statistically significant influence on mortality. The study consisted of 91 patients with heterotaxia with a mortality of 12.1% and 475 patients without heterotaxia with a mortality of 8.2%. The length of stay was analyzed in the 517 survivors. The median length of stay was 10 days, ranging from 3 to 220 days. The age at operation influenced the length of stay, being longer in the very young infant and this was true for those with the lowest body weight. The diagnosis also correlated with the length of stay, with hospitalization of patients with Ebstein's anomaly of the tricuspid valve (mean 23.5 days). Mitral atresia (mean 21 days), and hypoplastic left heart syndrome (mean 19.2 days) were longer compared to the shorter stay for patients with tricuspid atresia (mean 13.2 days), complex pulmonary stenosis (mean 10.4 days), complex pulmonary atresia (mean 10.2 days), and pulmonary atresia and intact ventricular septum (mean 12.2 days).

The bidirectional cavopulmonary connection as definitive palliation

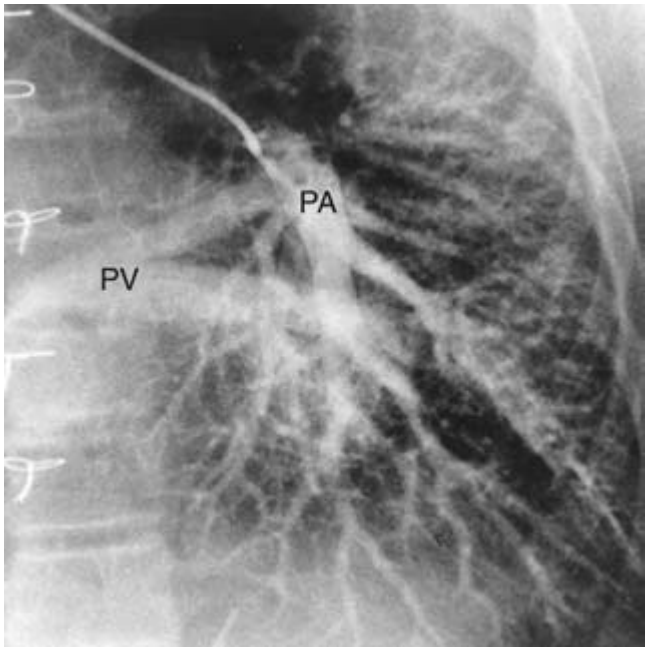
Some cardiologists have suggested that the bidirectional cavopulmonary shunt could be definitive palliation, the inference being that this operation will provide excellent long-term palliation without subjecting the patient to the risk of the Fontan.[107,126] This acknowledges as well the reality that there is no such outcome as the "perfect" Fontan.[127] We have provided data to suggest that survival following the cavopulmonary shunt is equivalent, with or without the Fontan.[13] In our institution from 1962 to 1997, 490 patients had a cavopulmonary shunt, excluding those who had a cavopulmonary shunt concomitant with a Fontan. We excluded an additional 55 patients in whom the cavopulmonary shunt was performed at or after a biventricular repair or after a Fontan. This left 435 patients in the analysis. The long-term survival 20 years after a cavopulmonary shunt is 56 ± 5% for the entire cohort of 435 patients. Survival from birth for 407 patients with a cavopulmonary shunt was 82% at 10 years, 65% at 20 years, 54% at 30 years, and 32% at 40 years. Survival at 20 years among the 220 patients who were subsequently converted to a Fontan circulation is 65 ± 8% compared to 50 ± 11% for the 187 patients who did not have a Fontan. Most of the apparent survival difference is because all early deaths after a cavopulmonary shunt occurred in the non-Fontan group. Multivariable analysis demonstrated that proceeding to a Fontan did have a small survival advantage which was not evident by univariate analysis. We also found that independent risk factors for death at any time were previous pulmonary artery banding or a common atrioventricular valve. The era of operation had no effect on survival. The mortality of 216 patients managed before 1992 is 6.0% and for the 219 patients after 1992, 8.3%. The late mortality after a cavopulmonary shunt was 23 of 179 patients (12.8%) in the era before 1992 and 9 of 196 patients (4.6%) in the recent era. Thus our data showed only a slight advantage in converting patients to a Fontan after a cavopulmonary shunt. And, in our hands, a marked reduction in the age of the cavopulmonary shunt and at Fontan has as yet not improved survival. How does one use these observations? Firstly, survival is but one aspect of any outcome analysis, and our data do not address functional outcome. Williams in discussion of this paper stated that in the patient with a stable cavopulmonary shunt, whom you consider at high risk for a Fontan, these data provide reason for not proceeding to a Fontan. Finally, the bidirectional cavopulmonary shunt has been used as an adjunct to biventricular repair.[128–134] The criteria for the performance of this combination of operations, namely biventricular repair and bidirectional cavopulmonary shunt, are unclear. Hanley in a recent editorial raises the question as to whether this approach confers any more benefit to the patient than the Fontan.[134] Other maneuvers have been introduced into the staging sequence such as the bidirectional inferior vena cava–pulmonary artery shunt.[135] We have had no experience with this operation, but certainly it would raise the hepatic venous pressure. We have used the bidirectional cavopulmonary shunt to palliate the infant with a large fibroma obstructing both the right ventricular inlet and outlet.[136]

Ventricular unloading: the downside

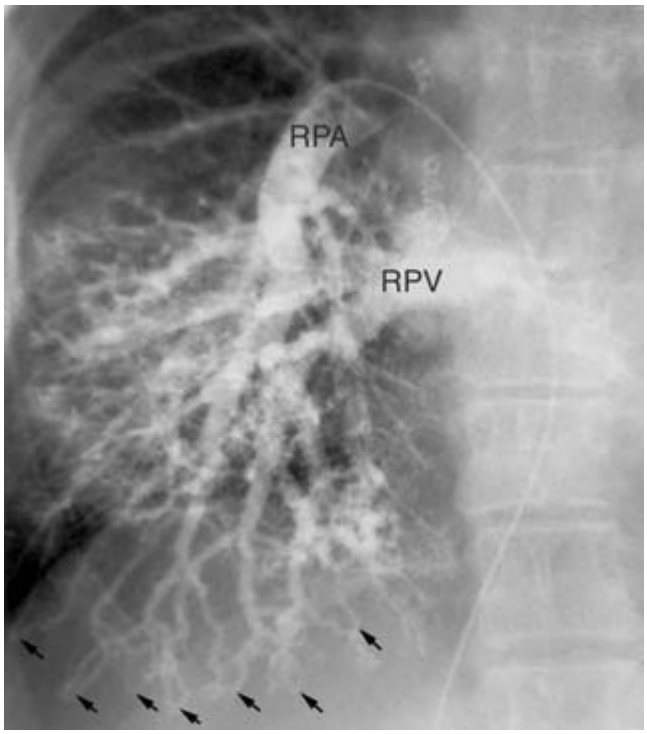
There is ample evidence that the bidirectional cavopulmonary shunt is advantageous in terms of palliation for the functionally univentricular heart.[67,96,99,101] It eliminates the inefficiency of pulmonary recirculation, and by reducing the volume load of the ventricle, this maneuver facilitates advantageous ventricular remodeling.[50] Important atrioventricular valve regurgitation may be improved after the construction of a bidirectional cavopulmonary shunt as shown by Mahle and others.[77,86] It may reduce early mortality and Fontan failure and this operation has been loudly praised in this regard.[67,96,99,101] However, we have already discussed the concern that the bidirectional cavopulmonary shunt may prevent the normal growth of the pulmonary arteries, especially that of the contralateral lung. There is also information that we have summarized indicating that staging to the Fontan may promote sinus node dysfunction (see also Chapter 37). An unusual complication subsequent to the bidirectional cavopulmonary shunt has been reported by Imanaka and colleagues.[137] Two patients both with pulmonary atresia, intact ventricular septum and major right ventricular coronary artery communication developed thrombosis in the right ventricle early after bidirectional superior cavopulmonary shunt.[137] They speculate that in this particular situation anticoagulation may prevent this complication.[137] In another situation as well, ventricular unloading and ventricular remodeling may be disadvantageous. Ventricular unloading is one factor contributing to systemic ventricular outflow tract obstruction in those hearts predisposed to this complication.[138–144] This complication and its management will be discussed in detail in Chapters 32 and 36. In the absence of competitive pulmonary blood flow, is the bidirectional cavopulmonary shunt causal to the development of pulmonary arteriovenous malformations?

The development of pulmonary arteriovenous fistulae

One of the fascinating chapters in the Quixotic quest to palliate the patient with a functionally single ventricle is the development of pulmonary arteriovenous malformations. This development provides a wonderful paradigm for bed-to-bench research.[145] Young infants and children are known to have primordial arteriovenous connections in their lungs which may reopen acutely leading to the development of clinically significant intrapulmonary right-to-left shunting.[145A] Yet, there is no simple etiology for the development of pulmonary arteriovenous malformations after cavopulmonary shunt surgery, or after the Fontan. Pulmonary arteriovenous malformations are intrinsic to the Weber–Osler–Rendu syndrome and have been seen in other patients with a structurally normal heart and without any internal stigmata of the Weber–Osler–Rendu syndrome.[42,146–152] First likely observed by Mathur and Glenn in 1973 in their long-term evaluation the classic cavopulmonary artery anastomosis,[21] the development of pulmonary arteriovenous malformations after the classic Glenn anastomosis was next fully documented by McFaul and his colleagues in 1977 (Fig. 35-14).[38] Citing the observations of Samanek and his colleagues who documented maldistribution of flow after the Glenn anastomosis to the right lower lobe using radioisotope imaging,[146] McFaul and his colleagues wondered whether absence of pulsatile flow contributed to their development,[38] a suggestion also proposed some years later by Cloutier and his colleagues.[41] Boruchow and his colleagues also noted these changes at angiography, but attributed the reduced flow to the right upper lobe to hypoxemia and secondary pulmonary vasoconstriction.[35] Yet the majority of patients after the Fontan procedure do not demonstrate symptomatic pulmonary arterio-



A



B

Fig. 35-14 Pulmonary arteriovenous malformation after bidirectional cavopulmonary anastomosis. **A**. Injection into the descending branch of the left pulmonary artery (PA) shows very early and dense opacification of the left pulmonary vein (PV). **B**. Injection into the right pulmonary artery (RPA) in a different patient after modified Fontan operation shows persistence of pulmonary arteriovenous malformation. Notice direct anastomosing channels (arrows) in the periphery of the lung. The pulmonary vein (RPV) shows early filling.

venous malformations, and thus absence of pulsatile flow to the lungs cannot be the only factor responsible for their genesis. There is an extensive literature addressing the frequency and possible etiologies of pulmonary arteriovenous fistulae which have been observed after the construction of a classical Glenn anastomosis, following total cavo-pulmonary bypass as part of the Kawashima operation; following the Fontan operation; and they have been recognized in patients with the polysplenia syndrome.[1,5,16,17,19–22,38–42,48–51,153–167] In 1 patient, with polysplenia, the cardiac malformations included dextrocardia, bilateral left atrial appendages, intact atrial and ventricular septa, interruption of the inferior vena cava, and connection of all the hepatic veins to the left-sided atrium.[165] One would wonder whether the hepatic veins were isolated from the pulmonary arterial bed, a suggestion from Srivastava and his colleagues as to the etiology of the development of pulmonary arteriovenous fistulae.[51] This patient also had hypoplasia of the portal vein, perhaps reminiscent of the hepatic–cirrhotic role in the genesis of pulmonary arteriovenous fistulae.[168–176] Many other patients with polysplenia/left isomerism have now been found to have pulmonary arteriovenous malformations, but in at least one patient the hepatic venous connections were shown to be normal.[166] It is of interest, however, that reversal of cirrhosis-related pulmonary shunting has been achieved in children by orthotopic liver transplantation,[168–176] lending credibility to the hepatic factor theory. Fewtrell and colleagues have fully analyzed intrapulmonary shunting in the biliary atresia/polysplenia syndrome and have demonstrated reversal after liver transplantation.[172] Summarizing their data, 173 children, including 93 with biliary atresia, received liver grafts at Addenbrooke's Hospital between 1983 and 1993. Of these, only 7 developed cyanosis owing to intrapulmonary shunting as a complication of their liver disease, and all 7 of these had the biliary atresia/polysplenia syndrome. Intrapulmonary shunting was confirmed by a radioisotope scan in 4 children. Only one child with the syndrome did not have cyanosis when undergoing transplantation. Seven of the 8 children are alive 6–54 months after transplantation, with normal pulmonary and hepatic function. Cyanosis recurred in 1 child who developed chronic rejection with liver failure. They concluded that: (1) there is a strong association between the biliary atresia/polysplenia syndrome and cyanosis due to intrapulmonary shunting; (2) intrapulmonary shunting is fully reversible after successful liver transplantation; (3) cyanosis, once present, is progressive, and these children should be considered for liver transplantation as soon as it occurs. Knight and Mee and then others have demonstrated reversal of acquired pulmonary arteriovenous fistulae which developed soon after a classic Kawashima procedure (see Chapter 36).[155–158,177–179] They diverted hepatic venous blood to the pulmonary arteries with a left lateral atrial tunnel. Laks and his colleagues have provided a modification of Fontan's procedure where the superior vena cava is connected to the left pulmonary artery and the lateral tunnel and thus the inferior caval vein and hepatic veins are diverted to the right pulmonary artery.[180] They caution that lack of hepatic venous flow to the left lung might contribute to unilateral pulmonary arteriovenous malformations, and this is exactly what we have observed in 1 patient who has undergone this operation. Lee and his colleagues have reported a child who, at the age of 6 years, became cyanotic, indeed progressively so over the next 3 years.[181] He was found to have an interrupted inferior caval vein with an azygos continuation. Both atrial and ventricular septa were intact, but all his hepatic veins drained into the pulmonary venous atrium.[181] Because pulmonary arteriovenous malformations were not clearly demonstrated by angiography, he underwent a bubble echocardiographic study which was confirmatory of pulmonary arteriovenous malformations.[182] The abnormal hepatic

venous connections were confirmed at surgery where they also documented that the coronary sinus drained as well into the pulmonary venous atrium. Surgical repair involved the diversion of the hepatic flow to the systemic venous atrium.[181] His preoperative oxygen saturation was 76%, and 3 weeks postoperatively, his oxygen saturation measured 95% and at 5 months 100%. At this time a bubble echocardiographic study was normal, confirming resolution of the pulmonary arteriovenous malformations. Thus this child did have forward pulsatile flow, but complete hepatic venous exclusion.[181] Similar resolution of pulmonary arteriovenous malformations has been reported in a patient who underwent repair of total anomalous systemic venous return[181A] and after other procedures to redirect hepatic venous flow to the lungs.[182D]

But the issue of exclusion of hepatic venous blood as causal to the development of pulmonary arteriovenous malformations is not "an all or none phenomenon." Unequal distribution of hepatic venous flow has been attributed to the causality of pulmonary arteriovenous malformations[162,163] and Uemura and colleagues and our group have redirected hepatic venous flow to remedy this complication.[162,163] Usually the development of pulmonary arteriovenous malformations following cavopulmonary surgery is one of progressive and inexorable deterioration. Less commonly their development can be rapid and severe.[179,183,184] The occurrence of symptomatic pulmonary arteriovenous malformations after a Fontan procedure is very uncommon if hepatic venous blood is conveyed to the lungs. Moore and his colleagues did report the development of pulmonary arteriovenous malformations after modified Fontan procedures in 2 patients.[161] However when one carefully reviews their case reports, it is apparent that the first patient had left isomerism with azygos continuation of the interrupted inferior vena cava, a univentricular heart of right ventricular type with a common atrioventricular orifice, single atrium, bilateral pulmonary arterial stenoses, and anomalous pulmonary venous connections. Following palliation with a left Blalock–Taussig shunt, she underwent a modified Fontan procedure at 5 years of age where the hepatic veins were diverted into the left pulmonary artery via a Gore-Tex vascular graft.[161] By 8 years of age, she had once again become cyanotic and she underwent a cardiac catheterization at 10 years of age which showed unilateral right-sided pulmonary arteriovenous malformations on selective right pulmonary artery angiography, a finding confirmed by saline contrast echocardiography. The left pulmonary artery was normal. The second patient of this report also had left isomerism with azygos continuation of the interrupted inferior vena cava to a left-sided superior caval vein and complex congenital heart disease.[161] He required pulmonary artery banding at 1 month of age and underwent a modified Fontan procedure at 7 months of age, but postoperatively the hepatic veins continued to drain into the atrium as in the classical Kawashima operation.[48–50] Postoperatively the cyanosis initially improved, but by 14 months of age, the cyanosis had worsened. A cardiac catheterization performed at 22 months of age demonstrated that the hepatic veins were the only source of an intracardiac right-to-left shunt. Pulmonary angiography demonstrated dilatation of those branch arteries supplying the middle and lower lobes of both lungs with early return of contrast material to the pulmonary veins. Again, saline contrast echocardiography with injection into the main pulmonary artery resulted in dense opacification of the pulmonary venous atrium.[161] Thus in both patients either partial (patient 1) or complete hepatic venous exclusion (patient 2) were likely responsible at least in part for the development of the pulmonary arteriovenous malformations.[48–51]

The exact prevalence of pulmonary arteriovenous malformations has been difficult to determine as their recognition depends on the methodology used to determine their presence. Bernstein and coworkers using contrast echocardiography found an incidence of pulmonary arteriovenous malformations to be 60%, and this complication was found to be higher in patients < 6 months of age and in those with heterotaxia.[185] Mahle and his colleagues using angiographic findings found that only 10 patients of 372 had pulmonary arteriovenous malformations (3%). The angiographic criteria included dilated distal pulmonary arteries, a classic reticular pattern in the late arterial phase, and rapid arterial-to-venous transit time as evidenced by simultaneous opacification of larger pulmonary arteries and veins.[51] We suspect that 3% is too low, and that positive angiographic findings would be a rather late finding.[42] This is exactly what was found by Chang and coworkers.[182] They compared bubble contrast echocardiography and pulmonary angiography in detecting pulmonary arteriovenous malformations. They found that 71% of patients studied with bubble contrast echocardiography had positive studies indicating the presence of pulmonary arteriovenous malformations compared with 21% detected by angiography.[182] All of their patients with complete hepatic venous exclusion had positive bubble contrast studies, while only 15.9% of those whose pulmonary circulations received hepatic venous were positive.[182] Others have also suggested the utility of contrast echocardiography in the detection of pulmonary arteriovenous malformations.[182A-C] Most of these studies support the increased sensitivity of contrast echocardiography as compared to angiography.

The numerous investigations cited in the last few paragraphs indicate that the etiologies of pulmonary arteriovenous malformations are complex and are not necessarily nor invariably related to lack of pulsatile flow nor to some hepatic factor. Kurotobi and colleagues have shown that patients after bidirectional cavopulmonary shunt show pulmonary endothelial functional attenuation and, of more importance, that decreased pulsatility of cavopulmonary flow is mainly responsible for this endothelial abnormality.[82] Technicium-labelled albumen microspheres have been used to detect intrapulmonary right-to-left shunting, and by inference pulmonary arteriovenous malformations.[186] All the patients studied with technicium-labelled albumen microspheres by Vettukattil and colleagues who had undergone a bidirectional superior cavopulmonary anastomosis were shown to have intrapulmonary right-to-left shunting.[186] This finding was also confirmed in those patients with a bidirectional superior cavopulmonary anastomosis who had as well competitive pulmonary blood flow. However, when quantified, those with competitive pulmonary blood flow had less intrapulmonary right-to-left shunting than those without competitive flow.[186] Kim and coworkers have confirmed these findings, showing that most patients with a bidirectional cavopulmonary connection as well as those with a total cavopulmonary shunt have subclinical evidence of right-to-left intrapulmonary shunting.[164]

It has been suggested for some years that angiogenesis may be responsible in part for the development of pulmonary arteriovenous malformations,[51,187] and perhaps the liver is responsible for the formation of an inhibitor of angiogenesis. What are the histologic correlates to the clinical findings of pulmonary

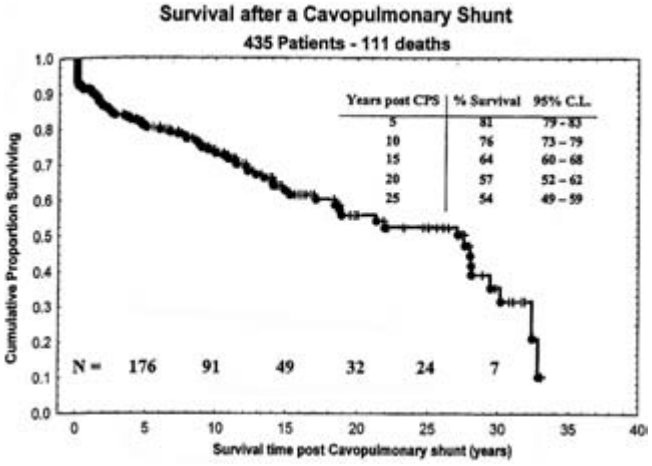


Fig. 35-15 Data from the Toronto Hospital for Sick Children. Kaplan–Meier curve showing survival after a cavopulmonary shunt in 435 patients with 111 deaths, 31 early and 80 late. Survival and 95% confidence limits for the selected time periods are shown in the table. N, number of patients entering each time period. (Reprinted from Yeh *et al.*,[13] Copyright (1999), with permission from Elsevier.)

arteriovenous malformations? It has been shown that in the areas of pulmonary arteriovenous malformations, the lung pathology is characterized by large dilated blood vessels or lakes and clustered smaller vessels or chains.[188] In addition, electron microscopy demonstrated in these vessels discontinuity of the basement membrane and endothelium.[188] Microvessel density has been shown to be a marker of angiogenesis.[189] Starnes and her colleagues have shown an increase in pulmonary microvessel density after cavopulmonary anastomosis, even in the absence of clinically apparent or symptomatic pulmonary arteriovenous malformations.[189] This observation supports the presence of a constant angiogenesis stimulus.[189] Furthermore, children with clinically apparent pulmonary arteriovenous malformations demonstrate large numbers of greatly dilated pulmonary microvessels, a finding absent in asymptomatic children after cavopulmonary bypass. The corollary to this observation is that it is likely and reasonable that the transition to clinically apparent pulmonary arteriovenous malformations may be due to influences that lead to vessel dilatation and remodeling.[187–189] Despite the presence of increased pulmonary microvessel density which suggests active tissue angiogenesis, immunohistochemical studies did not demonstrate greatly increased endothelial proliferation.[188,189] In a lamb model operated on to create an end-to-end superior vena cava-to-right pulmonary artery anastomosis, contrast echocardiography detected pulmonary arteriovenous shunting in all lambs evaluated 56 days or later.[190] Malhotra and coworkers showed using this model that superior cavopulmonary anastomosis results in an early but reversible reduction in activity and expression of angiotensin-converting enzyme, thus causing a decreased circulating level of the vasoconstrictor angiotensin II.[190] They went on to suggest that these results indicate that the ability of the pulmonary endothelium to regulate vascular tone is inhibited by the superior cavopulmonary anastomosis.[190] Starnes and her colleagues have also studied whether angiogenic proteins are increased in the lungs of children after cavopulmonary anastomosis.[191] They found that after cavopulmonary anastomosis patients demonstrated increased staining for vascular endothelial growth and its receptor and decreased staining for CD31. These findings are consistent with an increased angiogenic state, but interestingly, despite increased microvessel density, these vessels did not appear to be highly proliferative using PCNA staining.[191] The clinical observations involving the role of the liver support the hypothesis that normal vascular tone is maintained by a fine balance between stimulatory and inhibitory influences.[186,188,192,193] Vettukattil and colleagues believe that the factor(s) associated with the inhibitory effect on vasodilation are supplied in part by the liver, and that this hepatic factor is largely or completely removed by the systemic circulation in its first pass, resulting in its insignificant concentration in the superior venal caval blood.[186] They go on to suggest that unopposed precapillary and capillary vasodilation would follow in those parts of the lung perfused by blood without the hepatic factor (or without adequate amounts of hepatic factor). In view of these findings it would be interesting to create an animal model of an inferior vena caval-to-pulmonary artery bidirectional or unidirectional anastomosis and to study both the histopathology of the lung as well as using the specific immunohistochemical staining techniques to define the presence of angiogenic proteins, etc. In this regard, it would be interesting to know if patients palliated with a bidirectional inferior vena cava–pulmonary artery shunt developed pulmonary arteriovenous malformations.[135] Competitive pulmonary blood flow has been shown in some studies to reduce the severity of pulmonary arteriovenous malformations,[74,164,186] perhaps by conveying some of this hepatic factor to the pulmonary arteries, or from the pulsatility of the blood flow, or some combination thereof. Starnes and his colleagues showed that vascular endothelial growth factor and basic fibroblast growth factor were both increased in children with cyanotic congenital heart disease, possibly suggesting that the widespread formation of collateral vessels is mediated by these growth factors.[194] Malhotra and colleagues developed an ovine model that demonstrated the cavopulmonary anastomosis induced pulmonary expression of the angiotensin II receptor family, reliably inducing the development of pulmonary arteriovenous malformations eight weeks after a cavopulmonary connection.[194A] Finally,

Fig. 35-16 Kaplan–Meier curve showing survival from birth of 407 patients with a cavopulmonary shunt. Twenty-eight patients who had a later biventricular repair are excluded. (Reprinted from Yeh *et al.*,[13] Copyright (1999), with permission from Elsevier.)

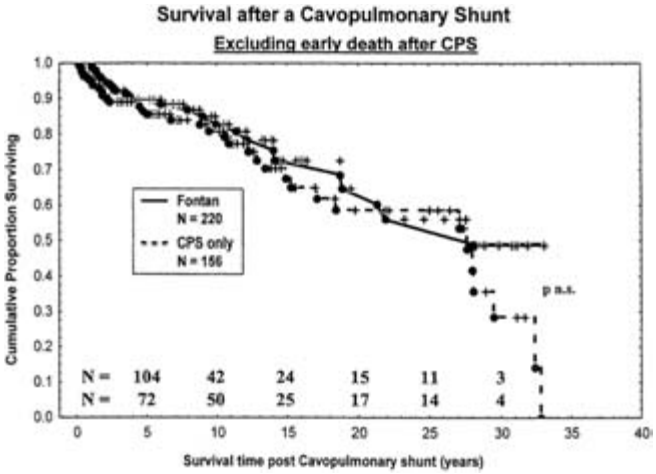


Fig. 35-17 Kaplan–Meier curves showing survival after a cavopulmonary shunt comparing 220 patients who went on to a subsequent Fontan with 187 who had no further definitive surgery. There is no significant difference in survival. (Reprinted from Yeh *et al.*,[13] Copyright (1999), with permission from Elsevier.)

Ashrafian and Swan in a scientific letter suggest that members of the transforming growth factor ß polypeptide superfamily or more precisely their antagonists may have an important role in the pathogenesis of pulmonary arteriovenous malformations after a superior cavopulmonary anastomosis similar to their role in the pathogenesis of pulmonary arteriovenous malformations in patients with hereditary hemorrhagic telangiectasia.[194B] In the conclusion of this letter, they ask the fundamental and provocative question: "why is the pulmonary circulation somatically modulated by the hepatopulmonary axis?"[194A]

The terms bidirectional cavopulmonary shunt and hemi-Fontan have been used interchangeably.[59,98,195] But there are differences as pointed out by Douville and colleagues.[84] After this procedure the physiology is that of a bidirectional cavopulmonary shunt, but all aortopulmonary shunts and ventriculopulmonary connections have been interrupted. This unloads the ventricle of all pulmonary work and any other potential Fontan risk factors have been corrected.[84] Most of the discussion thus far has focused on systemic venous and arterial collateralization, growth (or lack of) of the pulmonary arteries, the effect of competitive pulmonary blood flow and the development of pulmonary arteriovenous malformations. We should remember that protein-losing enteropathy and intestinal lymphangiectasia have developed after the classical Glenn anastomosis as has late-onset superior vena caval syndrome.[36,37] One of the dreaded complications of the Fontan procedure is the formation of acellular bronchial casts, the syndrome of plastic bronchitis.[196–203] This has been seen after the bidirectional cavopulmonary shunt as well. We have been reminded that persistence of the hepatic venous plexus with underdevelopment of the infrahepatic inferior vena cava[204,205] may exaggerate hypoxemia after the Kawashima operation.[48–50] We have learned much thus far about the bidirectional Glenn or hemi-Fontan (Figs 35-15 to 35-17), but the scientific derivatives of this clinical experience continue to challenge us as we evolve from the Glenn to the Fontan.[206]

In summary, there is now a 50-year history of the cavopulmonary shunt.

- The development of the cavopulmonary shunt is truly international in scope.
- The classical Glenn shunt provided excellent long-term palliation.
- This operation has the potential to lead to isolation of the contralateral pulmonary artery.
- Late failure of the classic cavopulmonary shunt can be attributed to several reasons, but the most egregious is the development of pulmonary arteriovenous fistulae.
- The bidirectional cavopulmonary shunt has been used for > 20 years usually as a staging maneuver to the Fontan.
- There is still discussion as to the merits of forward pulmonary blood flow in this situation.
- Systemic venous collateralization is frequent after the construction of a bidirectional cavopulmonary shunt. This may worsen hypoxemia by reducing the effective pulmonary blood flow and by connections to the pulmonary vein or left atrium.
- There are concerns about the growth of the pulmonary arteries after the bidirectional cavopulmonary shunt.
- When hepatic venous blood is excluded from the pulmonary circulation, pulmonary arteriovenous fistulae are a likely consequence.
- Pulmonary arteriovenous fistulae may be a universal consequence of the bidirectional cavopulmonary shunt.
- The development of pulmonary arteriovenous fistulae and the relationship to hepatic venous blood is a paradigm for bed-to-bench research.
- The cavopulmonary shunt increases effective pulmonary blood flow without volume-loading the ventricle.
- Ventricular volume unloading has the potential to improve the severity of atrioventricular valve regurgitation.
- Ventricular volume unloading may lead to a change in ventricular size and geometry in patients with a dominant left ventricle, rudimentary right ventricle and transposition of the great arteries, resulting in systemic outflow tract obstruction.[139,140,207,208]

All references can be found at the end of the book. See pp. 797–803 for Chapter 35.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

36

Robert M. Freedom, Shi-Joon Yoo, and W.G. Williams

The Fontan–Kreutzer Procedure

It seems a natural evolution from the partial right heart bypass, the classical Glenn or cavopulmonary shunt (see Chapter 35), to the complete right heart bypass as conceived and performed by Fontan of Bordeaux in 1968, and published with Baudet in 1971 (Fig. 36-1).[1,1A] Kreutzer of Buenos Aires almost simultaneously devised a similar procedure for the patient with tricuspid atresia.[2] Most involved with the care of children with congenital heart disease consider these contributions as one of the signal achievements in the last half of the 20th century for patients whose cardiac malformations are not amenable to biventricular repair.[3] Since this procedure was first performed in 1968 on the patient with tricuspid atresia, the procedure or any of its many modifications have been applied to a wide variety of congenitally malformed hearts not amenable to biventricular repair.[4] Indeed, some have used this procedure preferentially over a high-risk biventricular repair.[5] Throughout the early to late 1970s and well into the 1980s there was an exponential increase in publications devoted to virtually all aspects of the Fontan procedure, in the more recent era addressing surgical modifications and outcomes. In order to provide selection guidelines for the performance of the Fontan procedure, Choussat and his colleagues provided in 1978 a number of criteria for those considering this operation.[6] These criteria have been scrutinized and modified over the years in order to optimize outcome by reducing early and late Fontan mortality and morbidity. As one surveys the substantial literature that has addressed outcomes of the Fontan procedure over the past three decades, early mortality has continued to decrease and Kaplan–Meier survival curves suggest improved survival. It is difficult to define any single strategy that has enhanced outcome as the entire "platform" for congenital heart surgery has improved over this time frame. Furthermore, other maneuvers have been introduced including staging with a bidirectional cavopulmonary shunt and fenestration, in order to reduce mortality in so-called high-risk patients. In this chapter, we will review the original criteria as proposed by Choussat and colleagues and comment on those other innovative strategies. The Kawashima operation used in patients with complex congenital heart disease with interrupted inferior vena cava and its sequelae are discussed in Chapter 35. The original criteria proposed by Choussat are listed in Table 36-1.

In consideration of these original criteria as set out by Choussat and his colleagues, Graham and Johns pointed out that the following issues or criteria were not included or considered in the 1978 publication:[7]

- diastolic dysfunction
- ventricular hypertrophy
- systemic outflow tract obstruction
- right ventricular type of single ventricle.

One risk factor not addressed either by Choussat and his colleagues, or by Graham and Johns was the issue of extensive systemic aortopulmonary collateral arteries derived from the descending thoracic aorta, or subclavian artery or its tributaries, or both.[8–12A] Another new indicator that has been proposed is the diameter of the pulmonary veins in patients with univentricular hearts.[13]

Age 4–15 years

There is not unanimity as to the optimum age to perform the Fontan operation.[4,14–24] Certainly the operation can be carried out in children as young as two years of age or younger and in adults as well with excellent results. When the operation was performed in patients < 2 years of age, many times these particular patients were already considered at some risk for later exclusion from the Fontan. When patients at this age met the critieria for a Fontan procedure, the outcome was similar. Thus younger age in itself does not seemingly jeopardize the outcome for the Fontan procedure. Excellent results have been published for the older patient undergoing Fontan's operation as well.[20,21,23]

Normal right atrial size

In the early days of the Fontan experience, a large, thin-walled right atrium was considered a potential risk factor (Fig. 36-2).[6] It was felt that whatever "pump" function the right atrium contributed to Fontan hemodynamics would be lost in the original atriopulmonary connection. Whether this was true or not, the concern about right atrial form and function has been obviated by the evolution in surgical technique (Table 36-2) (Figs 36–1 to 36-5).

The contribution of de Leval and his colleagues with the total cavopulmonary connection is important to the history and indeed success of the Fontan strategy.[25] As stated in this paper published in 1988, the total cavopulmonary connection has the following advantages: they are technically simple and reproducible in any atrioventricular arrangement; the surgical connections are relatively distant from the atrioventricular node; most of the right atrium remains at low pressure reducing the risk for early and late rhythm disturbances; and reduction of turbulence in the enlarged right atrium prevents energy losses and hopefully should minimize the risk of atrial thrombosis. This

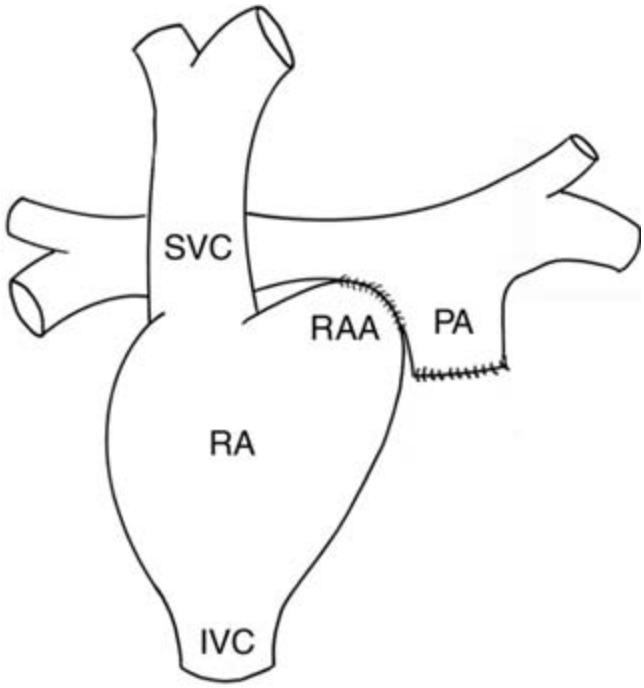


Fig. 36-1 Classical Fontan operation. The right atrial appendage (RAA) is anastomosed to the confluent part of the pulmonary artery (PA). The main pulmonary artery is divided and the proximal end oversewn. IVC, inferior vena cava; RA, right atrium; SVC, superior vena cava.

lateral tunnel form of total cavopulmonary bypass set the stage for extracardiac Fontan.

Normal sinus rhythm

Numerous studies have demonstrated excellent early survival in patients not in sinus rhythm undergoing the Fontan procedure.[4,15–19,23,26] There has been the suggestion that patients with complete heart block before the Fontan despite pacing do not fare as well, but that has not been our experience (acknowledging only a small patient population with heart block undergoing a Fontan operation).[23] Clinical experience does suggest that patients who are not in sinus rhythm before the Fontan operation are more likely to experience supraventricular dysrhythmias, both early and late, after the procedure.[26–35]

Table 36-1 Criteria for Fontan's operation

Age 4–15 years
Sinus rhythm
Normal drainage of caval veins
Normal volume of right atrium
Normal pressure ≤ 15 mmHg
Pulmonary resistance < 4 U/m^2
Ratio PA : AO ≥ 0.75
Normal ventricular function
No mitral insufficiency
No impairing effect of shunt

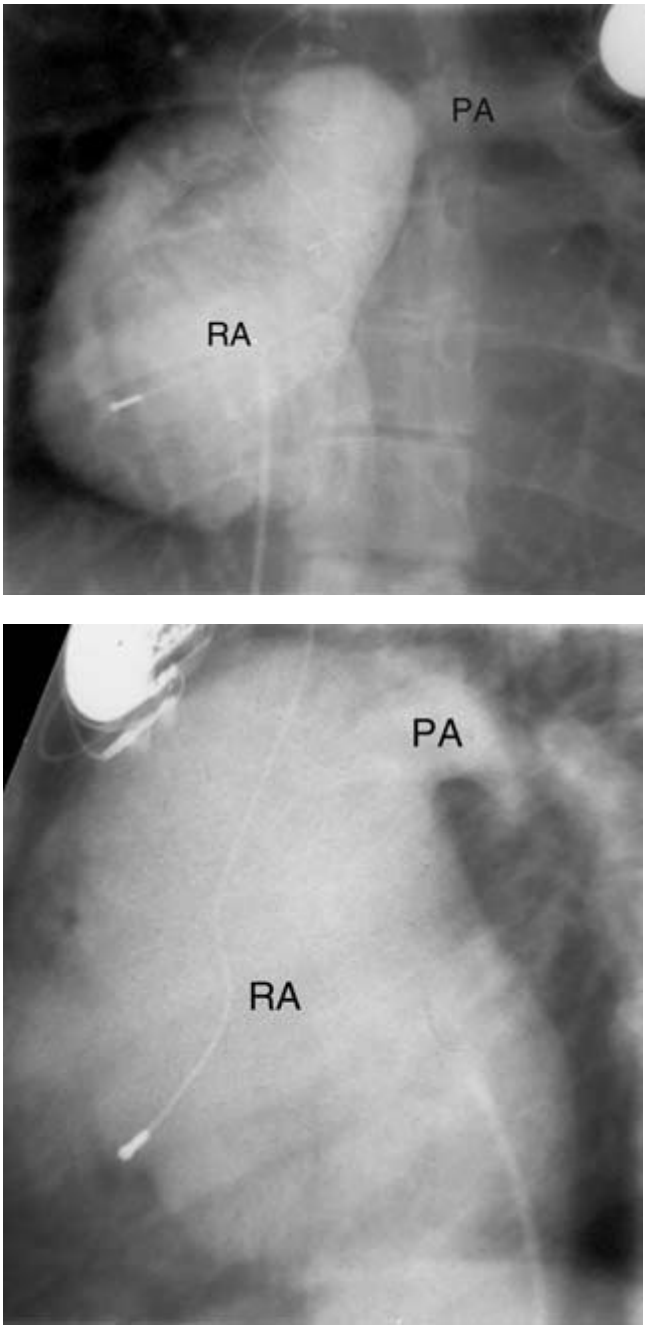


Fig. 36-2 Severe dilatation of the right atrium (RA) after classical Fontan operation. PA, pulmonary artery.

Table 36-2 Evolution in surgical techniques after the original Fontan procedure*

Procedure	Reference
Fontan	Fontan and Baudet[1]
Kreutzer	Kreutzer *et al.*[2]
Bjork	Bjork *et al.*[4A]
Total cavopulmonary bypass	de Leval *et al.*[25]
Fenestrated Fontan	Bridges *et al.*[51]
Extracardiac Fontan	Giannico *et al.*[4B]

*Not necessarily listed by primacy of report.

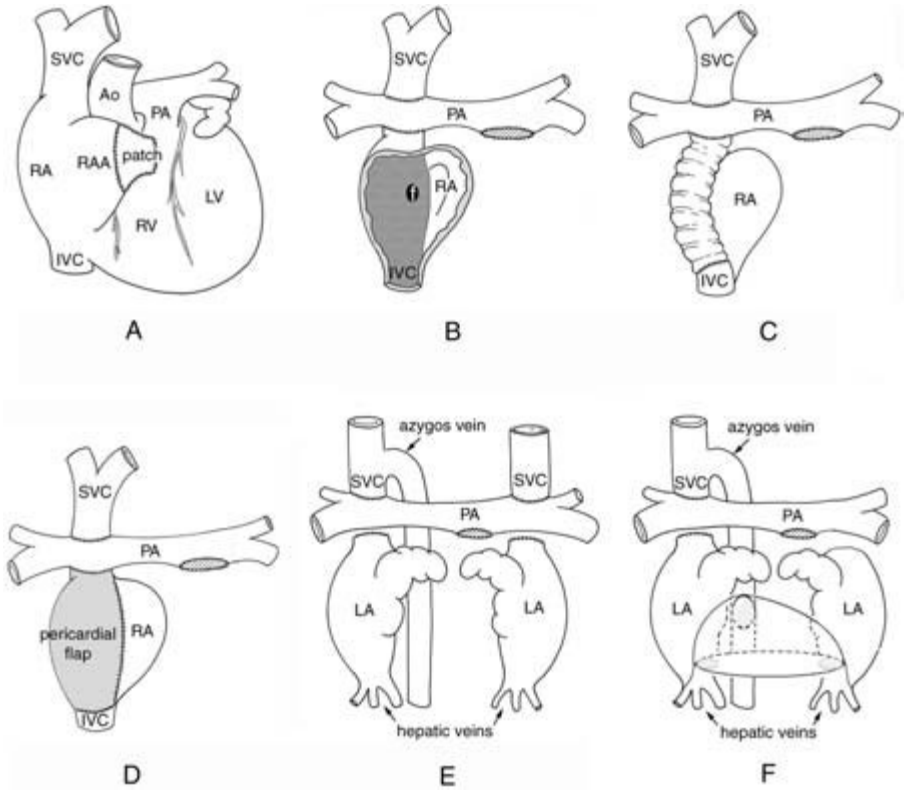


Fig. 36-3 Modifications of Fontan operation. **A**. Bjork's modification: for patients with a small but functioning right ventricle as in tricuspid atresia, a connection is made between the right atrial appendage (RAA) and the right ventricular outflow tract. **B**. Total cavopulmonary connection(TCPC): the divided superior vena cava (SVC) is anastomosed to the right pulmonary artery. The inferior vena cava (IVC) is tunneled along the right atrial wall using a tubular graft opened longitudinally and anastomosed just anterior to the right pulmonary veins posteriorly. Anteriorly the graft is closed to the two edges of the atriotomy incision. This variant has some growth potential. A fenestration (f) can be made. **C**. Extracardiac Fontan: a tubular graft (PTFE or allograft) is connected to a cuff of right atrium above the IVC, and top the inferior surface of the confluent pulmonary arteries. This operation can be done without opening the heart, and in some patients without cardiopulmonary bypass. **D**. Growing extracardiac lateral tunnel: a pericardial flap is sutured to the external surface of the right atrium to create a tubular connection between both cavae and the pulmonary arteries. This variant has some growth potential. **E**. Kawashima operation: for patients with azygos continuation of the IVC to a right (or left) superior vena cava, connection of the superior vena cava to the pulmonary artery (as for a bidirectional cavopulmonary anastomosis) diverts all but the hepatic blood flow into the pulmonary circulation. These patients are at high risk of developing pulmonary arteriovenous fistulae and must have their hepatic flow connected to the pulmonary circulation either at the time of the Kawashima operation or soon thereafter. One option for hepatic vein diversion is an end to side anastomosis with the azygos vein (**F**). Ao, aorta; f, fenestration in the lateral tunnel; IVC, inferior vena cava; LA, left atrium; PA, pulmonary artery; RA, right atrium; RAA, right atrial appendage; RV, right ventricle; SVC, superior vena cava.

Normal caval and pulmonary venous connections

In the earlier eras of Fontan surgery, patients with visceroatrial heterotaxy seemingly had a higher Fontan mortality. The reasons for this were certainly multifactorial, but one could assign risk to the often frequent abnormalities of systemic and pulmonary venous return,[36–41] as well as to the regurgitant atrioventricular valve. Any abnormal resistance posed by anomalously connected pulmonary veins had to be dealt with and this clearly prolonged the operation.[36–41] In some patients complex atrial baffles had to be constructed to completely separate the systemic from the pulmonary venous connections. The introduction of the bidirectional cavopulmonary connection or the hemi-Fontan as an intermediate step in single ventricle palliation served to neutralize these particular issues[42–54] (see also Chapter 35). It is at the time of the bidirectional cavopulmonary connection that specific anomalies of systemic and pulmonary venous connections are addressed. Furthermore, pulmonary arterial stenosis resulting from a previously constructed systemic-to-pulmonary arterial shunt or from "normal" ductal closure can also be repaired at this time.[55] Systemic outflow tract obstruction shown throughout the Fontan experience to be a risk factor for mortality could be neutralized at this staging and intermediate operation by either enlarging the often restrictive ventricular septal defect, or by constructing a proximal pulmonary artery-to-ascending aortic connection, the Damus–Kaye–Stansel procedure.[56–75]

Normal PA pressure and pulmonary vascular resistance

Surgical mortality at the time of the Fontan procedure has been stratified against pulmonary vascular resistance and it is evident that pulmonary vascular resistance be calculated at cardiac catheterization. This is of course easier in principle than in reality. The occurrence of pulmonary artery stenosis, multiple sources of pulmonary blood flow (from one or more previously constructed shunts as well as from aortopulmonary collaterals),

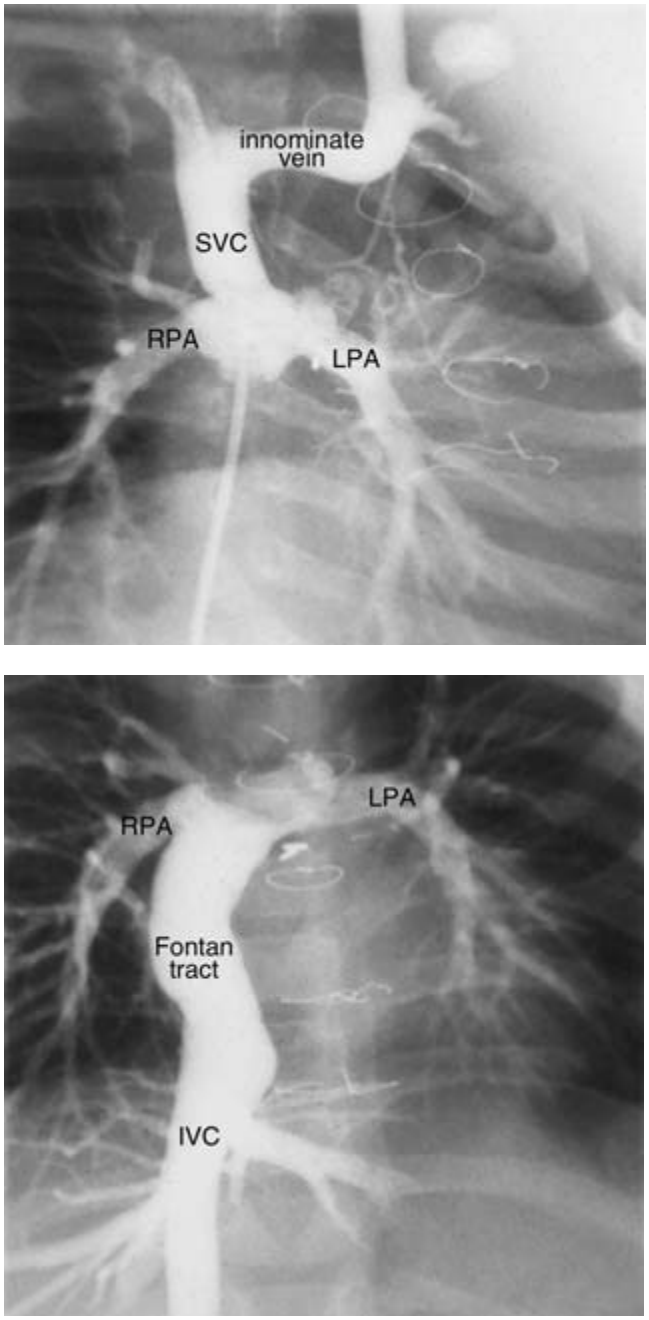


Fig. 36-4 Total cavopulmonary anastomosis with intracardiac lateral tunnel. Injections into the innominate vein (**A**) and Fontan tract (**B**) show unobstructed connections and pulmonary arteries. IVC, inferior vena cava; LPA, left pulmonary artery; RPA, right pulmonary artery; SVC, superior vena cava.

pulmonary arteries of disparate size, non-confluent pulmonary arteries as in those patients previously treated with classic unilateral cavopulmonary connection make that calculation frequently difficult and fraught with assumptions.[76,77] Data from the Mayo Clinic shown in Tables 36-3 and 36-4, demonstrate increased surgical mortality, early and late, when mortality is stratified against increasing pulmonary vascular resistance alone (Table 36-3)[77] or a against a score including indexed pulmonary vascular resistance and left ventricular diastolic function (Table 36-4).[78]

Data from the Mayo Clinic addressing mortality in terms of pulmonary vascular resistance are shown in Table 36-3.[77]

Using the indexed score from the Mayo Clinic that attempts to incorporate some aspect of diastolic function, the following data is shown in Table 36-4.[78]

The ability to apply this index requires one to measure pulmonary blood flow, and as mentioned earlier that may prove difficult. In addition, oxygen consumption should be measured, not assumed, for these calculations to have any significance. Modest differences in indexed pulmonary vascular resistance may have a minimal effect on the outcome of patients undergoing a biventricular repair (i.e. ventricular septal defect, etc.). However, for patients undergoing a Fontan-type operation the outcome

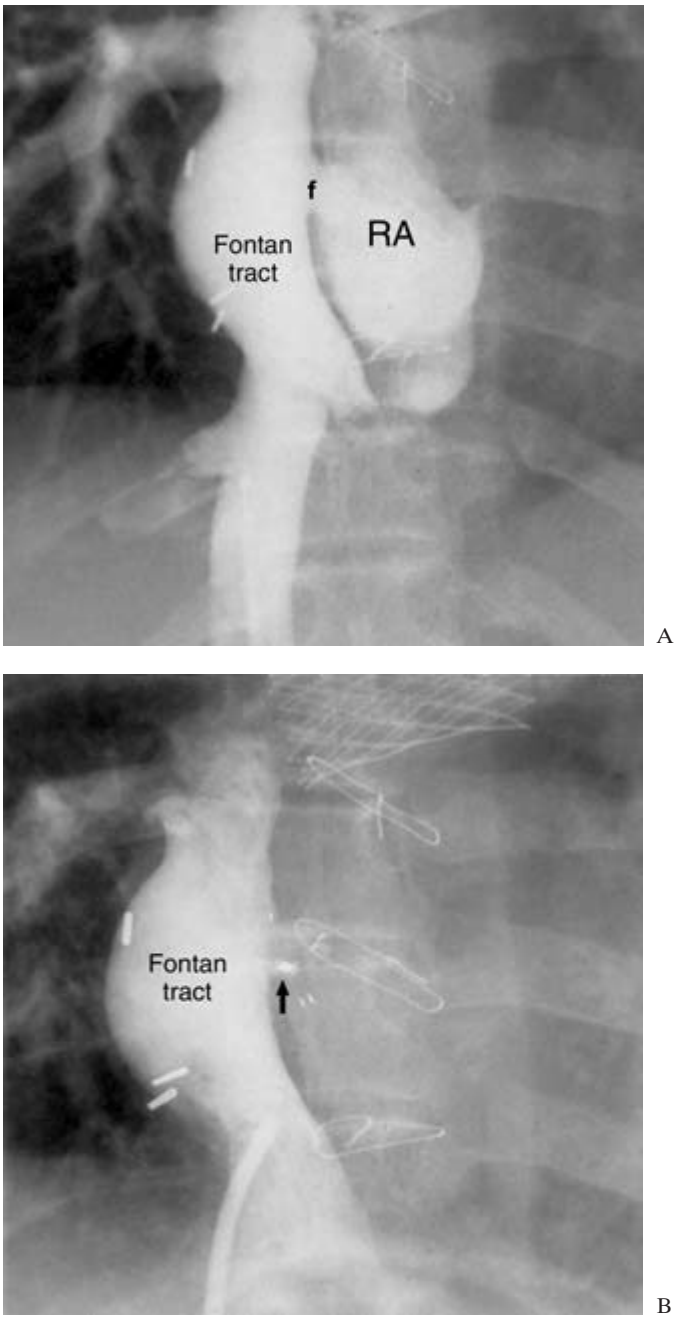


Fig. 36-5 Fenestrated Fontan operation. **A**. Injection into the Fontan tract demonstrates a fenestration (f) in the partition between the lateral tunnel and the rest of the right atrium (RA). **B**. The fenestration was closed by placing a Rashikind occlusion device.

Table 36-3 Relationship of preoperative pulmonary resistance and mortality in patients with double-inlet left ventricle

	Mortality (%)	
Resistance (U/m^2)	Early	Overall
< 2.0	3	15
21–3.0	11	44
3.1–4.0	50	50

(From Mair *et al.*[77] with permission.)

may be considerably worse with only a modest increment in pulmonary vascular resistance.

Pulmonary artery size (PA/AO ≥ 0.75)

Choussat and his colleagues suggest that the diameters of the pulmonary arteries when compared to the aortic diameter should be ≥ 0.75.[6] It would seem logical that patients with larger rather than smaller pulmonary arteries would have a better outcome of Fontan's operation as blood is conveyed into the lungs without a pump. Indeed, some, but not all, agree that pulmonary size as indexed to a variety of standards is necessary for a successful outcome at Fontan's operation.[79–82] But there is debate as to exactly what surface area of the pulmonary arteries is adequate or ideal for Fontan repair. Whether one uses the McGoon ratio, the Nakata index, or some amalgam thereof, these measurements of the caliber of the central pulmonary arteries do not provide information about the compliance of the pulmonary vascular bed.[83–86] The McGoon ratio is determined by summing the diameter of the immediately prebranching portion of the right and left pulmonary artery and dividing this sum by the diameter of the descending aorta at the level of the diaphragm, all the measurements being taken in systole.[83–85] When this ratio was as low as 1.2, the probability of death or takedown of the Fontan within 30 days of operation was 55% for an atriopulmonary connection.[79] The Nakata index or pulmonary artery index is determined by measuring the diameters of the right and left pulmonary arteries immediately proximal to the origin of the first lobar branches; the cross-sectional areas were then calculated, summed and divided by the body surface area.[86] The resulting value is called the pulmonary artery index. Nakata and his colleagues applied this index retrospectively to 15 patients undergoing Fontan's operation and based on 3 deaths in this small series concluded that the Fontan procedure should be reserved for those patients with a pulmonary artery index ≥ 250 mm^2/m^2.[86] In 1985, Girod and his colleagues correlated pulmonary artery index with operative mortality in 90 patients undergoing a modified Fontan operation.[87] They found no significant difference in mortality between those with an index > 250 mm^2/m^2 or in those with an index < 250 mm^2/m^2.[87] In this study survival was achieved in some patients with an index as low as 188 mm^2/m^2. Bridges and her colleagues also found the Nakata or pulmonary artery index to be a non-predictor of operative survival in patients undergoing the Fontan procedure.[80] Although the range of the pulmonary artery index in the Bridges' study differs from that published several years earlier by Girod,[87] their conclusions are the same. One should not be surprised by these results, because as Bridges and her colleagues point out, the greatest contribution to pulmonary vascular resistance comes from the precapillary arterioles, with the next most significant contribution from the postcapillary venules.[80] Data have been provided by Knott-Craig and his colleagues from the Mayo Clinic who also measured the pulmonary artery index of 173 patients undergoing Fontan's operation.[82] They were unable to define a lower limit of this index compatible with a successful outcome. Yet their data seemed to indicate that small pulmonary arteries in otherwise good-risk patients was associated with increased risk of "early failure or persistent effusions."[82] Senzaki and his colleagues have also studied the influence of pulmonary artery size on postoperative hemodynamics of the Fontan operation.[81] They calculated both the pulmonary artery index using the Nakata methodology and pulmonary vascular compliance. They did not find a correlation between the pulmonary artery index and pulmonary vascular resistance, but they did find a significant correlation between the pulmonary artery index and pulmonary vascular compliance.[81] They found that pulmonary vascular compliance influenced postoperative hemodynamics of the Fontan operation by affecting peak central venous pressure and total impedance. From their data, smaller pulmonary artery size promotes the disadvantages of the hemodynamics of the Fontan operation with a resultant rise in peak central venous pressure and increased afterload to the single ventricle. Lung biopsy, once advocated by some as possibly one arbiter, is now rarely indicated in the preoperative management of the patient considered for Fontan surgery.[88–90] Some, however, suggest that nitric oxide synthase expression by pulmonary arteries may be a predictive marker of Fontan outcome.[89] In a small retrospective study Levy and colleagues found in lung biopsy material a clear endothelial nitric oxide synthase overexpression in patients in whom the Fontan operation failed. As is well known, pulmonary arterial stenosis or stenoses impose an untenable impedance to Fontan hemodynamics and for this reason, such obstructive lesions must be adequately dealt with either before or at the time of the Fontan (Fig. 36-6). In this regard, Fontan operations have been carried out in patients with a single lung.[81A,B,C] Most of these series are small, but when the patients are carefully selected, the risk does not appear appreciably higher. Similarly, the Fontan operation has been performed successfully after reconstruction of non-confluent pulmonary arteries.[81D] Finally, Kawahira *et al*. suggest that the diameters of the pulmonary veins in patients with univentricular heart should be a new indicator for patients considered for the Fontan operation.[13] The diameters of the pulmonary veins are measured proximal to the entrance into the atrium from the late phase of a pulmonary arteriogram. The pulmonary vein index is calculated from the sum of the cross-sectional areas of these veins divided by the body surface area. For patients undergoing a successful bidirectional cavopulmonary shunt, the pulmonary vein

Table 36-4 Mortality at Fontan procedure stratified by preoperative catheterisation index

R_P (U/m^2) + LVEDP/(Q_{P1} + Q_{S1})	Early and late mortality (%)
1.1–2.0	5
2.1–3.0	6
3.1–4.0	14
4.1–5.0	27
≥ 5.0	57

(From Mair *et al.*[78] with permission.)

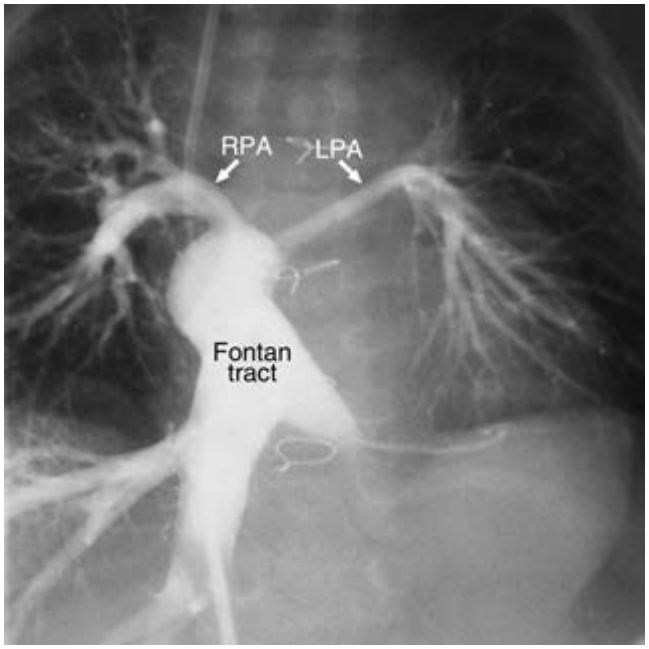


Fig. 36-6 Severely hypoplastic pulmonary arteries after Fontan operation. LPA, left pulmonary artery; RPA, right pulmonary artery.

index was 361 ± 153 mm^2/m^2 and for those whose outcome was poor, the pulmonary vein index was 275 ± 60 mm^2/m^2 ($P = 0.03$). Of their patients undergoing a successful Fontan procedure, the pulmonary vein index was > 275 mm^2/m^2 and for the unsuccessful Fontan, 137 mm^2/m^2. This group also calculated a "new" pulmonary vascular resistance (PVR): "new" PVR = 100 × (mPAP – mAP)/pulmonary vein index where mPAP and mAP are the mean pulmonary artery and atrial pressures respectively.[13] The "new" PVR value for those patients undergoing a successful Fontan procedure was < 2.0 $mmHg/mm^2$ per m^2 while that for an unsuccessful result was 4.4 $mmHg/mm^2$ per m^2. The concern about pulmonary vein size as a possible risk factor for poor Fontan outcome is certainly predicated in part by the observations of Jenkins and Heineman and their respective colleagues who studied pulmonary vein caliber in patients with heterotaxy.[91,92]

Normal ventricular function

It would be anticipated that Choussat and his colleagues list normal ventricular function as one of the tenets in consideration of Fontan's operation.[6] But what is "normal" ventricular function for a patient with a univentricular atrioventricular connection? Physicians caring for patients considered candidates for Fontan's operation have been concerned about the lower limits of ventricular function (systolic ejection fraction, shortening fraction, etc.) for a satisfactory outcome of this procedure. Ventricular function parameters for patients with a dominant left ventricle have been compared to the functional equivalent of the left ventricle in a biventricular situation and similar methodologies have been used for the patient with a dominant morphologically right ventricle. There are obviously important assumptions to all these determinations. Contractile or ventricular function has been assessed using a variety of methodologies before and following the Fontan procedure as has regional wall motion.[7,93–104] Graham and Johns suggest that patients considered for Fontan's operation should have a ventricular ejection fraction ≥ 50%, but in those with even lower ejection fraction data, an estimate of end-systolic stress and contractile state should be made.[7] It is also well known that some patients may have a marked increase in afterload which may lead to a decrease in ejection fraction. Since afterload can decrease after a Fontan operation, some patients with a borderline or frankly low ejection fraction may in fact still be candidates for Fontan's operation.[7] There is not unanimity as to the most meaningful methodology to ascertain diastolic function and ventricular compliance. If the ventricular end diastolic pressure is >12 mmHg and there is not conspicuous volume loading, then one should be concerned about the wisdom of performing a Fontan procedure. Yet, no single factor or "number" should automatically exclude a patient from consideration for Fontan completion. Contractile function can be anticipated to recover in some patients with "single" left ventricle after conversion to a Fontan circulation.[98] In the echocardiographic study of Sluysmans and colleagues ventricular volumes in patients with double-inlet left ventricle and tricuspid atresia before the Fontan were two to three times normal.[98] In patients < 10 years of age converted to either a Glenn or Fontan circulation, ventricular dimensions, volumes and wall stress all diminished and left ventricular function and contractility improved after surgery. In those undergoing surgery > 10 years of age, few demonstrated improvement in left ventricular function. Indeed, postoperative ventricular function and contractility were inversely related to age and to aortic saturation measured before surgery. Any number of studies have shown that regional wall motion abnormalities are common in univentricular hearts. Kurotobi and colleagues suggest that such ventricular systolic abnormalities are caused by the rudimentary right ventricle.[99] In their study, the rudimentary right ventricle caused a regional wall abnormality which resulted in asynchronous contraction of the main or dominant ventricular chamber. There are certainly factors other than the rudimentary right ventricle as indicated earlier that may depress or alter regional contractile function including a primary alteration in the arrangement of ventricular fibers, abnormal ventricular conduction, myocardial fibrosis from chronic volume and/or pressure overload, etc. These authors go on to suggest that the rudimentary right ventricle which is usually at systemic pressure affects the regional wall motion in the corresponding area of the dominant ventricle through the direct effects of a second high pressure chamber.

The relationship between diastolic function, ventricular hypertrophy and ventricular compliance is complex and not easy to calculate. There is considerable clinical experience that ventricular hypertrophy is a risk factor for poor outcome of a Fontan procedure.[56–71] Graham and Johns suggest that patients with a ventricular mass > 200% of predicted are at increased risk for Fontan procedure.[7] Others have related wall mass to ventricular end-diastolic volume as a possible index to use in this assesment,[64–66] and virtually all of these studies condemn abnormal ventricular hypertrophy as an important risk factor. Kirklin and his colleagues suggested > 15 years ago that ventricular hypertrophy was a risk for early mortality at Fontan's operation and that such ventricular hypertrophy was an inevitable consequence of aging and as well a consequence of systemic outflow tract obstruction.[19] The most common clinical situation where hypertrophy is an important concern for the patient considered for a Fontan operation is the anatomical sub-

strate of a dominant left ventricle, a rudimentary right ventricle, discordant ventriculoarterial connections, and a previously banded pulmonary artery trunk.[56–71] The ventricular septal defect in this situation is usually smaller than the aortic root, and thus intrinsically predisposed to disadvantageous diminution in size or closure.[57,61,105,106] Further volume reduction from banding the pulmonary trunk and myocardial hypertrophy from increasing the ventricular afterload all contribute to further diminution in size of the ventricular septal defect and systemic outflow tract obstruction.[59–66] These factors contribute to a disadvantageous wall mass/end-diastolic volume ratio. Patient outcomes reported from the Mayo Clinic, Toronto and elsewhere all provide evidence as to the egregious effects of systemic outflow tract obstruction and its consequence, ventricular hypertrophy, on outcomes.[19,56–63,65,67] This factor has been effectively neutralized by staging with a bidirectional cavopulmonary shunt and addressing the mechanism of the systemic outflow tract obstruction. Hiramatsu and colleagues have reported their excellent results of the surgical treatment of 25 patients with systemic ventricular outflow tract obstruction in Fontan patients.[106A] Twenty-one patients had undergone prior pulmonary artery banding and 10 patients had undergone prior arch repair. Systemic ventricular outflow obstruction progressed in 5 patients after the Fontan procedure. The mean age at operation was 6.5 years and the average preoperative pressure gradient across the ascending aorta and systemic ventricle was 29 mmHg (range 0 to 100 mmHg). The Damus–Kaye–Stansel procedure was performed in 18 patients (double-barrel anastomosis in 13, end to side anastomosis in 5), and subaortic resection or ventricular septal defect or bulboventricular foramen enlargement was performed in 7. A double-barrel anastomosis has been their first choice since 1994, if the pulmonary valve is intact. Follow-up ranged from 4 months to 14 years (average 5.0 years). Twenty-three of the 25 patients have undergone recatheterization (average 21.4 months later). No early deaths were found; 1 late death was reported of a patient with single right ventricle (4.0%). The postoperative average pressure gradient was 1.1 mmHg (0–10 mmHg), and the average right atrial pressure was 14 mmHg (9–20 mmHg). In all patients who underwent ventricular septal defect or bulboventricular foramen enlargement, regular sinus rhythm was maintained postoperatively. Regarding the Damus–Kaye–Stansel procedure, there was minimal progression of semilunar valve insufficiency except in 1 patient who underwent end-to-side anastomosis with moderate pulmonary regurgitation postoperatively. Clearly these results are excellent and depart from the experiences of other centers where staging provided better outcomes.

Decreased ventricular performance and increased muscle mass and dimension have been found in unrepaired and palliated patients with a "single" left ventricle.[7] Gewillig and his colleagues found a significant increase in ventricular wall thickness, particularly in diastole, immediately after a Fontan operation.[95] Some months after the Fontan operation, these parameters seemed to normalize in these patients. Penny and Redington and their colleagues have described incoordinate motion of the ventricular wall after the Fontan operation resulting in abnormal systolic atrioventricular flow.[107–110] These authors have also demonstrated abnormal patterns of intraventricular flow and diastolic filling after the Fontan operation which they suggest is also evidence for incoordinate motion of the ventricular wall. There are implications of these observations for diastolic filling, pulmonary blood flow and cardiac output in the Fontan patient. Thus there is considerable remodeling of the single ventricle after a modified Fontan procedure (see Table 36-5).

Table 36-5 Systemic ventricular remodeling after the Fontan operation

Reduction in end-diastolic volume
Increase in ventricular wall mass (i.e. mural wall thickness)
Marked changes in diastolic function
Altered filling pattern
Prolongation of time constant of relaxation
Incoordinate ventricular relaxation
Abnormal systolic atrioventricular flow
Possible increased myocardial stiffness

Does ventricular morphology impact on the outcome of a Fontan operation? Kirklin and his colleagues did not find ventricular morphology of the dominant ventricle as an incremental risk factor for death after a modified Fontan operation.[19] Yet Gentles and Matsuda and their respective colleagues and an earlier paper from the Mayo Clinic suggest that right ventricular morphology adversely affects outcome.[23,40] Julsrud and his colleagues from the Mayo Clinic in a comprehensive review found that ventricular morphology is a risk factor for early survival in patients undergoing a Fontan procedure, with left ventricular morphology associated with a better early survival than right ventricular morphology.[111,112] Kawahira and colleagues have asked whether the patient with a double-inlet morphologically right ventricle vs. other types of double or common inlet ventricle had a different Fontan outcome.[113] This group compared the outcome of 31 patients with double-inlet right ventricle, 45 with double-inlet left ventricle, 93 with common-inlet right ventricle, and 20 with common-inlet left ventricle. Pulmonary atresia was found in 58% of the patients with double-inlet right ventricle, and pulmonary atresia with non-confluent pulmonary arteries in 15%, both situations much more common in this series than in the patient with a double-inlet left ventricle. Twenty-one patients (68%) with a double-inlet right ventricle underwent the Fontan procedure, compared with only 37% of those with a common-inlet right ventricle. Survival rate after the Fontan in patients with double-inlet right ventricle was 95% at 10 years, nearly the same as for the patient with double-inlet left ventricle. The Kaplan–Meier survival curves were statistically better in the patients with either a double-inlet left ventricle or double-inlet right ventricle when compared to either ventricular morphology with a common-inlet.[113] It is not unexpected that atrial isomerism was identified in 36% of patients with a double-inlet right ventricle, 4% with a double-inlet left ventricle; 93% of those with a common-inlet right ventricle and 90% of those with a common-inlet left ventricle.[113] An abnormal myoarchitecture and increase in connective tissue has been described in hearts with tricuspid atresia.[114] The effect of this finding on cardiac performance has yet to be determined.

No regurgitation of the systemic atrioventricular valve

Important regurgitation of the systemic atrioventricular valve was identified as a risk factor for poor outcome and late mor-

tality and morbidity after a Fontan procedure.[6,15,23,27,36–41,115–117] The bidirectional cavopulmonary shunt unloads the ventricle and in some children where the primary mechanism responsible for the AV valve regurgitation was annular dilatation, improvement in the functionality of the valve was seen.[48–54,118–122] Unfortunately, many patients continued to have important atrioventricular valve regurgitation despite ventricular unloading procedures. Imai, his colleagues and others have published impressive series of patients undergoing annuloplasty/valvuloplasty either at the time of the bidirectional cavopulmonary shunt or Fontan procedure with gratifying results.[123–125] The complex atrioventricular valve morphology seen in patients with right isomerism does not lend itself to standard reparative procedures, and some have resorted to so-called endocardial cushion prosthesis in these difficult experiences. Most centers have some experience with the replacement of an atrioventricular valve either at the time of the bidirectional cavopulmonary shunt or at the Fontan itself.[126]

Systemic aortopulmonary collateral arteries

A number of studies have suggested that systemic aortopulmonary collateral arteries pose a risk factor for Fontan outcome, both in terms of mortality and morbidity.[8–12,27] There is some evidence that prolonged pleural effusions occur more commonly in those with substantial aortopulmonary collateral arteries. Thus it has become incorporated into our therapeutic algorithm that at the pre-Fontan catheter investigation important collateral vessels, both arterial and venous, be occluded with coils or other devices. Yet there is certainly ongoing discussion as to the significance of aortopulmonary collateral arteries. The experience of Kanter and Vincent would suggest that patients with extensive aortopulmonary collateral arteries fare poorly at and after Fontan surgery,[9,9A] an experience not shared by Bradley.[12,12A]

Staging and fenestration

Two maneuvers have been introduced to reduce mortality and morbidity in so-called high risk Fontan patients. Both maneuvers have been incorporated into the surgical algorithms for patients undergoing single ventricle palliation. These maneuvers are the interposition of the bidirectional cavopulmonary shunt (see Chapter 35) between initial palliation and the modified Fontan procedure itself and the fenestrated Fontan.[18,23,41–54,119–123] In the previous chapter we considered the role of the bidirectional cavopulmonary shunt as a staging maneuver, a maneuver usually combined with repair of risk factors for poor outcome of Fontan's operation, including pulmonary arterial stenosis, atrioventricular valve regurgitation, and systemic outflow tract obstruction. There is considerable clinical evidence that this staging maneuver provides excellent palliation for the infant or young child and that the bidirectional cavopulmonary shunt provides equivalent survival to a Fontan procedure.[127] The only caveat is that the adult is usually not effectively palliated by a bidirectional cavopulmonary shunt when this is the sole source of pulmonary blood flow,[128] reflecting the disadvantageous ratio between upper and lower systemic venous return.[129] There is less agreement as to whether an additional source of pulmonary blood flow is advantageous or not (see Chapter 35). In terms of conveying hepatic venous effluent into the lungs and minimizing the risk for pulmonary arteriovenous malformations, there may be some advantage to an additional source of forward ventricular flow (see Chapters 35 and 37).

What is the advantage to fenestrating the Fontan circulation?[130] Doesn't this defeat the purpose of effectively separating the systemic venous return from the pulmonary venous return? As Jonas stated in 1994, the Children's Hospital in Boston added the bidirectional cavopulmonary shunt in 1988 as an interim step for patients then considered to be at high risk for the Fontan, namely the patient with the hypoplastic left heart syndrome.[43] In 1989, this group added the fenestration to Fontan completion. The placement of a communication in the partition between the systemic and pulmonary venous circulations as an integral part of the Fontan operation results in lower superior and inferior caval venous and right atrial pressures.[43,131–135] Arterial oxygen saturation is lower, about 88% to 90%, but cardiac output is higher. This maneuver seemingly reduces the severity and duration of postoperative pleural effusions and the length of hospital stay as shown in at least one prospective, randomized study.[134A] Another disadvantage of fenestration is the increased risk for paradoxical systemic venous embolization to the central nervous system and other systemic organs. Clearly non-fenestration does not eliminate the possibility of stroke, etc. While fenestration was initially employed for the patient considered high risk for a Fontan procedure, many now routinely fenestrate all, or virtually all Fontan patients. One could then ask whether routine fenestration is justified. This question was posed by Airan and colleagues who found that elective fenestration of the intraatrial baffle was associated with decreased Fontan failure rate and decreased occurrence of significant postoperative pleural effusions.[136] Their conclusion was that routine elective fenestration of the atrial baffle is justified in all univentricular repairs. Hsu and her colleagues from Columbia University reported an excellent outcome after the single-stage non-fenestrated Fontan procedure in 61 patients.[137] Three of the 61 patients (4.9%) died in the early postoperative period. Of these 61 patients, 20 (33%) had no preoperative risk factors and were considered ideal candidates for a single-stage non-fenestrated Fontan. Forty-one patients (67%) had one or more risk factors and two or more risk factors were present in 23% of the patients. This group concluded that routine baffle fenestration is not indicated in a large cohort of patients with single ventricle physiology.[137] Thompson and his colleagues asked the same question for patients undergoing an extracardiac Fontan and arrived at basically the same conclusion.[138] For those who have fenestrated the Fontan, spontaneous closure of the fenestration has been well documented. Bando and his colleagues found that when the fenestration was 2.5 mm, 90% closed spontaneously within one year of surgery, while only 64% of 4.0 mm fenestrations spontaneously closed.[139] Similar results have been reported elsewhere.[140]

Fontan outcomes

In this chapter we have examined the classic guidelines for the performance of the Fontan operation or any of its modifications. Some of the initial guidelines have been obviated by evolution in surgical technique, while for others, the issues remain complex and confusing. As we have discarded some of the original criteria, we have added new criteria. But these new parameters are also complex and difficult to quantitate. What and how many risk factors should be used to include or exclude a patient from the Fontan operation? What candidates for Fontan's oper-

ation are considered high risk? Is risk based on anatomy, physiology, or some combination thereof? Yoshimura and colleagues in 2001 state that "patients with complex cardiac anomalies who have six or more risk factors should be excluded from total cavopulmonary connection candidates."[141] What is the optimum surgical technique,[142] the lateral tunnel Fontan operation as advocated by the Children's Hospital of Boston,[143] the extracardiac conduit, currently favored by Toronto or San Francisco,[144,145] or a growing extracardiac lateral tunnel with pedicled pericardium as advocated by the Loma Linda group?[146] Van Arsdell and the Toronto group have identified those interventions associated with minimal Fontan mortality.[147] The operative mortality for the first 400 Fontan procedures at the Toronto Hospital for Sick Children was 15%, and it declined to 4% for the next 100 procedures (Fig. 36-7).[147] Patient characteristics and risk factors were similar in the two groups. The extracardiac Fontan procedure and modified ultrafiltration after bypass were associated with lower mortality, and each of these had the potential to improve postoperative myocardial function. Knott-Craig and his Mayo Clinic colleagues reviewed their entire experience with 702 consecutive patients who had the modified Fontan operation at the Mayo Clinic between October 1973 and December 1989 to better understand risk factors associated with early postoperative death or failure.[15] The event rate for takedown of repair or death during the initial hospitalization or within 30 days of the operation was 14.8% (successful takedown of the repair, $n = 6$; death, $n = 98$). To identify variables associated with early death or Fontan takedown, they analyzed 33 clinical and hemodynamic variables in a univariate and multivariate manner. On the basis of a stepwise logistic discriminant analysis, patients who were younger and operated on before 1980 with a higher preoperative pulmonary artery mean pressure, asplenia, higher intraoperative (after Fontan operation) right atrial pressure, longer aortic crossclamp time, and pulmonary artery ligation were more likely to have the outcome event of interest ($P < 0.05$). A new variable, corrected pulmonary artery pressure (that is, mean preoperative pulmonary artery pressure divided by the ratio of pulmonary to systemic flow if the ratio of pulmonary to systemic flow is > 1.0), was significantly associated with the outcome event univariately ($P = 0.002$), but was no more predictive than the preoperative pulmonary artery mean pressure. Variables less predictive of the outcome event in this analysis included multiple prior operations, polysplenia syndrome, complex anatomy other than asplenia syndrome, and systemic atrioventricular valve regurgitation.

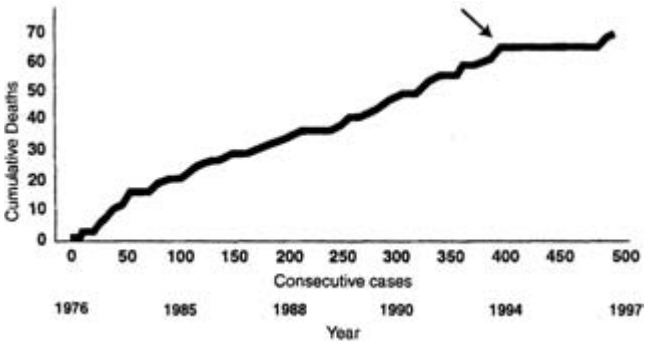


Fig. 36-7 Graph showing cumulative summation of patient mortality for Fontan procedure. There were 67 deaths among 500 patients, a mortality of 13.4%. The arrow points to an inflective point in the slope of the mortality curve. (Reprinted from Van Arsdell *et al.*,[147] Copyright (2000), with permission from The Society of Thoracic Surgeons.)

Surgical results and short-to-midterm outcomes have certainly improved over the eras after a modified Fontan procedure.[148–155] None the less, the reality is that it is unlikely that any form of Fontan operation will provide a Kaplan–Meier survival curve equivalent to that of a normal population. Indeed, there is no such thing as a perfect Fontan.[24]

Many reports of Fontan outcome stratified by type of cardiac malformation, specific ventricular morphology, type of connection, etc., have been reported giving mid- and long-term follow-up.[4,14–24,26–31,39,82,112,113,127,131–141,143–145,148–154] Various patient groups have been analyzed, including the younger Fontan patient, the adult-Fontan, the patient without pre-Fontan sinus rhythm, etc. Outcomes have been reviewed in those patients staged with a bidirectional Glenn and those who have or have not undergone routine fenestration. Outcomes have been analyzed in the context of specific anatomic risk factors (i.e. pulmonary artery caliber, subaortic stenosis, atrioventricular valve regurgitation, etc.) and by numbers of risk factors. With the Fontan experience extending now > three decades and with ongoing evolution in type of connection, it is not surprising that outcomes, both short-term and longer-term continue to improve. We have discussed earlier in this chapter how specific risk factors can adversely affect outcome and how with the various staging maneuvers and correction of the specific risk factor, outcomes can be enhanced. Amongst a cohort of patients with tricuspid atresia and followed for 25 years, overall survival was 79%.[152] In this Mayo Clinic experience, 79%. operative mortality steadily declined and was 2% (one of 58 patients) during the most recent decade. Late survival also continued to improve. Age at operation had no effect on operative mortality, and late mortality was significantly increased only in patients who were operated on at age 18 years or older. Eighty-nine per cent of surviving patients are currently in New York Heart Association class I or II. When one looks back at the earlier Fontan experience at the Mayo Clinic, Mair and his colleagues reported the mortality for double-inlet ventricle from 1974 through 1980 to be 21%, declining to 9% in the years 1981 through 1989.[77] Gentles and his colleagues from the Boston Children's Hospital had a similar experience as reported in their 1997 publication.[23] Mortality in the first quartile of their large experience was 27.1%, dropping to 7.5% in the most recent quartile. In a multivariate model, the following variables were associated with an increased probability of earlier failure: a mean preoperative pulmonary artery pressure of 19 mm hg or more, younger age at operation, heterotaxy syndrome, mitral atresia, an atriopulmonary connection at the right atrial body or appendage, and absence of a baffle fenestration. The probability of survival in the Fontan state was 84.9% at 1 month, 80.5% at 1 year, 78.5% at 5 years, and 71.4% at 10 years. Their analysis by era showed improved survival in the 1990–91 cohort compared with their earlier experience. Their data also showed poorer long-term survival in patients requiring a pacemaker before the Fontan and in those whose ventricular morphology departed from a single left ventricle with concordant ventriculoarterial connections or with a single right ventricle or ventricle of indeterminate morphology. Obviously the era in which the Fontan was performed influenced outcome. Again, looking at data from the Mayo Clinic, they reported on 352 patients who underwent the Fontan operation before 1985. The overall 1-, 5-, and 10-year survival was 77%, 70%, and 60%, respectively. In this experience a univentricular heart or complex heart malformation other than tri-

cuspid atresia, earlier year at operation, heterotaxia, increased pulmonary artery pressure, atrioventricular valve regurgitation, and worse New York Heart Association class were associated with poorer survival. Stamm and his colleagues reported in 2001 the long-term results of the lateral tunnel Fontan operation performed on 220 patients between 1987 and 1991.[143] The median age at the operation was 3.9 years with a mean follow-up of 10. 2 years. There were 12 early deaths, 7 late deaths, 4 successful takedown operations and 4 heart transplantations. The Kaplan–Meier estimated survival was 93% at 5 years and 91% at 10 years. Freedom from new supraventricular arrhythmias was 96% at 5 years and 91% at 10 years, while freedom from a new bradyarrhythmia was 88% at 5 years and 79% at 10 years. Imai and his colleagues reported in 1997 a 10 year survival after a modified Fontan procedure in the absence of atrioventricular valve regurgitation to be 93%, compared to a survival of 84% of those with atrioventricular valve regurgitation.[123] Bando and his colleagues have reported a 10-year actuarial survival of 93.5%, with overall early and late mortality of 5.4% and 0.8% respectively, of a cohort of 129 patients operated between 1988 and 1998.[139] This group identified Down syndrome as a risk factor for decreased late survival,[139] although certainly a successful Fontan operation can be performed in the patient with this syndrome.[139A] Gates and his colleagues reported a 5% operative mortality in adults undergoing the Fontan procedure, with actuarial survival rates at 3, 6, and 12 years of 95%, 95%, and 81%, respectively.[14] These results are similar to those reported from Toronto.[20] Veldtman and his colleagues reported on 61 adults older than 18 years of age at the time of the Fontan operated on between 1882 and 1998. The median age at operation was 36 years with a median follow-up of 10 years (range 0–21 years). The actuarial survival was 80% at one year, 76% at five years, 72% at 10 years, and 67% at 15 years.[20]

We have reported over the years our Fontan mortality at the Toronto Hospital for Sick Children. Coles and his colleagues reported on our Fontan experience from January 1976 to December 1985.[155] The surgical mortality in these 109 patients was 13.8%, and we identified as risk factors for early and late mortality the diagnosis of univentricular heart, previous pulmonary artery banding, the use of a direct right atrial–pulmonary artery connection in the patient with tricuspid atresia. We had previously reported those morphological features contributing to a poor Fontan outcome, specifically myocardial

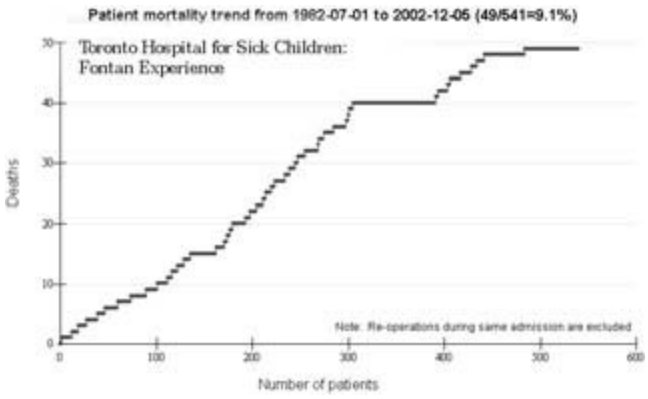


Fig. 36-8 Toronto data showing cumulative summation of patient mortality for Fontan procedure was extended to December 5, 2002. Most of the mortality occurred in the first 300 Fontan operations.

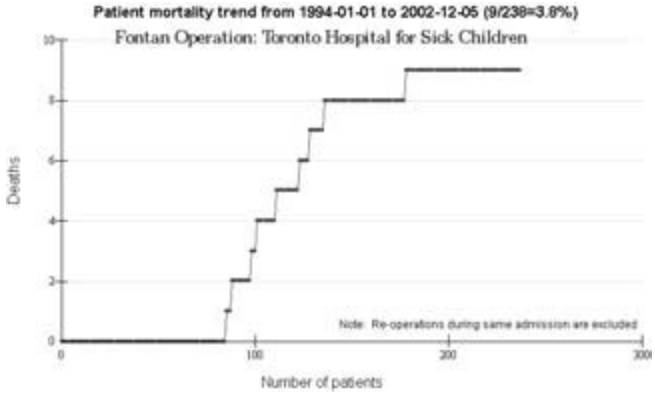


Fig. 36-9 Again the Toronto experience showing dramatic improvement in Fontan mortality.

hypertrophy and previous pulmonary artery banding.[63] We addressed the utility of right ventricular incorporation in the repair of tricuspid atresia, and with this approach from 1976 to 1986, our mortality was 16.1%.[155A] This approach amongst others was abandoned for later more energy efficient connections. In 1991 we reported the results of the Fontan procedure in 306 patients with a univentricular heart operated between 1978 and 1989.[155B] Twenty-five patients died in hospital and 10 died during follow-up. Actuarial survival was 77% at 1 year, 66% at 5 years, and 49% at 10 years. Multivariate analysis identified preoperative poor ventricular function and ventricular hypertrophy as risk factors for death. Our current results show a similar decline in operative mortality as reported by Van Arsdell and his colleagues, from 15% for the first 400 Fontan operations to 4% in the next 100.[147] We attributed this improvement to both staging with cavopulmonary anastomosis and to an extracardiac Fontan, amongst other reasons. In this regard, Azakie and his colleagues of the Toronto Hospital for Sick Children have compared the impact on outcomes of the lateral tunnel vs. the extracardiac Fontan.[144] There was no difference in mortality, but the lateral tunnel group had a higher incidence of postoperative sinoatrial node dysfunction. Results of the Fontan procedure in those with anomalies of systemic and pulmonary venous connections, often those with heterotaxia, continue to improve, with mortality (early and late, nearly 56% a decade ago[41]) to 13%,[156] or lower. Others have also reported improving Fontan results in those patients with heterotaxia.[144A] As we commented earlier whether or not an atrial fenestration currently improves Fontan outcomes is uncertain. Hsu and her colleagues have reported excellent results after the single-stage, non-fenestrated Fontan.[137] So many issues in Fontan surgery "cry out" for randomized trials.[134A,138,139,157,158] One can be reassured, however, that the clinical outcome of fenestrated Fontan patients 10 years after closure is excellent, with improved oxygenation, reduced need for anticongestive medication, and improved somatic growth at latest follow-up.[159] Death (1.3%) or chronic decompensation (3.2%) was rare in this large experience.

While the Fontan–Kreutzer operation has extended and enriched the lives of many patients with complex heart malformations,[23,150,152,160] this operation in any of its forms is in fact only palliation (see Chapter 37). Depending on the type of connection, the presence or absence of fenestration, etc., a number of patients will require ongoing surgical or catheter-based intervention after their Fontan operation (see also Chapter 37). Still,

the evolution from the Glenn to the Fontan–Kreutzer procedure and its modifications has dramatically improved the lives of so many patients with complex heart malformations.[161] The operation has evolved from an atriopulmonary connection with cavo-atrial valves, to total cavopulmonary bypass, lateral tunnel and extracardiac Fontan using pedicled pericardial tunnel vs. conduit reconstruction.[162]

In summary:

- The principle of atriopulmonary connection and atrial separation as introduced by Fontan and Kreutzer and their colleagues is now in its fourth decade of clinical application.
- There continues to be evolution in the surgical construction of the most advantageous Fontan circulation; a circulation that in the absence of forward pulsatile flow is the most energy-efficient. Most centers have evolved away from the classical atriopulmonary anastomosis.
- Early Fontan mortality in well-selected cases is < 5% (Figs 36–8, 36-9).
- The criteria for the performance of a Fontan circulation continue to be examined and refined. Some of the original criteria as outlined by Choussat *et al.*,[9] have been obviated by the evolution to a total cavopulmonary connection and staging procedures (see Chapter 35).
- Outcomes of the Fontan operation are seemingly improved in those with the fewest risk factors.
- There is no such thing as the "perfect" Fontan. Ongoing attrition is a reality in the best of circumstances. At the present time, 10–20 years' survival is often 80% or more.
- Staging with a bidirectional cavopulmonary shunt and correction of anatomic risk factors has likely improved Fontan outcome.
- It is unclear whether aortopulmonary collateral arteries jeopardize Fontan outcome and whether they should be interrupted preoperatively.
- The ideal age for the Fontan operation is unclear. This operation may carry more risk in the adult and in the infant.
- There is ongoing debate as to the value of fenestrating the Fontan circulation.
- The value of post-Fontan lifelong anticoagulation is unclear and if one chooses to anticoagulate, the specific protocol is also unclear.
- Patients surviving Fontan palliation are subject to a wide panorama of complications (see Chapter 37).
- There remains substantial attrition before and exclusion from the Fontan procedure. Strategies must be used to capture more of the "denominator."

All references can be found at the end of the book. See pp. 803–7 for Chapter 36.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

37

Robert M. Freedom and Shi-Joon Yoo

Complications of the Fontan Procedure

Most would agree that the Fontan operation is one of the signal achievements in the care of patients with congenital heart disease that took place in the last half of the 20th century.[1] It is entirely appropriate that the designation "Fontan operation" is now firmly entrenched in the vernacular of those who care for children with congenital heart malformations not amenable to a biventricular repair. The benchmark contribution of Fontan and Baudet was published in 1971, having been first performed in 1968 and thus clinical experience with this operation is now in its fourth decade of clinical application.[2] We reviewed in Chapter 36 the evolution in surgical technique, types of heart subjected to Fontan palliation, scrutiny of the original "ten commandments" and evolution in the application of these criteria, as well as those maneuvers that have reduced mortality and morbidity and have enhanced Fontan outcomes.

Suffice it to say, Fontan operative mortality has been reduced to < 5% in most contemporary series, and some report mortality of < 2%[3,4] (see Chapter 36). Such data are of course encouraging, but as we have documented elsewhere many patients who start out on the road of single ventricle palliation either die or are eventually excluded from Fontan palliation.[5–8] Even after a so-called "perfect" Fontan operation, there is ongoing attrition and the need for reintervention.[9] Furthermore, there are a large number of complications that can exact a toll on patients who have undergone the Fontan operation.[10–11A] As shown some years ago by the Mayo Clinic with its very extensive experience with the Fontan operation, both mortality and morbidity can be improved by operating on patients with few if any important risk factors.[11] Indeed, because of the ongoing attrition and reality of late complications, some have questioned the wisdom of "completing" single ventricle palliation with the Fontan operation.[12] The remainder of this chapter will examine in some detail the potential complications of Fontan palliation, and will focus on neurodevelopmental outcome of these patients. Outcomes, early and late, were discussed in the previous chapter.

The list of potential issues is substantial and include:

- right atriomegaly and hepatic dysfunction
- dilatation of the coronary sinus
- freedom from reintervention/reoperation
- thromboembolic events
- protein-losing enteropathy
- pulmonary arteriovenous malformations
- myocardial dysfunction and failure
- ventricular outflow obstruction
- obstruction of pulmonary veins
- recanalization of ligated main pulmonary trunk
- atrial rhythm disturbances
- systemic venous collateralization
- plastic bronchitis
- surgical creation of Wolff–Parkinson–White syndrome
- neurodevelopmental outcome.

Right atriomegaly and hepatic dysfunction

Amongst those patients who underwent a classical type of Fontan operation with a right atrial-to-pulmonary artery connection, a conduit connection between the right atrium and right ventricle, or a Bjork modification, substantial dilatation of the right atrium was inevitable (Fig. 37-1).[10,13–21] This was especially true with the Bjork modification of the Fontan because when the right atrial appendage was anastomosed to the right ventricular infundibulum, there was no atrioventricular valve in the circuit and systolic regurgitation into the right atrium was a certainty.[3] Impressive hepatomegaly was observed with corresponding dilation of the hepatic veins. While we have documented biochemical evidence of hepatic dysfunction, we are not aware of any patient from our institution who progressed to unequivocal cirrhosis related to this complication.[13–15] Others have documented frank liver fibrosis after the Fontan operation or one of its modifications,[14,15] but the incidence of this complication is unclear. With the current tendency towards the lateral tunnel, total cavopulmonary connection or extracardiac Fontan, often with fenestration, it is hoped that this complication should become even less frequent. It is clear, however, that in any patient with a Fontan circulation systemic venous pressure will be higher than normal and thus the sequelae of chronically elevated hepatic venous pressure must be assumed and anticipated.[16,21] Finally, in any patient with ongoing evidence of hepatic dysfunction, postoperative disadvantageous anatomy and hemodynamics must be excluded with a complete hemodynamic and angiographic investigation.[10]

Dilatation of the coronary sinus

In contemporary Fontan surgery, the coronary sinus is positioned in the lower pressure left or pulmonary venous atrium. This results in a small right-to-left shunt.[10,17–21] However, early in our Fontan experience as well as in other centers, the coronary sinus was frequently left to drain into the systemic venous atrium. The substantially higher pressures in the systemic venous atrium had the potential to promote disadvantageous coronary blood flow hemodynamics, perhaps impacting on myocardial perfusion/function, and this could lead to important

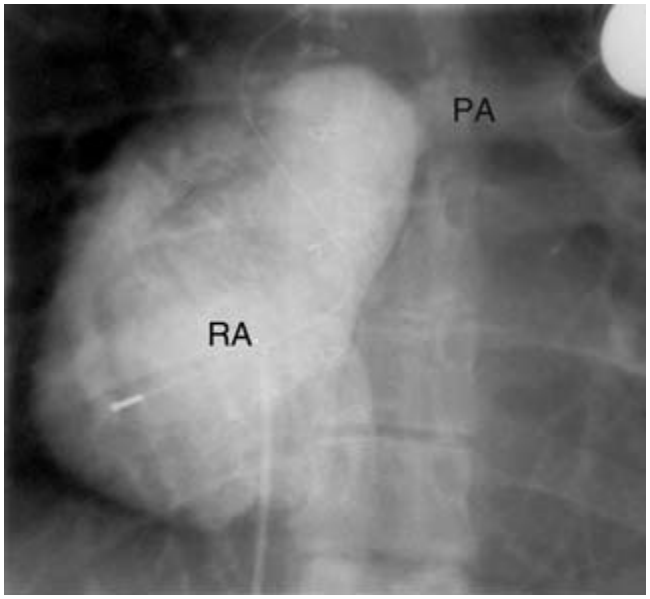
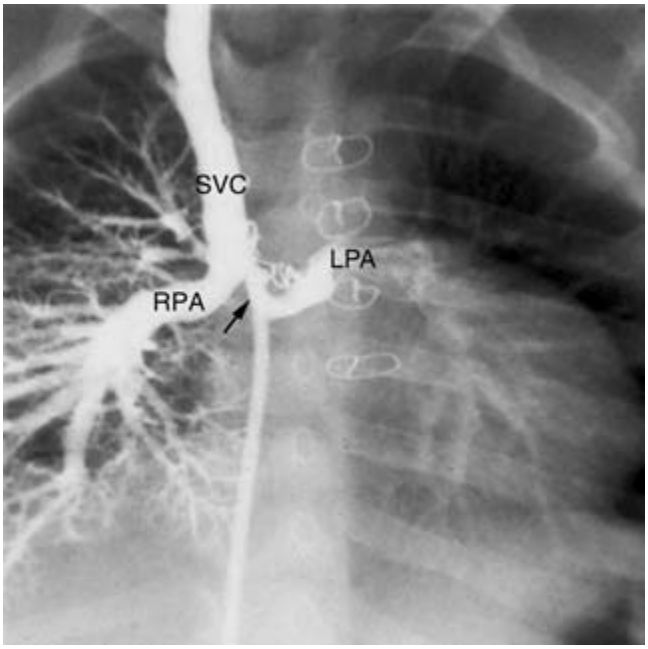


Fig. 37-1 Severe dilatation of the right atrium (RA) after classical Fontan operation. PA = pulmonary artery.

dilatation of the coronary sinus.[17–20] In at least one patient in our series, a very dilated coronary sinus contributed to mitral inflow tract obstruction, and this eventuated in surgical revision.[10,22] In another patient where a left superior caval vein connecting to coronary sinus was not excluded before construction of a Fontan circulation, and with the coronary sinus remaining in the systemic venous circulation, the coronary sinus assumed truly aneurysmal proportions.[10] We have demonstrated reopening of a left superior caval vein connecting to the coronary sinus, and this has been documented both after a bidirectional cavopulmonary shunt and after Fontan surgery as well.

Freedom from reoperation or reintervention

For those institutions routinely fenestrating their Fontan patients, the majority will require some maneuver, usually catheter-based, to close the fenestration.[10] Depending on the initial size of the fenestration, the smaller fenestration often spontaneously closes. But in any large cohort of patients who have undergone Fontan-type surgery, some will require reoperation. Among 334 patients undergoing the Fontan operation at two institutions and followed for a long time, freedom from reoperation for Fontan pathway obstruction was 99% at 1 year after operation and 96%, 86%, and 59%, respectively, at 5, 10, and 15 years after operation.[9] The hazard function for reoperation had an initial very rapidly declining phase and a second phase that was still rising 15 years after operation. Twelve (17%; confidence limits [CL], 13% to 23%) of 69 patients with a right atrial to right ventricular conduit (valved or nonvalved) connection underwent reoperation for pathway obstruction, whereas only 2 (4%; CL, 1% to 10%) of 45 patients with a direct connection to the right ventricle required reoperation. Five (8%; CL, 4% to 13%) of 65 patients with a right atrial to pulmonary artery conduit connection required reoperation for pathway obstruction, and only 2 (1.3%; CL, 0.4% to 3%) of 155 patients with a direct right atrial to pulmonary artery connection required reoperation. We have seen obstruction at the proximal or distal end of an extracardiac Fontan and distal obstruction at a lateral tunnel Fontan (Fig. 37-2).[10] Operations have been required because of conduit obstruction within the Fontan circuit and for residual interatrial communications promoting a substantial right-to-left shunt.[23–26] We have had relatively little experience with conversion from an atriopulmonary connection to either a lateral tunnel or extracardiac



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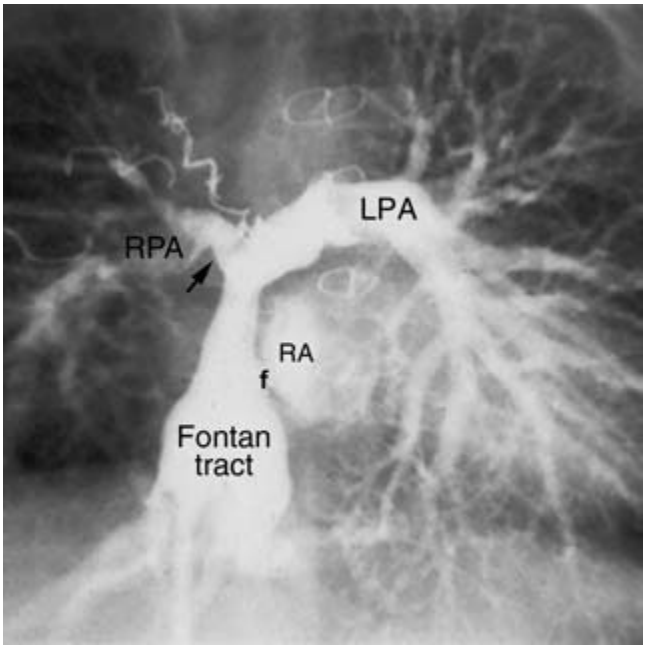


B

Fig. 37-2 Narrowing of the Fontan tract and pulmonary artery. Injections into the superior vena cava (SVC) (**A**) and Fontan tract (**B**) show kink and narrowing of the pulmonary arterial segment between the anastomoses of the superior vena cava and Fontal tract (arrow). The Fontan tract also shows narrowing. A fenestration (f) is seen in the partition between the lateral tunnel and the rest of the right atrium (RA). LPA, left pulmonary artery; RPA, right pulmonary artery.

type of Fontan as has been reported by Kreutzer, Mavroutis and others.[27–31] Some have suggested that adding a bidirectional cavopulmonary connection improves mechanical efficiency in dilated atriopulmonary connections.[32] But clearly patients who underwent a Bjork modification,[32A] any type of Fontan with a right atrial to right ventricular conduit, a direct right atrial-to-pulmonary connection and thus the predisposition to atriomegaly (and rhythm disturbances and thrombosis) may become candidates for reintervention.[10A,B] As discussed later in this chapter, systemic venous collateralization is likely to be an ongoing phenomenon. With some of these patients developing systemic venous to pulmonary vein or pulmonary venous atrium connections, some of these channels will have to be interrupted. The late development of systemic outflow tract obstruction, atrial rhythm disturbances, thrombosis and pulmovention can exact their toll in terms of morbidity and mortality. It is difficult to show a Kaplan–Meier actuarial survival curve(s) that depicts a realistic appreciation for freedom from reoperation/reintervention. In each era, technical modifications may make one operation and its specific complications obsolete, while the new operation has its own intrinsic hazards. Fontan and colleagues found freedom from reoperation in their first 100 patients with tricuspid atresia at 10 years to be about 80%. In Toronto at the Hospital for Sick Children, 86 of our first 569 Fontan patients required reoperation/reintervention, and freedom from reoperation was 88%, 77%, and 54% at 5, 10, and 15 years, respectively.[10] Amodeo and colleagues showed in 1997, a 5-year freedom from reoperation for the extracardiac Fontan of about 85%.[11A]

It is likely that in some patients there will be an ongoing requirement for intervention.

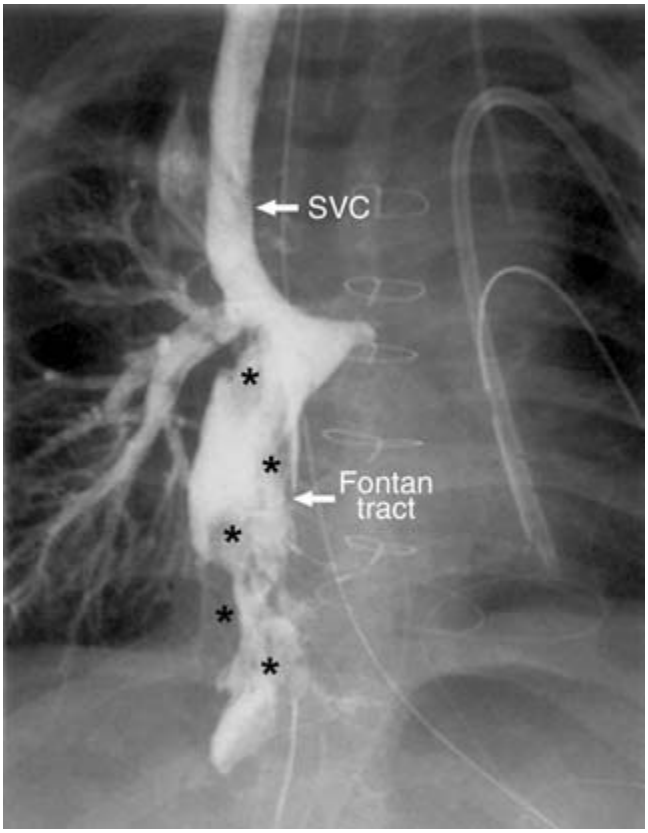


Fig. 37-3 Massive thrombus formation (asterisks) in the Fontan tract and pulmonary arteries. The left pulmonary artery is completely occluded. SVC, superior vena cava.

Thromboembolic events

There is still ongoing discussion and debate as to whether anticoagulation is required for the Fontan patient, and if so, for how long and in what form. Certainly thromboembolic events have been documented to occur acutely after surgical conversion to a Fontan circulation, and late thromboemboli with systemic, including fatal myocardial infarction and pulmonary events have also been substantiated (Fig. 37-3).[33–52] Because of the changing surgical type of connection, presence or absence of a surgically-created fenestration, and various approaches to anticoagulation, both in type and duration, it is difficult to hazard an incidence and to define causality. From a retrospective analysis of 645 patients who underwent the Fontan procedure at the Children's Hospital in Boston between August 1978 and July 1993, 17 patients (2.6%) suffered a stroke after the Fontan procedure.[52,53] The clinical onset of strokes from the time of Fontan operation ranged from 1 day to 32 months (median 40 days). Only 2 patients were receiving prophylactic coumadin therapy at the time of the cerebrovascular accident. The median platelet count in these 17 patients was 274 000/mm^3 ranging from 61 000/mm^3 to 561 000/mm^3. The majority of patients in this series had undergone a lateral tunnel type of connection with the majority fenestrated. Rosenthal and his colleagues from Yale University School of Medicine reviewed the clinical course of 70 patients who underwent this surgery between January 1978 and March 1994.[38] They found that 14 patients (20%) developed a thromboembolic complication during a mean follow-up of 5.2 ± 4.7 years, and the type of surgical connection did not influence the rate of thrombosis. The time from Fontan operation to the thrombotic event averaged 6.1 ± 5.0 years and the overall rate of thromboembolic events was 3.9 per 100 patient years. Thrombus after the Fontan operation has been seen in the right atrium; atrial septum, left atrium and ventricle and is perhaps best appreciated with transesophageal echocardiography. There is some evidence that coagulation abnormalities, both procoagulant and anticoagulant factors, in patients with single ventricle physiology precede the cavopulmonary connection, thus setting the stage for thromboembolic events.[52A] Finally, the study of Varma and colleagues found that 17% of adult patients with the Fontan procedure have clinically silent pulmonary emboli.[33A] The long-term implications of these findings are unclear.

Protein-losing enteropathy

Protein-losing enteropathy is one of the more serious complications of the Fontan procedure and carries with it important morbidity and mortality.[54–72] In the international multicenter study of protein-losing eneteropathy (PLE) after a Fontan procedure, the incidence of PLE in the survivors was 3.7%, although considerably higher in some centers, indeed 25% in one center.[60] The diagnosis of PLE was not just biochemical evidence of protein loss in the stool, but the development of clinical symptomatology related to documented hypoproteinemia caused by gastrointestinal loss. For inclusion into this study, other causes of hypoproteinemia had to be excluded. One-hundred and fourteen patients of 3029 patients undergoing Fontan's procedure or one of its modifications between 1975 and 1995 in 35 participating centers developed clinical evidence

of PLE. For the entire cohort the mean surgical mortality was 13.3% ± 9.5%. There has not been one consistent treatment protocol and any number of therapies have been utilized with varying success. These include dietary manipulation; steroids; heparin; atrial fenestration; takedown to either a bidirectional cavopulmonary anastomosis or to circulation where the pulmonary circulation is dependent on a systemic-to-arterial shunt; or cardiac transplantation. This is a particularly egregious complication with very important morbidity and mortality. In any patient with enteric protein loss, a cardiac catheterization should be carried out to assess post-Fontan hemodynamics and anatomy, but pericardial constriction must be excluded as well. Finally, one must remember the experience recorded by McMahon and colleagues and others who described the appearance and exacerbation of PLE by exposure to high altitude.[73,74] The likely mechanism was an increase in pressures in the pulmonary artery which was then reflected in increased pressures in the venoatrial compartment. Rychik and Gui-Yang have provided evidence that raised superior mesenteric vascular resistance is found in patients with protein-losing enteropathy.[74A] The mortality of protein-losing enteropathy has been suggested to be as high as 50% at 5 years from the time of initial diagnosis.[54,60] Rychik and Spray have recently summarized those strategies to treat protein-losing enteropathy.[62] It is clear from the many studies of PLE, that the patient should undergo a complete postoperative cardiac catheterization with angiography to obtain filling pressures and to exclude any source of mechanical obstruction to systemic venous flow.

Worsening cyanosis following the Fontan procedure

The patient after a successful Fontan procedure is usually acyanotic at rest unless an atrial fenestration has not been closed, thus permitting an obligatory right-to-left shunt. The overwhelming majority of patients with no fenestration at atrial level have a transcutaneous oxygen saturation of at least 94% or higher. If the arterial oxygen saturation is < 90%, then one is obliged to define the etiology of the hypoxemia.[10,75] The following are the more common anatomic causes for hypoxemia following the Fontan operation:

- shunting through a surgically created atrial fenestration
- shunting through a residual interatrial communication
- systemic venous collateralization with connection either to pulmonary venous atrium or to a pulmonary vein
- pulmonary arteriovenous malformations
- unrecognized (pre-Fontan) connection of a hepatic vein with the coronary sinus or left (pulmonary venous atrium) atrium or pulmonary vein
- reopening of a left superior caval vein to the coronary sinus (with coronary sinus draining into the pulmonary venous atrium)
- partially or completely unroofed coronary sinus
- reopening of a levoatrial cardinal vein
- interatrial right-to-left shunting via thebesian veins
- intrinsic pulmonary pathology
- diaphragmatic paresis.

Pulmonary arteriovenous malformations

From the list shown above, one etiology for post-Fontan progressive hypoxemia is the development of pulmonary arteriovenous malformations (Fig. 37-4).[10] This development is very serious and portends clinical deterioration often leading over a protracted period to death. The etiology for the development of pulmonary arteriovenous malformations following the Fontan operation remains uncertain.[10,76–98] Clinical observations suggest that exclusion of the hepatic veins and thus the hepatic venous effluent from the pulmonary circulation may be causal to the development of pulmonary arteriovenous malformations,

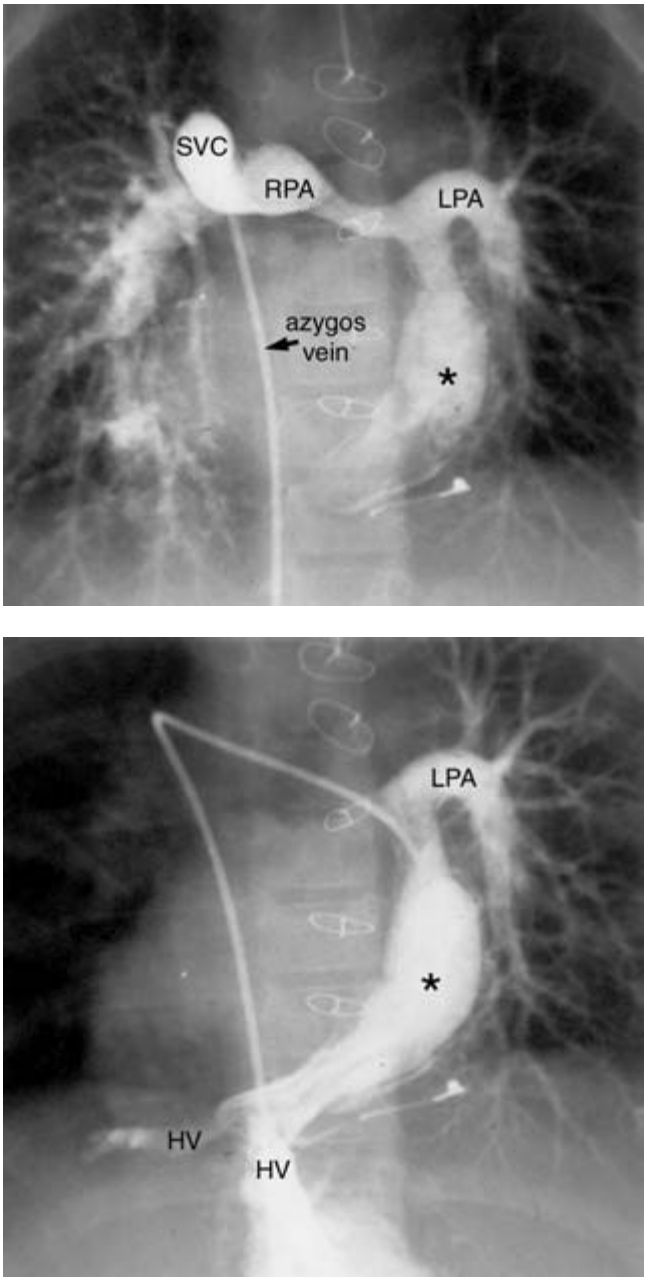


Fig. 37-4 Pulmonary arteriovenous malformation after Kawashima operation. The patient with left isomerism and interruption of the inferior vena cava underwent connection of the right superior vena cava draining the azygos vein to the right pulmonary artery. The patient developed pulmonary arteriovenous malformation. The patient underwent diversion of the hepatic venous flow to the left pulmonary artery (LPA). Injections into the right pulmonary artery (RPA) (**A**) and lateral tunnel (asterisk) (**B**) demonstrate that the right lung shows angiographic features of arteriovenous malformations, while the left lung does not. HV, hepatic vein; SVC, superior vena cava.

and that inclusion of the hepatic venous blood into the pulmonary circuit may reverse their formation.[76–98] This observation was apparently overlooked in one of the earliest reports of pulmonary arteriovenous shunting following Fontan's operation.[85] The similarities to pulmonary arteriovenous shunting in severe liver disease are interesting and their reversal by liver transplantation is provocative.[86–90,99] Indeed, the development of pulmonary arteriovenous malformations has been well documented following the Kawashima operation where the hepatic veins are excluded from the pulmonary circulation[76,77,79,80,81,83,91] and reversed in most after hepatic vein inclusion, a successful maneuver also reported by others.[93–95] Historically, the development of pulmonary arteriovenous malformations following the classical Glenn anastomosis has been very well documented.[100–104] In none of the substantial reviews of this complication that emanated from either Yale or Toronto was hepatic venous exclusion considered as causal.[102–104] Indeed, the Toronto group speculated that maldistribution of flow to the dependent portion of the right lung and lack of pulsatile blood flow were possible etiologies.[102,103] Indeed, in other earlier reviews of the causes of late deterioration after the classic cavopulmonary connection hepatic vein exclusion was not considered causal.[105,106] In one patient in our institution who underwent the Laks modification of the Fontan procedure,[107] with diversion of inferior caval blood to the right lung and superior caval blood to the left lung, pulmonary arteriovenous malformations developed only in the left lung. We have identified a number of patients with left atrial isomerism who developed bilateral pulmonary arteriovenous malformations following the classic Kawashima operation.[10,95] Indeed, while some degree of hypoxemia should be anticipated after the Kawashima operation with oxygen saturations often in the mid-80s, systemic oxygen saturations substantially lower suggest the development of pulmonary arteriovenous malformations.

Duncan and his colleagues have performed a histologic analysis of pulmonary arteriovenous malformations in two children with cyanotic congenital heart disease.[84] Their study did not elucidate the role of the liver in the formation of pulmonary arteriovenous malformations. The histologic correlate of pulmonary arteriovenous malformations seems to be greatly increased numbers of thin-walled vessels, but application of immunohistochemical techniques suggests that the rate of cellular proliferation is not increased. It is unclear whether the histologic and immunohistochemical markers of the pulmonary arteriovenous malformations in these patients with cyanotic congenital heart disease are the same as in patients with the Weber–Osler–Rendu condition. The incidence of the development of pulmonary arteriovenous malformations in patients with cyanotic congenital heart disease is uncertain and their ascertainment is in large part methodology-dependent as shown by Chang and colleagues.[82] The issue of methodology is of paramount importance in establishing the diagnosis of pulmonary arteriovenous malformations. Contrast or bubble-echocardiography is helpful in making this diagnosis. It is important that if this technique is used that contrast or bubbles be injected directly into the pulmonary artery(s). The early appearance of bubbles/contrast in the left or pulmonary venous atrium is very suggestive of this diagnosis. Yet false positives are common if the injection is performed in a peripheral or even a central vein because of potential anatomic connections between systemic veins and the pulmonary veins or left or pulmonary venous atrium as we have discussed earlier in this review and elsewhere.[10] Furthermore, even very small communications between the right atrium or lateral tunnel and the pulmonary venous atrium will contribute to early appearance in the pulmonary venous atrium.[10] The angiographic appearance of diffuse pulmonary arteriovenous malformationss may be diagnostic, but all-too-often this recognition occurs relatively late in the course of the disease (Fig. 37-4).[10] Some years ago we suggested that the incidence of pulmonary arteriovenous malformations following the classic cavopulmonary shunt ranges from about 11% to 21%.[102,103] It will likely escalate with time in those patients with the classic Glenn operation or Kawashima-type operation.[10,95] Other surgical maneuvers have been reported to resolve pulmonary arteriovenous malformations in a patient with a Kawashima operation. Heart transplantation provided for resolution of pulmonary arteriovenous malformations in one patient, and a heart and single-lung transplantation in another.[96,97] Others have modified the cavopulmonary connection so as to include hepatic venous blood in the pulmonary circulation.[92,93] Because pulmonary arteriovenous malformations have been seen in the patient with Weber–Osler–Rendu syndrome and can be seen in other cardiac malformations where hepatic venous blood is conveyed to the lungs, the role of hepatic venous effluent has yet to be fully defined.[97] In this regard, unequal distribution of hepatic venous flow has been attributed to the causality of pulmonary arteriovenous malformations[92,93,94A] and Uemura and colleagues and others have redirected hepatic venous flow to remedy this complication.[92,93] This has usually been achieved by reconstructing the geometry of the intra-atrial tunnel.[92] Another approach to direct or convey hepatic venous blood to the lungs after a Kawashima-type operation is to connect the hepatic veins to the azygos vein as reported by Baskett, Kaneko and their colleagues and others.[92A,B,C] Finally, in some patients with left atrial isomerism, both systemic and pulmonary arteriovenous malformations have been seen,[108,109] although we did not appreciate systemic arteriovenous malformations in the large cohort of patients with left atrial isomerism seen in Toronto.[8]

Myocardial dysfunction and failure

One should not be surprised that all centers performing Fontan surgery have documented ongoing morbidity and mortality following Fontan surgery.[9–11,16,110,111] The reasons for this attrition are clearly multifactorial and complex, but one factor contributing to this attrition is deteriorating ventricular function, both systolic and diastolic. One can postulate many reasons why a patient with a "single" ventricle, either left or right, might have abnormal ventricular function. Firstly, the underlying myocardial substrate might be intrinsically abnormal, as suggested by Sanchez-Quintana *et al*. in their analysis of the myoarchitecture and connective tissue of hearts with tricuspid atresia.[112] Supporting this view, Akiba and Becker also found that the left ventricle was intrinsically abnormal in hearts with pulmonary atresia and intact ventricular septum,[113] indeed perhaps the "Achilles" heel of this disorder. One should expect that myocardium chronically volume-loaded and/or subjected to longstanding hypoxemia would have depressed ventricular function. While the relationship between ventricular diastolic function and compliance is complex, there is ample literature showing that myocardial hypertrophy is a risk factor for the Fontan procedure, and that patients with systemic outflow tract

obstruction and myocardial hypertrophy had both a higher Fontan mortality and in follow-up did less well than those without myocardial hypertrophy.[114–124] Observations from a series of papers published from Toronto some years ago clearly showed that "abnormal" myocardial hypertrophy was a risk factor for poor outcome of Fontan surgery.[116–120,123] In our center, this risk factor has been essentially neutralized with staging with a bidirectional cavopulmonary shunt and either enlargement of the ventricular septal defect or construction of a proximal pulmonary trunk–aortic anastomosis of the Damus–Kaye–Stansel type, an approach advocated by the Mayo Clinic as well which preferred enlargement of the ventricular septal defect.[121]

Contractile or ventricular function has been assessed using a variety of methodologies before and following the Fontan procedure as has regional wall motion.[125–129] Contractile function can be anticipated to recover in some patients with "single" left ventricle after conversion to a Fontan circulation.[129] In the echocardiographic study of Sluysmans and colleagues ventricular volumes in patients with double-inlet left ventricle and tricuspid atresia before the Fontan were two to three times normal.[129] In patients < 10 years of age converted to either a Glenn or Fontan circulation, ventricular dimensions, volumes and wall stress all diminished and left ventricular function and contractility improved after surgery. In those undergoing surgery > 10 years of age, few demonstrated improvement in left ventricular function. Indeed, postoperative ventricular function and contractility were inversely related to age and to aortic saturation measured before surgery. Any number of studies have shown that regional wall motion abnormalities are common in univentricular hearts. Kurotobi and colleagues suggest that such ventricular systolic abnormalities are caused by the rudimentary right ventricle.[130] In their study, the rudimentary right ventricle caused a regional wall abnormality which resulted in asynchronous contraction of the main or dominant ventricular chamber. There are certainly factors other than the rudimentary right ventricle as indicated earlier that may depress or alter regional contractile function including a primary alteration in the arrangement of ventricular fibers, abnormal ventricular conduction, myocardial fibrosis from chronic volume and/or pressure overload, etc. These authors go on to suggest that the rudimentary right ventricle which is usually at systemic pressure affects the regional wall motion in the corresponding area of the dominant ventricle through the direct effects on a second high pressure chamber. We had previously shown considerable variability in size and position of the rudimentary right ventricle, but how these morphologic features translate into such regional wall motion abnormalities, both their presence and severity, is unknown at this time.[131] The role of ventricle–ventricle interaction has been tentatively explored in patients with "single" left ventricle.[132,133] Others have demonstrated changes in right ventricular geometry in patients with the hypoplastic left heart syndrome after the hemi-Fontan procedure,[134] reflecting ventricular unloading and remodeling. Because the native subpulmonary infundibulum in patients with the hypoplastic left heart syndrome is so well expanded, one would not anticipate ventricular outflow tract obstruction after volume unloading surgery. However, **v**entricular volume-unloading surgery including the bidirectional cavopulmonary shunt, the hemi-Fontan, and Fontan and subsequent ventricular remodeling can promote rapid ventricular outflow tract obstruction.[134–136] Furthermore Senzakie and coworkers have shown that Fontan physiology is associated with disadvantageous ventricular power and afterload profiles and has limited ventricular reserve capacity.[134A]

Finally, in the consideration of ventricular form and function after Fontan surgery, a host of other findings have been documented including what has been designated an acute hypertrophic cardiomyopathy as an early response of the systemic ventricle during transition to the Fontan circulation.[137] Penny and his colleagues from the Brompton Hospital in a series of papers showed incoordinate motion of the ventricular wall after the Fontan operations.[138–140] These observations were based on Doppler findings of abnormal systolic atrioventricular inflow and diastolic filling. With deteriorating ventricular function, one might anticipate the development or worsening of atrioventricular valve function.[110,111] The "chicken and egg" phenomenon must of course be taken into consideration, but we have certainly observed worsening tricuspid valve function in the patient with mitral atresia after Fontan surgery, and progressive regurgitation of the common atrioventricular orifice after Fontan surgery, especially in the group of patients with so-called isomerism of the atrial appendages, The prevalence of worsening atrioventricular function after Fontan surgery is uncertain.

Systemic outflow tract obstruction

Systemic outflow tract obstruction has been amply documented to occur in some patients after a Fontan operation.[141] The substrate for systemic outflow tract obstruction is likely present in many of these patients before the Fontan operation, especially those with a discordant ventriculoarterial connection and a history of increased pulmonary blood flow.[116,118–120,142,143] The ventricular septal defect in these patients is frequently marginal in size from the start and thus predisposed to disadvantageous diminution in size.[116,118–120,142,143] There are any number of mechanisms responsible for the development of ventricular outflow tract obstruction after the Fontan operation.[144–147] The ventricular septal defect as characterized by Anderson and his colleagues and others is usually muscular and often smaller than the aortic root, especially in those who required pulmonary artery banding.[116–118,148] Changes in ventricular geometry occurring relatively early after volume unloading surgery as found in the study of Chin and Fogel and their colleagues contribute to functional alterations in the VSD.[128,149] Donofrio and her colleagues have also demonstrated early changes in ventricular septal defect size in the "single" left ventricle after volume unloading surgery.[135] Their observations showed that in the "single" left ventricle, diminution in size of the ventricular septal defect occurs early and is related in part to acute alterations in ventricular geometry accompanying ventricular unloading surgery. Van Son and his colleagues have shown instantaneous subaortic outflow tract obstruction after volume reduction in hearts with a dominant left ventricle, rudimentary right ventricle and discordant ventriculoarterial connections.[136] As we have shown in a series of papers emanating from this institution many of the patients with either pre- or post-Fontan systemic outflow tract obstruction had required banding of the pulmonary trunk ± repair of aortic arch obstruction in the staging towards the Fontan.[116,118–120,142,143] Banding of the pulmonary trunk promotes both myocardial hypertrophy and volume reduction, and thus this maneuver contributes to diminution in size of a VSD predisposed to spontaneous diminution in size. Finta and her colleagues from Ann Arbor reported a series of patients who

developed systemic outflow tract obstruction after the Fontan procedure.[146] They found a 12% incidence of ventricular outflow tract obstruction after the Fontan procedure. This complication was recognized at a median of 28 months after the Fontan operation. Some years ago[144] we identified 12 children from a population of 306 Fontan patients (3.9%) who developed systemic outflow tract obstruction. In our population, this complication was recognized at a median of 2.5 years after the Fontan operation. Because of our long interest in the pathology of systemic outflow tract obstruction in these hearts, we have had a relatively low threshold for enlarging a potentially restrictive ventricular septal defect or performing a Damus–Kaye–Stansel operation before or at the time of the Fontan operation. This could explain the difference in the incidence of this complication between Toronto and Ann Arbor.[147] Because systemic outflow tract obstruction with the resulting myocardial hypertrophy has been identified as a risk factor for the Fontan procedure this complication has largely been neutralized by staging and either construction of a pulmonary–aortic connection or enlargement of the ventricular septal defect.[120,121,123,124,150–157] In some patients developing systemic outflow tract obstruction late after a modified Fontan operation, Suhara and colleagues were able to performa Damus–Kaye–Stansel-type operation reopening the closed pulmonary trunk.[157A] This approach requires a competent or nearly so pulmonary valve.

Obstruction of pulmonary veins after the Fontan

Any impedance to pulmonary artery flow can compromise the functionality of the Fontan circulation. Obstruction to pulmonary venous flow has been observed in some patients after a modified Fontan procedure.[158–164] Fogel and Chin identified 12 cases of pulmonary venous obstruction amongst 297 patients who had undergone 307 Fontan procedures.[158] The mechanisms responsible for the obstruction included narrow pulmonary vein ostia in six patients; narrow left atrial outlet in four; and atrial baffle obstruction in three. Berman and his colleagues reported two patients, both with heterotaxia, in whom late onset pulmonary venous pathway obstruction was recognised, after the Fontan procedure.[161] In one of the two patients, venous orifice obstruction was caused by the intra-atrial baffle and a fibrotic remnant of septum primum. A 5.0 mm diameter common pulmonary venous orifice was further narrowed by the atrial baffle suture line in the second patient. A grossly enlarged right atrium following an atriopulmonary connection has been identified as the etiology for obstruction of the right pulmonary veins in some patients.[159,162–164] Several such reported patients have shown improvement after conversion to a total cavopulmonary connection as documented both by Kreutzer and her colleagues and others.[27–31] We have identified similar mechanisms but have not systematically Dopplered the right pulmonary veins in all of our patients who had undergone a right atrium–pulmonary artery type of Fontan connection. Magnetic resonance imaging has also proven helpful in defining the mechanism of extrinsic pulmonary vein compression between the enlarged atrium and the spine and/or descending aorta.[159,160] It is likely that a mild degree of right pulmonary vein obstruction would not be clinically apparent if there was even modest redistribution of pulmonary blood flow. O'Donnell and colleagues from the Children's Hospital in Boston in 2003 reported 29 patients with pulmonary vein compression from a cohort of 1995 patients undergoing a hemodynamic catheterization between June 1999 and March 2001.[161A] Of these 29, 19 had single-ventricle physiology and 10 had two-ventricle physiology. Six of these patients showed no measurable pressure gradient at catheterization with a mean gradient of 2.4 ± 1.9 mmHg in the remainder. The authors raise the suggestion of endovascular stenting of the compressed pulmonary vein as a possible therapeutic maneuver.

Recanalization of ligated main pulmonary trunk

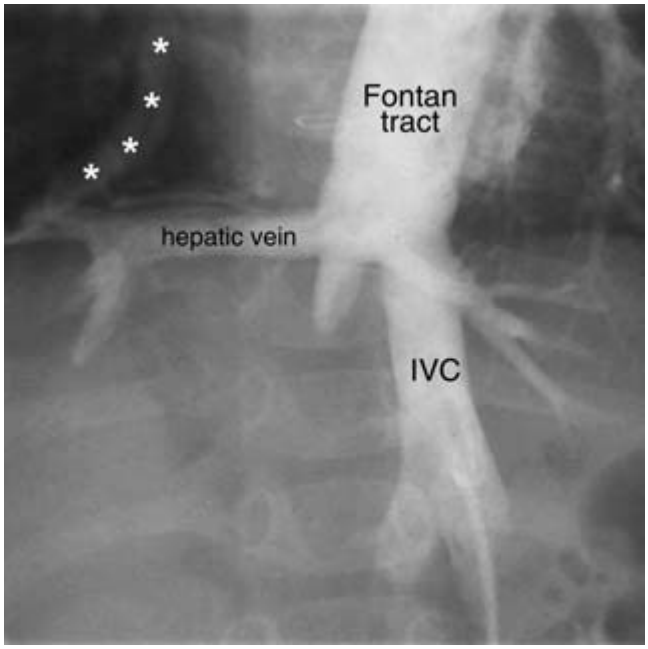
Of > 600 Fontan procedures performed at the Toronto Hospital for Sick Children we have identified three patients in whom recanalization of a ligated pulmonary trunk promoted a substantial left-to-right shunt. The three patients developed very early after the Fontan surgery a loud systolic ejection murmur and echocardiographic-Doppler interrogation showed patency of the main pulmonary trunk. Two patients underwent surgical division of the main pulmonary trunk. In the third patient, two attempts were made to coil occlude in the catheter laboratory the residual connection. Although these attempts did reduce the amount of shunting, residual patency still caused an important left-to-right shunt and surgical intervention was eventually undertaken to completely interrupt the main pulmonary trunk. This complication should be avoidable by completely dividing the main pulmonary trunk, not ligating it.

Atrial rhythm disturbances

The history of atrial surgery for transposition of the great arteries including the Blalock–Hanlon atrial septectomy and the Senning and Mustard forms of atrial repair is interwoven with atrial dysrhythmias reflecting damage to the sinus node and its artery (see Chapter 25A). One should not be surprised, therefore, about the occurrence of atrial rhythm disturbances after the Fontan procedure.[27–31,110,111,162–180] Indeed, the construction of a bidirectional cavopulmonary shunt or the hemi-Fontan procedure may also precipitate atrial rhythm disturbances,[163] implicit to the surgical variations in carrying out these procedures.

The annual incidence of new dysrhythmias in Fontan patients ranges from 0.4% to 13.9% with a mean of 5.0% per year.[162–180] Gelatt when in Toronto and his colleagues reviewed 270 consecutive patients who had undergone the Fontan procedure between 1982 and 1992.[168] Atrial tachyarrhythmias were seen early postoperatively in 55 patients (20%), preoperative atrial tachyarrhythmias being the only risk factor. Follow-up was achieved for 228 early survivors (97%) at a mean interval of 4.4 years. Twenty late deaths occurred. Late tachyarrhythmias were documented in 29% of patients who had undergone an atriopulmonary connection; 14% of those who received a total cavopulmonary connection; and 18% of those receiving a right ventricular connection. Early postoperative atrial tachyarrhythmias, longer length of follow-up, and atriopulmonary connection were independent risk factors for the presence of late atrial tachyarrhythmias. In an earlier paper Weber addressed predictors of rhythm disturbances and subsequent morbidity in 30 patients after the Fontan procedure.[165] Sixty per cent of the patients in this study had undergone an atriopulmonary connection, but for the entire cohort, atrial abnormalities on the preoperative electrocardiogram predicted those patients who developed rhythm disturbances both immediately and late after Fontan's operation. Balaji and colleagues from the Great

Ormond Street Hospital for Sick Children compared the incidence of atrial arrhythmias in patients who had undergone an atriopulmonary connection with those who had undergone a total cavopulmonary connection.[164] Their data suggested that early arrhythmia appeared to be less after a total cavopulmonary connection than after an atriopulmonary connection. In almost all studies, atrial flutter was associated with increased mortality and morbidity. Fishberger and his colleagues from the Children's Hospital in Boston sought to determine those factors influencing the development of atrial flutter after the Fontan.[174] Multivariate analysis identified age at operation (older rather than younger), longer duration of follow-up, extensive atrial baffling, previous atrial septectomy, and type of atrial repair were all associated with development of atrial flutter after Fontan's operation. Just as with a large cohort patients who have undergone atrial repair of transposition, there is likely to be a decreasing stable sinus rhythm and with increased duration of follow-up, an increased incidence of atrial flutter. Reports of sudden death after the Fontan operation have been reported, but such events are fortunately uncommon, and are presumably on a dysrhythmia basis.[162–180] Ghai and colleagues from the Toronto congenital cardiac center for adults have studied the outcome of late atrial tachyarrhythmias in adults after the Fontan procedure.[180] They found that systemic atrioventricular valvular regurgitation and biatrial enlargement are commonly observed in patients who develop atrial tachyarrhythmias after the Fontan procedure and that these patients are more likely to develop right atrial thrombosis and heart failure.[180]



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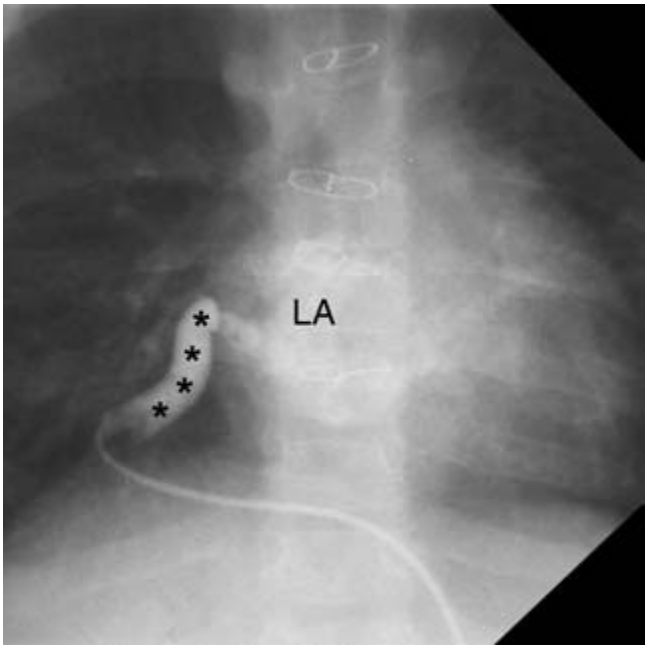

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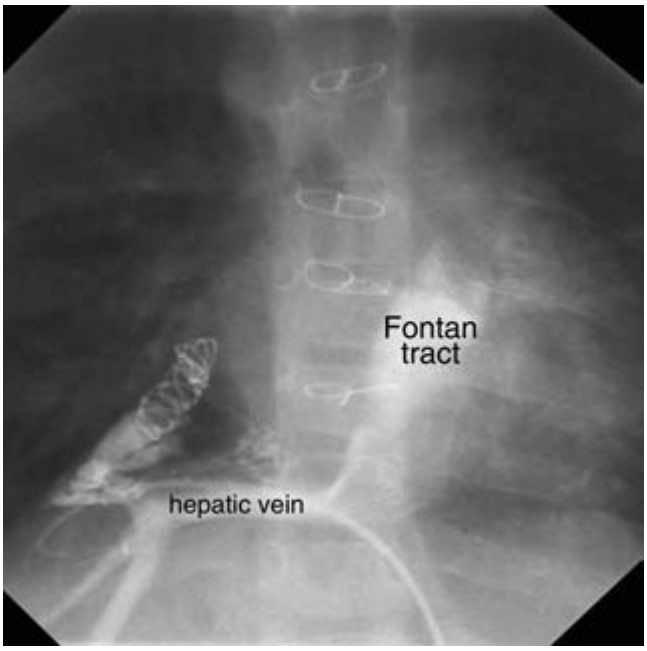

C

Fig. 37-5 Systemic venous collateral connection to the left atrium. **A.** Injection into the inferior vena cava (IVC) visualizes a large right hepatic vein that gives rise to a collateral channel (asterisks). **B.** Selective injection into the collateral channel shows shunting into the left atrium (LA). **C.** The channel was occluded with coils.

Systemic venous collateralization

Systemic venous collateralization will be for many patients a complication following either palliation with a bidirectional cavopulmonary shunt or a Fontan operation, or both. Considerable data about the development and incidence of systemic venous collateralization after the bidirectional cavopulmonary shunt have been published.[181–190] In some patients, the systemic venous connections are to a systemic vein, while in other patients, the systemic venous collaterals connect either to a pulmonary vein or to the left atrium (Figs 37-5, 37-6). Data from Toronto indicated that systemic venous collaterals are seen in about a third of patients after a bidirectional cavopulmonary anastomosis and are found postoperatively when a significant pressure gradient occurs between the superior vena cava and right atrium.[181] Such collateralization occurred more frequently when bilateral bidirectional cavopulmonary shunts were performed as compared to a unilateral cavopulmonary anastomosis.[191] A similar incidence of collateral formation was reported by McElhinney and his colleagues.[190] In the setting of a bidirectional cavopulmonary anastomosis, systemic venous collateralization can promote systemic hypoxemia by reducing effective pulmonary blood flow and by direct connection to either the left atrium or the pulmonary vein. Such venous collaterals can develop very rapidly, indeed within hours of a bidirectional cavopulmonary shunt.[182,185] Systemic venous collaterals may develop from a wide variety of venous channels. Furthermore, such venous collaterals may be occult and unmasked as we have demonstrated using the technique of balloon occlusion venography.[182] The virtually immediate demonstration of systemic venous collaterals by this technique supports the etiology as dilatation of pre-existing venous channels rather than angiogenesis. Peculiar venous collateralization originating at the level of the diaphragm or below the diaphragm has been observed both following a bidirectional cavopulmonary connection or a Fontan, and again such collateralization may connect to a systemic vein or to a pulmonary vein or to the left atrium, or both.[10,192] The pleuropericardial vein is observed quite frequently in this type of collateralization (see Fig. 35-8B).[10] Reed and his colleagues have described a peculiar intrahepatic venovenous fistula following the modified Fontan procedure.[193] From their data it is unclear whether this really developed after the Fontan operation or was present before the Fontan surgery as virtually identical findings have been observed in patients who have not undergone Fontan surgery.[194,195] A similar case with similar conclusions was published by Schneider and colleagues.[196] These observations have led us and others to study the infradiaphragmatic inferior caval vein with angiography before construction of either a bidirectional cavopulmonary shunt or a Fontan-type of procedure.[10,192,197]

There are perhaps fewer data on the incidence of systemic venous collateralization after the Fontan procedure.[188,189] But the incidence of collateralization after either a bidirectional cavopulmonary shunt or a Fontan procedure is unlikely to be static and we would anticipate an increasing incidence of collateralization with longer time from the time of surgery and with changing hemodynamics. We and others have documented the same spectrum of systemic venous collateralization originating from the superior caval vein and its branches after Fontan surgery as observed after the bidirectional cavopulmonary shunt. In addition to collateralization from the superior compartment, fascinating venous collaterals originating from the inferior caval vein and involving the portal vein have been observed. In addition, most peculiar venous channels originating from the atrial septum and coronary sinus (? thebesian veins) and connecting with the pulmonary venous atrium have been observed and some have been obliterated using a transcatheter-positioned device (Fig. 37-6).[24,181,183,198] Finally, one must exclude peculiar connections of the hepatic vein or veins to the coronary

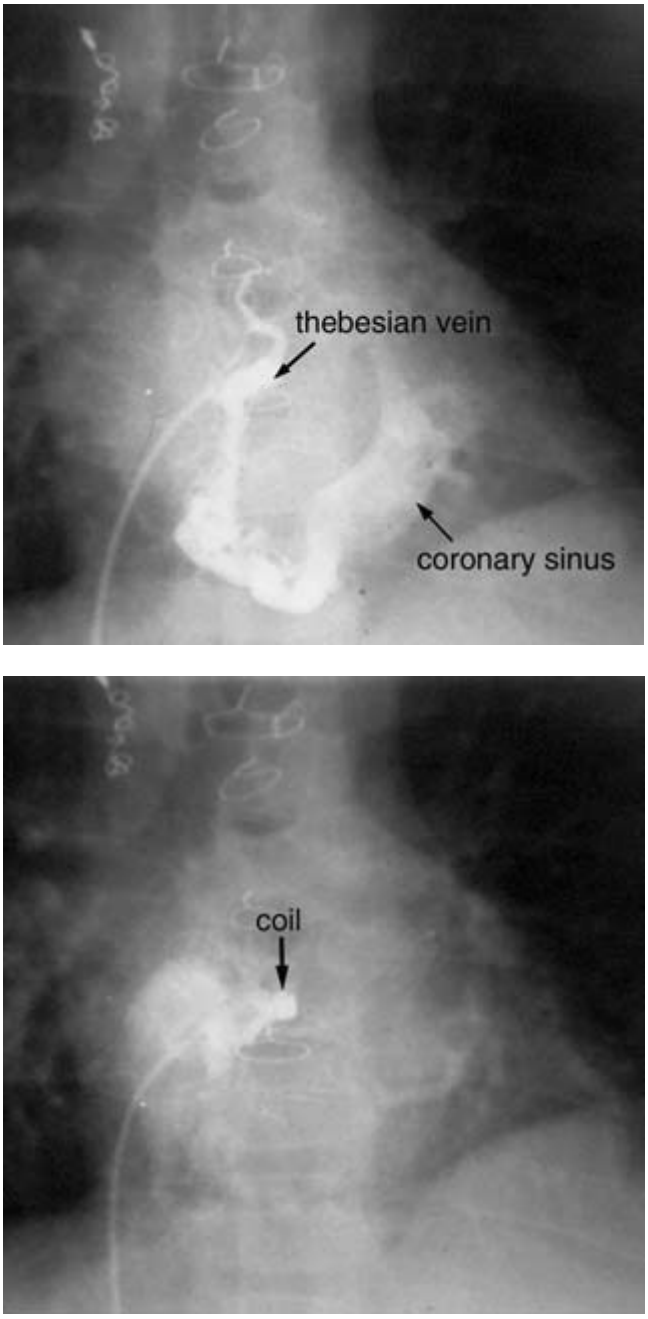

Fig. 37-6 Thebesian vein functioning as a shunting channel of the systemic venous flow into the functional left atrium. **A.** Selective injection into a thebesian venous channel in the Fontan tract shows retrograde filling of the coronary sinus that remained open to the functional left atrium. **B.** The opening in the Fontan tract was occluded with a coil.

sinus or to the left atrium because after conversion to a Fontan circulation, an unrecognised connection may promote a right-to-left shunt.[199–205] Many but not all of these patients with this complication have visceroatrial heterotaxia and one should always define the connection of all of the hepatic veins to the atrial mass as in some patients the hepatic veins may not be advantageously lateralized. With connection of one or an accessory hepatic vein to the lower pressure pulmonary venous atrium, one might anticipate intrahepatic veno-venous steal from the higher to the lower pressure circuit, promoting a progressive right-to-left shunt. Rarely, a congenital communication between the pulmonary vein and hepatic vein will contribute to cyanosis after the Fontan operation.[200] We and others have demonstrated reopening of a left superior vena cava connecting to the coronary sinus after the coronary sinus has been positioned on the low-pressure left atrial side (see Fig. 35–9**)**.[10,185] Similarly, reopening of a levoatrial cardinal vein after Fontan surgery has been shown to be a reason for progressive cyanosis.[10,206] At times it may be difficult to distinguish this congenital venous malformation from an acquired venous collateral.

Plastic bronchitis

Plastic bronchitis is a rare and extremely serious complication of the Fontan procedure, probably occurring in < 1–2% of patients.[207–215] Plastic bronchitis in this setting is characterized by non-inflammatory mucinous casts formed in the trachea and bronchi, producing airway obstruction, and this may result in asphyxiation. This complication has also been rarely observed after a bidirectional cavopulmonary shunt, modified Blalock–Taussig shunt, and the Waterston anastomosis. Languepin and colleagues have suggested that lymphatic leakage into alveolar air spaces may be the mechanism leading to the formation of bronchial casts.[215] This was shown beautifully in the post-mortem study of Hug and colleagues.[214] In their 4 year old patient who died some weeks after a Fontan procedure with elevated central venous pressures, histopathology showed massively dilated pulmonary lymphatics within the lung, and rupture of these lymphatic channels with extravasation into the alveoli. The material in the alveoli was demonstrated to be chyle by lipid staining. Similar findings have been reported by McMahon *et al*.[211] who prefer the designation "Fontan bronchial cast syndrome" to plastic bronchitis. Their patient also had unfavorable post-Fontan hemodynamics related in part to stenoses within the Fontan circuit. Transcatheter stent placement reduced the elevated central venous pressures and transiently reduced the production and expectoration of casts. This youngster seemed improved for about 6 weeks, before once again forming bronchial casts and succumbing with airway obstruction. In one patient seen in Toronto who developed recurrent mucinous bronchial casts requiring multiple bronchoscopies following a Fontan procedure, fenestration of the Fontan circuit did not provide relief, but cardiac transplantation provided prompt resolution of bronchial cast formation. Limited success in the treatment of this serious and life-threatening complication has been achieved using aerosolized urokinase.[210] The etiology of so-called plastic bronchitis or "Fontan bronchial cast syndrome" still remains obscure, but is likely related to unfavorable post-Fontan hemodynamics with elevated central venous pressures and a "fragile" pulmonary lymphatic system.

Surgical creation of Wolff–Parkinson–White syndrome

The appearance of WPW after the Bjork-type of Fontan surgery is consistent with the surgical "creation" of a bypass tract.[179] This finding is very uncommon and limited to those Fontan patients where continuity between right atrium and right ventricle has been achieved by connecting the right atrium directly with the right ventricular infundibulum using a flap of atrial musculature. We have documented this development in only a few patients.

Pancreatitis

Syed and colleagues have reviewed the relevant literature of post-cardiac repair pancreatitis, commenting that this complication is reasonably well described in adult cardiac surgery, but relatively less well studied in the pediatric population.[215B] They cite studies from Finland indicating that children with greater than a 10-fold rise in isoamylase have a higher mortality than those without such a rise. Syed and colleagues report that 4 of 40 patients undergoing a Fontan procedure developed acute pancreatitis after operation, and these patients had evidence for impaired ventricular relaxation.

Neurodevelopmental outcomes

Outcome analysis for any patient who has undergone "repair" of a single ventricle-type malformation must include assessment of neurodevelopmental outcome.[216–223] Uzark and her colleagues have assessed intellectual development in 32 children who have undergone a Fontan repair of complex cardiac malformations from 1986 to 1994.[216] Assessment tools included the Stanford-Binet Intelligence Scale, the Bayley Scales of Infant Development, and the Developmental Test of Visual Motor Integration (VMI). This last tool was used to assess visual spatial and visual motor integration ability. Most children who had undergone the Fontan procedure scored within the normal range for intelligent quotient. The mean score for the VMI was 94.8 with a median score of 93, suggesting a relative mild weakness in visual motor integration. In this relatively small study, no correlation was found between intellectual function or visual motor integration and age at Fontan, pre-Fontan oxygen saturation, or duration of cardiopulmonary bypass. No difference could be found whether the systemic ventricle was of left ventricular or right ventricular morphology. Children who had required deep hypothermic circulatory arrest tended to have lower mean IQ scores than those who had not undergone circulatory arrest. The meaning of these data is uncertain as so many factors including parental socioeconomic and educational status can influence these results. Data for patients surviving first-stage palliation for the hypoplastic left heart syndrome are even more concerning, but in the small series reported by Rogers and colleagues, it is uncertain whether the abnormal neurodevelopmental testing results reflect intrinsic neuroanatomic developmental abnormalities, or the sequelae of surgery, or both.[217] This perspective is important remembering that both acquired and congenital neuropathology have been reported in patients with the hypoplastic left heart syndrome.[218,219] However Kern and colleagues in a small study of children who had undergone at least two of the three palliative

operations for the hypoplastic left heart syndrome found that children with HLHS most often function in the low-normal range of intelligence and adaptive behavior. They go on to suggest that a prolonged circulatory arrest time may result in decreased intellectual function.[220] Forbess and colleagues studied the neurodevelopmental outcome of a recent cohort of patients who underwent the Fontan operation and compared them with a historical cohort of Fontan patients from this institution. This study showed that a staged approach to Fontan earlier in life is not detrimental to neurodevelopmental outcome. While neurodevelopmental outcomes in children after Fontan are in the normal range, their overall performance remains lower than the general population. These results are of course concerning.[223]

In conclusion, the survivor of Fontan palliation is a potential host to a wide variety of complications, including the complications of the arterial switch for those patients with a complex univentricular heart treated with this maneuver including an atriopulmonary connection[224,225] (see also Chapter 25B). Yet we are not persuaded to abandon this approach as Fontan surgery performed in the current era has a lower mortality and morbidity. While we have shown that a cavopulmonary connection may provide equivalent survival,[226] survival is but one aspect of outcome analysis.

All references can be found at the end of the book. See pp. 807–14 for Chapter 37.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom

Coronary Arteriovenous Fistula

Since the first description by Krause in 1865 of the patient with a coronary arteriovenous fistula,[1] there is now an extensive record of these malformations, with descriptions in young babies and indeed embracing all age-groups including those in their ninth decade of life.[2] Abbott described in 1906 the pathology of some of these lesions.[3] Some 40 years later, Bjork and Crafoord were likely the first to report the surgical treatment of a coronary arteriovenous fistula.[4] Fagan and his colleagues[5] suggest that Haller and Little were the first to report the use of preoperative angiography to diagnose coronary artery fistula.[6]

The site and size of the fistulous communication likely determines in large part the clinical and hemodynamic consequences.[7–20] A wide range of potential complications have been attributed to coronary arteriovenous fistulae including cardiac failure, bacterial endocarditis, coronary and myocardial insufficiency and calcification, dissection and rupture of a dilated vessel.[5,7–12,14,17–34] Fortunately clinically important coronary arteriovenous fistulae are uncommon in childhood,[5,7–10,12–14,17,19,35] but these have been recognized with increasing frequency especially in the adult since the introduction of selective coronary arteriography in the latter half of the 20th century. Their recognition has been enhanced as well by cross-sectional echocardiographic and color flow mapping and magnetic resonance imaging.[36–47] The malformations of the coronary arteries characterized by anomalies of connection or termination can be viewed as those with cardiac or extra-cardiac communications. This chapter will deal with coronary–cameral or arteriovenous fistula with the coronary artery(s) having a normal proximal aortic origin and distal cardiac or extra-cardiac connections (Figs 38-1, 38-2).[5,7–10,46–50] The anomalous origin of the right, left (anterior descending or circumflex), or both coronary arteries originating from the pulmonary trunk are considered separately in Chapter 12.

Incidence

The incidence of coronary arteriovenous fistulae is difficult to ascertain. Increasingly, small fistulae are being detected due to the frequency of coronary angiography in patients with atherosclerotic disease, valvular heart disease or other lesions[11] and owing to the advances in echocardiographic and magnetic resonance imaging.[37,39]

The New England Regional Infant Cardiac Program did not identify any infant with a primary coronary arteriovenous fistula, suggesting how uncommon this condition is.[51] Certainly since this survey was completed before the routine application of cross-sectional echocardiography it is likely that the true incidence was under-appreciated. Interestingly, however, the prospective Bohemia Survival Study also does not mention the birth prevalence of coronary arteriovenous fistulae.[52] Based on some clinical studies, Vlodaver and his colleagues in 1975 suggest a population incidence of 1 in 50 000 for coronary arteriovenous fistula.[48] There is not an obvious gender bias. Kallfelz summarizes some of the literature indicating that coronary arteriovenous fistulae or coronary–cameral anomalies constitute about 0.2% to 0.4% of all congenital cardiac anomalies.[53] He suggests as well that these have been identified in 0.08% to 0.18% of routine coronary arteriograms in adults, constituting 8–13% of the congenital coronary artery anomalies observed in these studies.[53] Yamanaka and Hobbs found 163 instances of small coronary arteriovenous fistulae in 126 595 patients (0.13%) who underwent cardiac catheterization at the Cleveland Clinic.[54] In 62 patients there were multiple or large-sized fistulae (0.05%).

Ventriculocoronary connections are well described in patients with pulmonary atresia and intact ventricular septum (see Chapter 34) and some forms of hypoplastic left heart syndrome (see Chapter 35). Other less common situations where ventriculocoronary connections are conspicuous including aortic atresia with transposition and intact ventricular septum [55] or double-outlet left ventricle and intact ventricular septum have been dealt with elsewhere.[55–59] Coronary–cameral fistulae may complicate other forms of congenital heart disease, including transposition of the great arteries, tetralogy of Fallot, ventricular septal defect, patent arterial duct, etc.[60–69] Acquired fistulae are reported increasingly following trauma,[70,71] coronary or valve surgery,[11] and cardiac transplantation, the latter a sequela of right ventricular endomyocardial biopsy.[72,73] We have observed a small coronary arteriovenous fistula following a right ventricular infundibular incision as well. An interesting case reported by Rozenman *et al*. of a fistula developing in association with progression of atherosclerosis coronary artery disease, raises the possibility that not all 'incidental' fistulae in this group of patients are 'congenital'.[74]

Definition

In this chapter we will consider those conditions where both coronary arteries have a normal origin from the aorta, but one or more branches of the coronary artery connects directly with one of the four cardiac chambers, coronary sinus, coronary vein, superior vena cava, or pulmonary trunk (Figs 38-1, 38-2).[5,7–10,12,46–49] Small interconnections between the coronary vascular bed and bronchial arteries have been amply described,

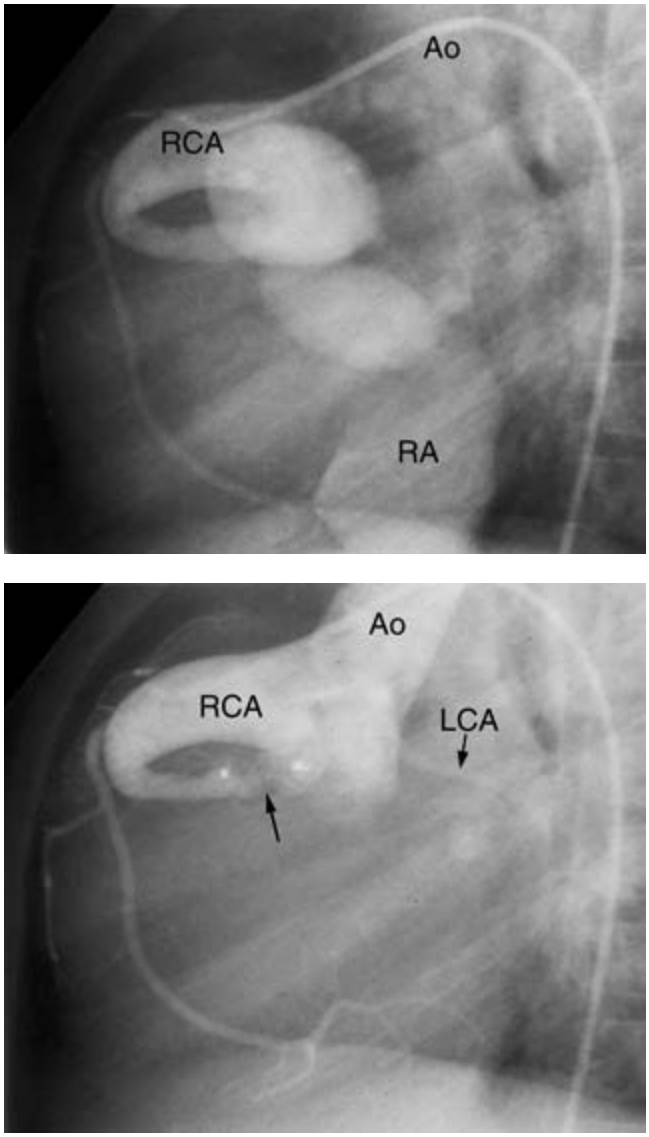

Fig. 38-1 Coronary artery-to-right atrial fistula. **A**. Right coronary arteriogram demonstrates a large fistulous connection of the proximal part of the right coronary artery (RCA) to the right atrium (RA). **B**. Aortogram obtained after deployment of an Amplatzer device (arrow) demonstrates successful occlusion of the fistula. Ao, aorta.

are likely normal and will not be dealt with further in this chapter.[60,61] Rarely a large connection between coronary artery and bronchial artery will result in a coronary artery steal.[24] Coronary arteriovenous fistulae should not be considered pathologic curiosities. They predispose to myocardial ischemia, bacterial endocarditis, at times substantial left-to-right shunts when connected to right heart chambers and congestive heart failure.[5,7–12,14,17–34] When connected to the left heart chambers, they "behave" like aortic regurgitation, depending on their size.[5,7–12,14,15,17–23,39,44,46–49,62,63] Occasionally a coronary arteriovenous fistula will become aneurysmal, dissect and then may rupture with resulting pericardial tamponade.[4,5,7–14,17–20,27,29,32,33,40,44,45,64]

Angelini differentiates coronary–cameral fistulae (those having a direct connection with a cardiac cavity) from arteriovenous fistulae (those having connections between arterial and venous plexii, the latter usually draining to the coronary sinus given that this is the usual drainage of most of the cardiac veins).[49] Other authors[7] include both groups as "coronary arteriovenous fistulae," presumably due to the similar clinical presentations and owing to the difficulty at times in demonstrating the venous segment of "arteriovenous fistula" angiographically, as well as pathologically: the presence of arterial flow in veins may lead to intimal hyperplasia and medial hypertrophy.[50]

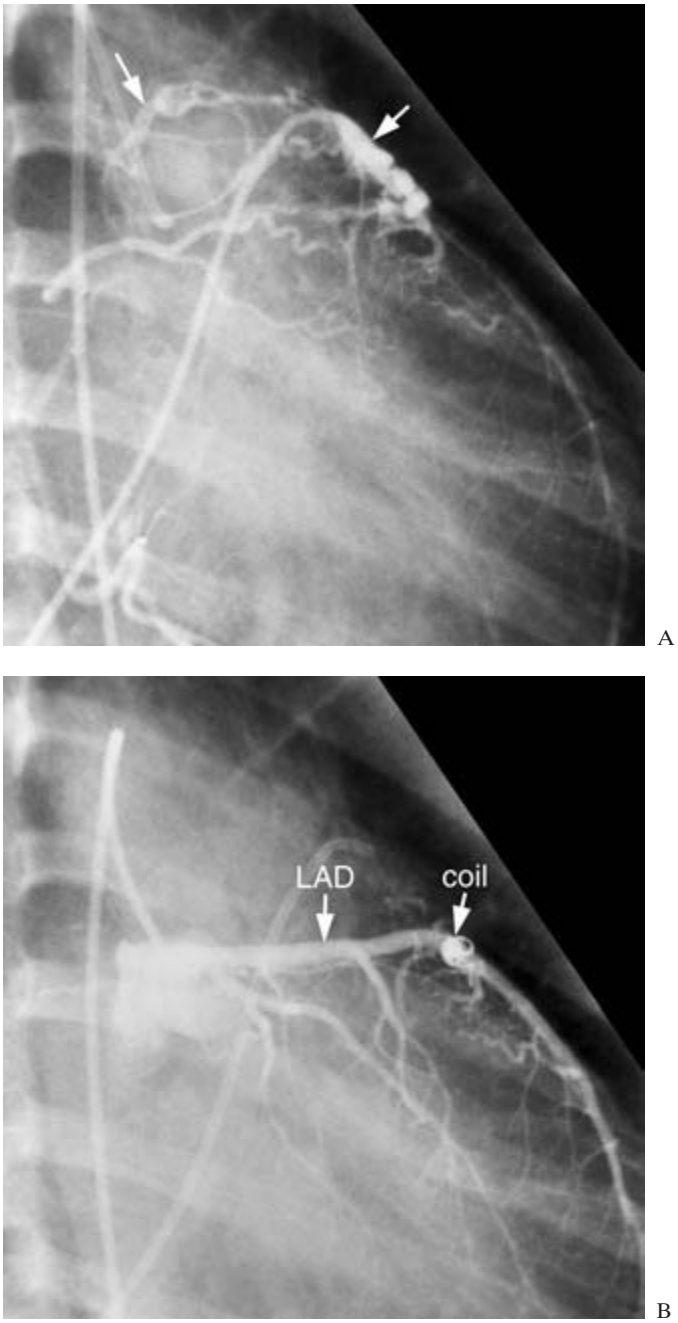

Fig. 38-2 Coronary artery-to-pulmonary artery fistula. **A**. Injection into the pulmonary arterial side of the fistula shows opacification of tortuous coronary arterial branches (arrows). **B**. Left coronary arteriogram obtained after coil embolization of the main fistulous tract shows only minimal shunting. LAD, left anterior descending coronary artery.

Neufeld and Schneeweiss have pointed out that technically, those connections between coronary arteries and left-sided chambers do not represent "arteriovenous fistula" but rather, arterial–arterial fistulae.[8] Despite this, the accepted practice in the literature of including all of these coronary connections to cardiac structures as "AV fistulae", will be followed. Those patients having a direct connection between aorta and a ventricular cavity (aortocameral communications) are discussed in Chapter 15A. We acknowledge the recent embryological thinking that these malformations represent direct communications between the proximal aspects of coronary arteries and persisting sinusoids, would argue for their inclusion in a discussion of coronary arteriovenous fistulae.

Site(s) of origin and termination

The fistulae originate from the right coronary artery in 50–60% of patients, from the left coronary artery in 30–40% and from multiple sites in 2–5%.[5,7,10–12,48,49,62,64–66] More than 90% of the fistulae connect to the right side of the heart, with the right ventricle being most frequent recipient, followed by the right atrium and pulmonary trunk. Connections to the left atrium and left ventricle are considerably less common, accounting for < 10% of the cases. The connections to a cardiac cavity or to coronary veins/sinus may be single, small, insignificant tracts,[10,11] single large or multiple large fistulae,[10,11,50,65] multiple small tracts,[20,21] or racemose angiomas.[22] Fagan and his colleagues also catalogue the types of fistulous connections into four types: (1) simple fistula to a chamber with a side or end connection; (2) multiple connection sites; (3) plexiform or telangiectatic connections (usually to the left ventricle or pulmonary trunk); (4) side-to-side (Fig. 42-2).[5]

Fagan and his colleagues have summarized the features of coronary fistulae in pediatric patients. These are probably the same issues for the adult population with coronary arteriovenous fistulae superimposed on the developing adult matrix of arteriosclerotic heart disease.[5]

Connections to a cardiac cavity or to coronary veins/coronary sinus may be single, small, insignificant tracts,[10,11] single large or multiple large fistulae,[10,11,50,65] multiple small tracts[20,21] or racemose angiomas.[22] The incidence of coronary arteriovenous fistulae is difficult to ascertain. Increasingly, small fistulae are being detected due to the frequency of coronary angiography in patients with atherosclerotic disease, valvular heart disease or other lesions[11] and owing to the advances in echocardiographic and magnetic resonance imaging.[37,39] The right coronary artery gives origin to the fistula slightly more commonly than the left but > 90% of the connections are to the right side of the heart.[5,7,65,10–12] Fistulae involving both coronary arteries occur in 4–5% of patients.[5,7,48,49,62,64,66]

Kirklin and Barratt-Boyes[7] note that the fistulae almost always are part of the normally distributed coronary artery, and may involve either the main vessel or a branch. The involved segment is usually dilated and elongated and may be serpiginous, usually reflecting the size of the shunt. The dilatation may be uniform or focal to a point of being aneurysmal. Associated congenital heart defects have been reported sporadically, including patent arterial duct, complete transposition, tetralogy of Fallot.[67–69] Acquired fistulae are reported increasingly following trauma,[70,71] coronary or valve surgery,[11] and cardiac transplantation, the latter a sequela of right ventricular endomyocardial biopsy.[72,73] We have observed a small coronary arteriovenous fistula following a right ventricular infundibular incision as well. An interesting case reported by Rozenman of a fistula developing in association with progression of atherosclerosis coronary artery disease, raises the possibility that not all "incidental" fistulae in this group of patients are "congenital.[74]"

Noninvasive imaging is now being used to map fistulae.[36–43,45] Until recently, the mainstay of diagnosis was angiography (Figs 42-1, 42-2). This was first reported in the diagnosis of coronary arteriovenous fistula in 1959.[46,47,81] Aortic root injection or selective coronary angiography will show the coronary artery which may be focally or generally dilated, with opacification of the draining chamber or vessel. Branches beyond the fistula may be small and poorly filled due to the myocardial steal. The malformation may be erroneously diagnosed, if, during selective coronary angiography, the catheter tip becomes wedged because of a small vessel, large catheter, or arterial spasm. In this situation, contrast will rapidly appear in veins or cardiac chambers, mimicking shunting. The differential diagnosis of coronary–cameral fistulae from aorto-cameral tunnels is clearly of clinical importance.[82] The clinical recognition of these peculiar communications is discussed in detail in Chapter 15A. The differentiation from acquired fistulous communications has also been discussed.[83] Coronary arteriovenous fistulae may be mimicked by two other abnormalities, the vascularization of cardiac tumours and organized thrombus.[84–89]

Outcome analysis

There is little if any literature documenting fetal recognition and outcome of coronary arteriovenous fistula. As with cardiac tumors (see Chapter 44), the clinical recognition of coronary arteriovenous fistulae has been heightened by noninvasive imaging modalities and thus there is increasing recognition of apparently clinically silent coronary arteriovenous fistula. The clinical findings have been reviewed elsewhere.[7,10] Suffice it to say, symptoms may be apparent in the neonate and young infant, but this is uncommon. Indeed as Liberthson and his colleagues pointed out some years ago, 80% of patients < 20 years of age with coronary arteriovenous fistula are asymptomatic, with only about 20% having symptoms related to the coronary arteriovenous fistula itself.[10] In some patients symptoms reflect the coronary arteriovenous fistula-related complications including congestive heart failure, bacterial endocarditis, or sudden death.[12] In the era of surgical ligation, complications related to surgical interruption in the young patient were quite uncommon, but were more common in the older patient.[10]

Hudspeth *et al.* pointed out the association with a myocardial "steal", especially in the adult with underlying arteriosclerotic vascular disease.[75] While progressive dilatation within the fistula is well recognized, rupture with cardiac tamponade is rare.[4,5,7–14,17–20,27,29,32,33,40,44,45,64] Spontaneous closure of a coronary–cameral fistula has been documented.[76–80] Coronary arteriovenous fistulae may clinically mimic the patent arterial duct, aortopulmonary window, ventricular septal defect with aortic regurgitation, or an arteriovenous malformation of the chest wall or lung. While these fistulae occur in early life, few result in symptoms until the second decade. The incidence of congestive heart failure from long-standing left ventricular volume overload increases with age,[23] as does myocardial ischemia and angina (from the "steal" effect).[24] The latter may

potentiate associated coronary artery obstructive lesions in the adult population.

As indicated above, symptoms from fistulae increase with age.[10] Additionally, older patients have a higher morbidity and mortality associated with the traditional management of fistula ligation.[7,10] These data support a role for elective and early intervention. Thus most investigators advocate closure (surgically or more recently by catheter methods) of hemodynamically significant communications, even in the absence of symptoms. The risks of surgical therapies are low[7] although operative deaths have been reported,[23] as had post-surgical myocardial infarction.[90] Recurrence rates after surgical intervention are not known. Embolization of large fistulae has been reported, either using coils[91–99] or detachable balloons, and other devices (Figs 38–1, 38-2).[100–105] When a fistula is large, visualization of normal distal coronary branches may be difficult due to the rapid run off toward the fistula. It is essential that visualization be complete and the embolization occur distal to all normal branches. Additional proximal fistulous communications may become apparent after the distal lesion is embolized, and underscore the need for careful post-implantation angiography.

A number of technical considerations highlight the potential difficulties involved in occluding high flow lesions within the coronary circulation. While detachable balloons allow precise implantation localization, large guiding catheters are required and early balloon deflation and inadvertent embolization may occur. When coils are utilized, it is critical that the delivery catheter tip is positioned at the point where the coil is desired. With torturous vessels and distal occlusion requirements, standard catheters may be difficult to place and microcoils or detachable coils may be required that are better suited to these specialized situations. With large, high flow lesions, placement of multiple coils may be required. It is important therefore, to select an embolization technique which is suitable for the size and location of the fistula to be occluded.

Connections to extracardiac structures

Connections between coronary arteries and extracardiac structures include connections to pulmonary arteries, pericardial, bronchial and mediastinal arteries and to the superior vena cava. Connections to pulmonary arteries are, like coronary fistulae to cardiac structures, increasingly recognized as an increasing number of patients have cardiac imaging (Fig. 38-2).[5,11,40,65,106–108] They typically extend from proximal left or right coronary arteries to mediastinal or hilar pulmonary arteries and may be single or multiple. While they are often incidental findings, they certainly may be large, tortuous communications of functional significance. Connections between coronary arteries and extracardiac veins are rare, but usually are to the superior caval vein.[5,7–12,14,46–49,66,102] Imaging by echocardiography is possible but the mainstay remains angiography, particularly selective coronary studies. The differential diagnosis includes acquired fistulae, either vascularized adhesions following cardiac surgery, or indirect collateral formation such as in patients with cystic fibrosis. Surgical approaches to management have both been reported, with increasing emphasis on catheter-based therapy.[5–7,10,12–19,24,90–105,109–114] Cheung and his colleagues have shown that after surgical intervention, the native coronary artery either remained dilated and tortuous, or more frequently demonstrated thrombosis with a short proximal stump.[114] Of the 41 patients included in this report, four patients demonstrated recurrence of the fistula.[114] The Pediatric Cardiac Care Consortium reported the outcomes for 35 patients undergoing 37 operations for a coronary arteriovenous fistula between 1984 and 1995.[115] During this time period 27 678 patients were operated on by members of the consortium. Infants under 1 year of age accounted for 12 (35%) of the patients. In this series all but one fistula drained to the right side of the heart. There were no operative deaths, but 2 patients required reoperation for recurrence.[115] The general experience of transcatheter closure has been good, with only a small percentage of patients demonstrating early trivial residual shunting.[116–118]

The clinically silent coronary arteriovenous fistula

One of the more important issues is the prognostic significance and management issues of the clinically silent coronary arteriovenous fistula.[80,106] Some of the considerations in these patients are similar to those patients recognized only by color flow mapping to have a small, clinically silent arterial duct (see Chapter 9). Sherwood and her colleagues have reported the clinical, echocardiographic, electrocardiographic, angiographic findings, and documented follow-up of 31 patients with an echocardiographic finding of a clinically silent coronary arteriovenous fistula.[80] The mean age at diagnosis was 7.2 ± 8.4 years. The indications for echocardiography were heart murmur in 23, congenital heart disease in 2, cardiomegaly in 2, chest pain, stridor, syncope and chest trauma in 1 each. Interestingly in this series of 31 patients, the origin of the fistula was from the left coronary artery system in 27, the right coronary artery in 3, and bilateral in 1.[80] At least one other report of asymptomatic coronary arteriovenous fistulae found a greater incidence of fistula origin from the left coronary artery system.[80] The sites of termination were the pulmonary trunk in 18, right ventricle in 8, right atrium in 2 and left ventricle in 3. Global and regional left ventricular function were normal in all patients at presentation and at follow-up. Stress-dobutamine studies were not performed in these patients. Complete spontaneous closure of the fistula was documented in 7 patients (23%) at a mean follow-up of 2.6 ± 2.0 years. All the other patients remained free of adverse clinical events and free from clinical myocardial ischemia. Thus these authors advocated conservative management with continued surveillance.[80] These authors specifically mention that in these patients with clinically silent coronary arteriovenous fistulae, the life-long risk of complications including aneurysm formation, rupture, dissection, accelerated atherosclerosis, and thromboembolism is unknown. As pointed out in this study and others, spontaneous closure of a coronary arteriovenous fistula is a well-documented phenomenon,[76–79] and Liberthson and his colleagues estimate the rate of spontaneous closure of the coronary arteriovenous fistula to be 1–2%.[10]

Despite a substantial literature devoted to the diagnosis and potential therapeutic strategies for patients with coronary arteriovenous fistula, controversy remains about the indications for and timing of intervention. There is perhaps less discussion when the fistula is large, when symptoms are present, or when there are findings of myocardial ischemia. Many authors advocate interruption of the fistula at the time of diagnosis even in the asymptomatic patient with a small left-to-right shunt, hoping to prevent later adverse events.[7,10,12]

All references can be found at the end of the book. See pp. 814–16 for Chapter 38.

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Robert M. Freedom

Cardiac Diverticulum and Aneurysm

Cardiac aneurysms and diverticulum are uncommon in the pediatric population, and while most are congenital in origin, some certainly have their basis in a post-inflammatory or ischemic sequela. There is now some literature documenting fetal recognition of these malformations as well.[1–9]

Cardiac diverticulum have been observed originating in the right atrium;[10–23] coronary sinus;[10,23–37] right ventricle;[10,38–56] left atrium,[10,57–83] left ventricle[10,84–129] and atrioventricular septum or valve[125,126] (Fig. 39-1). Again, none of these diverticula are particularly common, and those found in the right atria and right ventricle are considered rare. Some cardiac diverticula have been found as an incidental finding for investigation of other cardiovascular abnormalities, while in others investigation of atrial or ventricular dysrhythmias led to the recognition of the diverticulum. An abnormal cardiac silhouette on a chest radiograph has also led to the recognition of cardiac diverticulum, especially the large aneurysm of the left atrium or its appendage. The aneurysm of the atrial septum and ductal diverticulum are considered elsewhere (see Chapters 4 and 9). The so-called aneurysm of the membranous ventricular septum is not really an aneurysm, but rather tricuspid valve tissue adhering to the margins of the ventricular septal defect (see Chapters 3 and 26A). Aneurysms and rupture of the sinus of Valsalva are also considered in a separate chapter (see Chapter 15B).

In the consideration of cardiac ventricular diverticulum, some have designated these malformations as diverticula, while others have used the designation, aneurysms. There is certainly not a consensus when designating these conditions. Some have used the term diverticulum when it is associated with other congenital intracardiac and midline thoracoabdominal defects and when the connection to the ventricular cavity is narrow. Others have used the designation aneurysm when it resembles an acquired aneurysm with a wide connection to the ventricular cavity and absence of midline thoracoabdominal defects. This differentiation is not satisfactory because as Hamaoka and colleagues point out the designation diverticulum has been used in the absence of midline defects, and in other reports, the terms aneurysm and diverticulum have been used interchangeably.[54] Others have tried to use the morphology of the condition as the basis for designation. When the wall of the defect contains all three cardiac layers, endocardium, myocardium, and pericardium, and contracts normally or synchronously with the left ventricle, it has been called a ventricular diverticulum. It has been designated an aneurysm when it consists of a fibrous saccular wall, contracts paradoxically, and has a wide communication with the ventricle. But is the aneurysm an acquired or congenital condition? Mardini summarizing those issues about terminology, suggested that the designation of aneurysm has both acquired and congenital implications.[92] An aneurysm may be acquired when it results from trauma, infection, ischemia, postoperative coronary disease, etc. He goes on to suggest that a congenital left ventricular aneurysm may have its etiology in an anomalous left coronary artery originating from the pulmonary trunk. While the coronary lesion is certainly congenital, the left ventricular aneurysm has its origin in an ischemic myocardium. Thus in this instance both causality and terminology have overlapping features.

Right atrial diverticulum or aneurysms

Presumably congenital diverticulum or aneurysms originating from the right atrium are uncommon.[10–23] Varghese and his colleagues and subsequently others have described patients with multiple saccular aneurysms originating from the free wall of the right atrium and the atrial appendage.[11] In the patients described, atrial dysrhythmias have been causally linked to the atrial aneurysms, and these have been successfully treated in some patients by resection of the aneurysms. A congenital diverticulum of the right atrium situated on the floor of the coronary sinus was reported by Petit and colleagues in 1988.[35] In their report of a 50-year-old man with multiple diverticula of the right atrium, Morishita and colleagues suggest that there has been some difficulty in differentiating between a diverticulum and idiopathic enlargement of the right atrium.[14,17,18] Okita and colleagues report a 3-year-old boy with multiple congenital aneurysms of both right and left atria.[12] This child was known to have fetal supraventricular tachycardia, and recurrent rhythm disturbances which led to echocardiography and angiocardiography where the aneurysms were recognized. They were resected with resolution of the rhythm disturbance; histopathology revealed they were composed of fibrous tissue, attenuated myocardial fibers with an endothelial lining. Surgical excision has been recommended to eliminate a potential source of emboli and for treatment of supraventricular arrhythmia.[11–14,18] We are not aware of spontaneous rupture of a congenital aneurysm or diverticulum of the right atrium.

Diverticulum of the coronary sinus

Diverticulum of the coronary sinus has been recognized with increasing frequency since catheterization of the coronary sinus became routine in invasive electrophysiological procedures.[10,23–37] Imaging of the coronary sinus on the levophase of selective coronary arteriography has also led to an increased

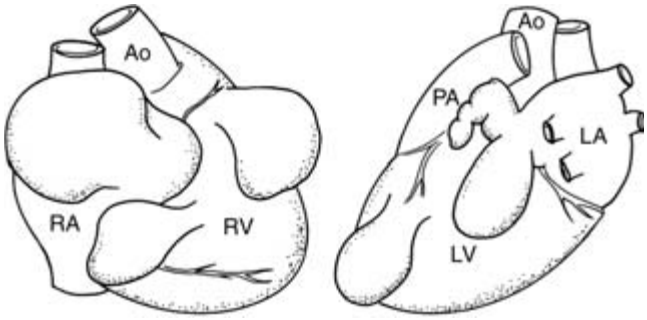

Fig. 39-1 Various cardiac diverticula. A composite drawing shows diverticula arising from the right atrium (RA), right ventricle (RV), left atrium (LA) and left ventricle (LV). Ao, aorta; PA, pulmonary artery.

awareness of abnormalities of coronary sinus shape and position, and thus has led to increased focus on variations in coronary sinus anatomy from the pathologist's perspective.[37] McGiffen and Guiraudon and their respective colleagues amongst others have noted the association between diverticulum of the coronary sinus and the Wolff–Parkinson–White syndrome.[23–32] This association is not always present as in the report of Hamano and colleagues.[36] The coronary sinus diverticulum reported by Di Segni and colleagues was diagnosed by echocardiography in a 2-day-old baby with a hypoplastic left heart syndrome.[33] Occasionally, more than one coronary sinus diverticulum may be present.[31] An enlarging diverticulum of the coronary sinus has been observed, and for this reason the "neck" of the diverticulum was oversewn.[36]

Right ventricular diverticulum

In the consideration of ventricular diverticulum or aneurysm, the occurrence is far less common in the right ventricle than in the left ventricle.[10,38–56] Bharati and her colleagues discussing a 2-month-old infant with a muscular diverticulum of the right ventricle states that there are two types of right ventricular diverticula, muscular and fibrous.[38] A diverticulum of the right ventricle may originate from the apex or from the anterosuperior wall. Hofbeck and his colleagues described three patients with diverticulum of the right ventricle associated with a perimembranous ventricular septal defect.[47,50] The diverticulum in these three patients arose from the anterosuperior aspect of the right ventricle at the junction of the inflow and infundibular portions of the right ventricle and in all three patients the diverticulum behaved like an accessory ventricular chamber, contracting synchronously with the ventricular myocardium, consistent as well with a muscular origin. A divided right ventricle was found in 1 of Hofbeck's 3 patients. In the review from the literature of patients with a right ventricular diverticulum conducted by Hofbeck, 5 of the 22 patients had no associated cardiac anomalies. Amongst those congenital heart malformations encountered in this review were tetralogy of Fallot, double-outlet right ventricle, atrioventricular septal defect, and tricuspid atresia.[38,40,43,45,46,47,51] Terai and colleagues reported 2 patients with a congenital diverticulum of the right ventricle and a perimembranous ventricular septal defect.[46] The right ventricle was hypoplastic in one of their 2 patients, and thus at the time of surgical repair of the ventricular septal defect, the diverticulum was not resected. In their review of the literature, they concluded that two-thirds of the reported cases were not true diverticula, but in fact were fibrous aneurysms. Rarely, a patient will be found to have diverticula originating from both ventricles. Bandow and his associates described a 45-year-old man with apparently a congenital diverticulum originating from both the right and left ventricles.[55] Bogers and colleagues described the unusual findings of right and left ventricular diverticula in a patient with Cantrell's syndrome.[51,55,88,102,104,108,109,114,128] Fatal spontaneous rupture of a congenital diverticulum of the right ventricle was responsible for sudden death of a 1-month-old infant with type 1 truncus arteriosus. This outpouching from the free wall of the right ventricular outflow tract was characterized as a congenital fibrous diverticulum.[45] A similar case with a fatal outcome was reported by Farnsworth and colleagues in 1972.[18A] A right ventricular diverticulum in a neonate with severe congestive cardiomyopathy was documented by Laperal in 1994.[56] Two muscular aneurysms of the right ventricle have been recognized in 1 patient. Two of our patients with a large right ventricular diverticulum had associated ventricular septal defects, and in 1 of these patients, fibromuscular left ventricular outflow tract obstruction. There is little clinical information on which to base the decision for intervention. In at least 1 patient investigation of chest pain led to the recognition of the right ventricular diverticulum, and its resection alleviated the pain.[48] In other patients, resection or marsupialization was performed at the time of repair of associated cardiac defects.[39,40,41,43,46] When the diverticulum or aneurysm contracts synchronously with ventricular myocardium, and when serial MRI studies demonstrate no change in size, one can take a conservative posture. In this regard, serial MRI investigations are probably the best imaging modalities to assess and follow patients with aneurysms originating in the atrium or ventricle.[48,49] Paradoxical motion of the right ventricular diverticulum is perhaps more cause for concern, suggesting that the structure is likely thin-walled, fibrous and devoid or nearly so of normal myocardium.[45,48,49] One would also be concerned by the appearance of a right ventricular diverticulum with a very narrow neck as this area may be able to develop disproportionately high systolic pressures. In any patient with a cardiac diverticulum, one should be especially sensitive to adverse neurologic episodes, perhaps indicative of thromboembolic events. Similarly, cardiac palpitations, documented ventricular dysrhythmias, or syncope should provoke concern and focus on the diverticulum as possibly causal.[49,54] Since spontaneous rupture with death has been documented, one must be concerned about the fate of these structures, especially when coexisting cardiac lesions promote high right ventricular pressures. John and colleagues have published the fetal ultrasound of a patient with a right ventricular aneurysm.[54A] This patient had associated supraventricular tachycardia with left bundle-branch block aberrancy. They speculated that this patient could have an atypical presentation of arrhythmogenic right ventricular dysplasia.[54A]

Left atrial aneurysms

An extensive literature defining the clinical features and radiologic/angiocardiographic appearance of the aneurysm of the left atrium has accumulated over the past two decades.[10,57–83] It is of interest that these lesions of the left atrium almost uniformly have been referred to as aneurysms of the left atrium, not diverticulum. These aneurysms considered congenital in origin take their origin from the atrial appendage as well as the atrial wall

itself, although origin from the left atrial appendage is far more common.[64,66,83] Aneurysmal dilatation of the left atrium is frequently associated with mitral valve disease, and this condition is usually recognised in the third and fourth decades of life.[64,69,73] Stone and colleagues and Behrendt and Aberdeen reported an isolated aneurysm of the left atrium in a 5-month-old and a 10-month-old infant respectively, clearly indicating a congenital origin.[64,74] Cabrera and colleagues have reported the peculiar findings of a newborn infant with an aneurysm of the left atrial appendage, ascending aorta and sinus of Valsalva associated with a ventricular septal defect, fibromuscular subaortic stenosis and single coronary artery.[63] The recognition of a left atrial aneurysm has been based on an abnormal chest radiograph, echocardiography, angiocardiography, computerized axial tomography, or magnetic resonance imaging, these investigations often performed in the investigation of supraventricular rhythm disturbances, chest pain, embolic phenomenon, or an abnormal cardiac silhouette.[57–83] In the differential diagnosis of aneurysmal dilatation of the left atrial appendage, a congenital defect of the left pericardium should be considered.[71,72,76,85] It has been suggested that herniation of the left atrial appendage through such a defect may cause it to distend.[57] This association between congenital left atrial aneurysm and partial absence of the left pericardium has been stressed as well by Vargas-Barron and colleagues.[71] These authors indicate the potential difficulty in differentiating between these two conditions. This differentiation is of course important because of the possibility of strangulation of the left atrial appendage in a small left pericardial defect.[72] The etiology of idiopathic left atrial aneurysm or atrial diverticula is unknown. Accorsi and colleagues advance the hypothesis that idiopathic atrial dilatation could be due to a degenerative process affecting the atrial components derived from primitive atria, in which the muscular layer is structured into pectinate muscles.[79] They also distinguish, even from the etiopathogenetic point of view, between aneurysmal dilatation (localized and fortuitous lesion) and generalized dilatation (diffuse degeneration of pectinate muscles). This distinction could well be related to the different outcomes of atrial arrhythmia in the two types of dilatation.

Surgical resection of the left atrial aneurysm has been necessitated by chronic rhythm disturbances, thromboembolic phenomenon, and a changing size of the aneurysm. In some asymptomatic patients where serial imaging has not demonstrated a progressive change in the size of the aneurysm, a "wait and see" approach has been taken. It is likely that most of these patients will eventually require surgical intervention. Whether these patients before surgical resection (? or after) should be fully anticoagulated or placed on an anti-platelet factor is unclear.

Left ventricular diverticulum and aneurysms

It has been suggested that the congenital left ventricular diverticulum or aneurysm constitutes about 0.05% of all congenital heart malformations. A muscular left ventricular diverticulum can originate from either the cardiac apex or base.[10,84–129] When the diverticulum originates from the apex of the left ventricle, it is often associated with a midline thoracoabdominal defect; i.e. the Cantrell–Ravitch syndrome.[51,55,88,102,104,108,109,114,128] This syndrome is characterized by midline supraumbilical wall defect, cephalocaudal sternal wall shortening, deficiency of the anterior portion of the diaphragm, a congenital pericardial defect, intracardiac abnormalities and frequently cardiac malposition. A pulsatile mass in the relatively superficial epigastrium is very suggestive of this unusual constellation of visceral and cardiac anomalies.[51,55,88,102,104,108,109,114,128] When the left ventricular apical diverticulum is associated with an abdominal wall defect, the diverticulum protrudes inferiorly and forward into the epigastrium through a midline hernia sac and it is contained within a serous sac that is continuous with the pericardium. The diverticulum freely communicates with the left ventricular cavity, and contracts synchronously with the left ventricle. Other left ventricular diverticula may occur singly or multiply from the diaphragmatic surface of the left ventricle, may be muscular or fibrous, and thus may contract synchronously or paradoxically. Kato and his colleagues found 2 such cases amongst 3000 left ventriculograms.[89] The aneurysms usually have a wide orifice of communication with the true left ventricular chamber. While many such aneurysms of the left ventricle are considered congenital in origin, some being recognized from fetal echocardiography, there is a wide spectrum of etiologies including ischemic/infarction, traumatic, inflammatory, sarcoid, cardiomyopathy, etc.[1,2,7,8,105–107] The recognition of those aneurysms/diverticula not associated with midline thoracoabdominal defects may be incidental to evaluation of a ventricular rhythm disturbance, other structural or congenital cardiac anomalies, from echocardiographic and angiocardiographic evaluation of possible ischemic heart disease or a primary cardiac muscle disorder.[59] Some ventricular aneurysms are calcified, and others have been recognized in the setting of hypertrophic cardiomyopathy or Ebstein's anomaly of the tricuspid valve.[105] In those patients with so-called apical left ventricular aneurysm or diverticulum in the setting of hypertrophic obstructive cardiomyopathy, one must exclude mid-cavity obstruction.[105,106] We have studied 2 patients with a large left ventricular diverticulum producing the image of a bifid left ventricle. Both patients had some features of a congestive cardiomyopathy, but 1 could not implicate an ischemic etiology.[10] Certainly some left ventricular aneurysms in infants and children have a clear-cut ischemic basis, including those patients with an anomalous left coronary artery from the pulmonary trunk; infantile coronary calcinosis, or a sequela of Kawasaki disease. In other patients, the left ventricular aneurysm clearly has its origin in an inflammatory etiology. The appearances of the left ventricular diverticulum or aneurysms are diverse. Some are tiny and multiple, but do not require intervention. Others are dealt with at the time of repair of associated cardiac malformations in the setting of Cantrell's syndrome. Some fetal left ventricular aneurysms and those identified in the neonates will remain stable and perhaps as the left ventricle remodels, they may become less conspicuous. As with other forms of cardiac diverticula and aneurysms, the indications for surgical intervention are "soft." Clearly an enlarging aneurysm, one associated with important ventricular arrhythmias, and paradoxical motion of the aneurysm may be indications for intervention. Paradoxical motion of the aneurysm may suggest that the aneurysm is thin-walled and fibrous, and thus may be at risk for spontaneous rupture.

Subvalvar aneurysms of the left ventricle constitute a rare form of heart disease first described in the Black African, and then also found in other tropical parts of the world, i.e. South America and India.[130–139] These aneurysms are submitral or subaortic, sometimes congenital and originating in the aortic–mitral fibrosa, or what is termed now the attenuated left-sided

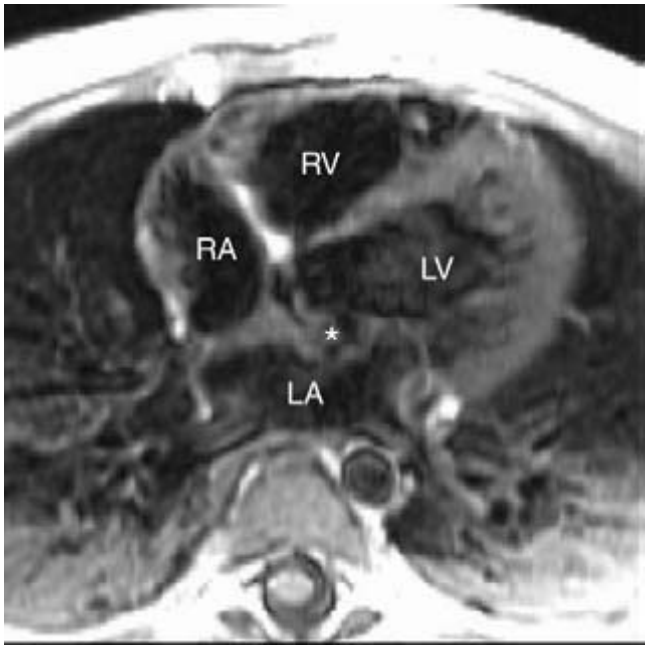

Fig. 39-2 Aneurysm of the central fibrous body. An aneurysm (asterisk) arises from the junction between the aortic and mitral valves and projects into the left atrium (LA). LV, left ventricle; RA, right atrium; RV, right ventricle.

ventriculoinfundibular fold (Fig. 39-2).[140–142] These aneurysms are non-ischemic and are of unknown etiology. Clinical recognition is difficult, as symptoms and findings are non-specific including tachyarrhythmias, systemic embolism, and mitral regurgitation.[88–92] The recognition is facilitated by echocardiographic and angiocardiographic imaging. Normann documented a subvalvular aneurysm in a 34-year-old black woman that had developed beneath the left coronary cusp of the aortic valve and extended in the epicardium between the aortic root and left atrium.[116] This woman was asymptomatic until she expired suddenly from myocardial ischemia caused by compression of the circumflex coronary artery by the aneurysm. A review of the literature conducted by this author revealed 13 reports of subaortic and 58 submitral aneurysms but only two instances of myocardial infarction secondary to coronary artery compression by spontaneous subvalvular aneurysms in either the subaortic or submitral position. Definition of this unusual expression of left ventricular submitral aneurysm has been made with transesophageal echocardiography and left ventricular angiocardiography. Because of the tendency for spontaneous rupture, adverse thromboembolic events and ventricular rhythm disturbances, most consider recognition of this entity an indication for surgery.[133–137]

Gelehrter and her colleagues have reported 9 children with left ventricular outflow tract pseudoaneurysms complicating congenital heart disease in 8 of these.[143] Seven of the 9 patients had left ventricular outflow tract pseudoaneurysms originating in the aortomitral intervalvular fibrosa and in 2 the pseudoaneurysm originated in the native right ventricular free wall following complex left ventricular outflow tract surgery. Seven of the 9 patients were asymptomatic on presentation. One baby with coarctation and a large ventricular septal defect was found at birth to have a left ventricular outflow tract pseudoaneurysm. This mass compressed the left atrium and pulmonary vein. This patient died at surgery. One other patient died late after repair likely due to myocarditis.[143] With the exception of the 1 patient with normal intracardiac anatomy, the others tended to have left-sided obstructive lesions.

Atrioventricular septal or valve diverticulum

In the investigation of a 63-year-old woman for severe aortic regurgitation, Lin and colleagues found a diverticulum or aneurysm of the atrioventricular membranous septum without any communication. This was demonstrated both by transesophageal echocardiography and left ventriculography.[125] Gerlis and his colleagues have recorded at post-mortem a diverticulum of the atrioventricular valve in a patient with right atrial isomerism.[126] This rare condition was not diagnosed during life. Finally, as stated earlier, the aneurysm of the membranous interventricular septum is rarely that, but rather tricuspid valve tissue adherent to the margins of the perimembranous ventricular septal defect.[144]

All references can be found at the end of the book. See pp. 816–20 for Chapter 39.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Freedom and Shi-Joon Yoo

Cardiac Tumors

While cardiac tumors are not truly congenital heart malformations, they are with increasing frequency being detected in the fetus. After birth their clinical presentation can certainly simulate congenital heart malformations. Considerable literature concerning cardiac tumors in infancy and childhood has accumulated summarizing the prevalence, histologic types, clinical presentation and outcome, and changing imaging algorithms.[1–50] We have previously reviewed our institutional and thus pediatric experience with cardiac tumors,[30] and have recently published a selected review of cardiac tumors in the pediatric age group stressing imaging algorithms.[51] This chapter will focus primarily on the cardiac rhabdomyoma and fibroma, the two most common cardiac tumors in the pediatric population.

The ability to detect cardiac tumors non-invasively has led to an apparent increase in this diagnosis.[25,30] It is unlikely that this increase reflects a true increase in incidence or prevalence, but rather a manifestation of changing diagnostic/imaging practice.[29–51] This apparent increase in the diagnosis of cardiac tumors has been noted by the Mayo Clinic as well.[25] While for many years, cardiac angiography was considered the "gold standard" for the diagnosis of cardiac tumors,[11,50] today, cardiac ultrasound, computerised tomography and magnetic resonance imaging have largely supplanted invasive imaging.[29–49] Cardiac angiography including selective coronary arteriography may be required to define coronary arterial involvement/compression by the cardiac tumor.[50] However, as one reflects on the nature of cardiac imaging in the diagnosis of cardiac tumors, it is evident that echocardiography has emerged as the current primary diagnostic modality.[31–37] Its non-invasive nature has allowed for earlier detection in asymptomatic patients. Delineation of tumor location and extent and tissue characterization by magnetic resonance imaging have been important advancements.[36A] Tranesophageal echocardiography provides superior image quality and readily visualises the left atrial appendage, superior vena cava and the anterior surface of the heart.[31–37] These areas are less readily imaged from transthoracic echocardiography. In the future dynamic three-dimensional echocardiography may provide exact spatial information in intraoperative views. Finally, computerized tomography and magnetic resonance imaging provide complementary information about intra- and pericardiac masses in the pediatric population.[38–49]

Incidence

Data from the New England Regional Infant Cardiac Program showed of 2251 infants surveyed by this program with congenital heart disease, 11 had cardiac tumors, including 2 mediastinal tumors, 3 pericardial, and 6 cardiac tumors.[26] Primary heart tumors are uncommon in all age groups, with an incidence of 0.0017% in a large autopsy series reviewed by Straus and Merliss.[27] Nadas and Ellison reviewing the large pediatric experience of the Boston Children's Hospital cited a frequency of 0.027% among 11 000 pediatric autopsies.[22] These studies were all carried out before the routine application of cross-sectional echocardiography. Data published from our institution showed that from 1980 to 1995, 27 640 patients from fetuses to 18 years of age were referred or assessed for cardiac disease, and 56 of these had primary cardiac tumor.[30] The mean age at diagnosis of these patients was 27 ± 40 months, with the median age at diagnosis 4.7 months, ranging from 0.03 to 204 months. More than 50% were < 1 year of age at the time of diagnosis, with 10 patients diagnosed in the first month of life and 8 in the first week. A prenatal diagnosis was made in 12 patients.

The cardiac rhabdomyoma

As summarised by Becker, the presentation of the cardiac rhabdomyoma is diverse, leading in some to stillbirth or perinatal death.[52] In other patients clinical findings are dominated by cardiomegaly, congestive heart failure, cardiac rhythm disturbances and less commonly by sudden unexpected death. The clinical impact may be in large part determined by the tumor size, its or their location and whether or not they expand into an atrial or ventricular cavity, and whether the tumor mass obstructs the ventricular inflow or outflow. Cardiac rhabdomyomas tend to be multiple although solitary tumor masses have been described (Figs 40-1, 40-2).[52–126] The cardiac rhabdomyoma is a benign tumor of cardiac myocytes. It is considered by some a hamartoma occurring exclusively in the heart, often as multiple nodules composed of altered myocytes with large vacuoles and considerable glycogen. Observations about the regression process lend support to the fact that the cardiac rhabdomyoma is more likely neoplastic in origin rather than being a hamartoma.[76] The specific cell type that gives origin to the cardiac rhabdomyoma is still the subject of scientific debate,[63,104] although many believe these tumors have a myocardial origin, possibly representing aberrant development of cardiac myocytes.[63,76]

Cardiac rhabdomyomas occur in three clinical groups: (1) with tuberous sclerosis (30–50% of cases); (2) as sporadic lesions; (3) rarely in association with congenital heart malformations.[52–120] They have similar gross appearance in these settings; however, with tuberous sclerosis the rhabdomyomas are

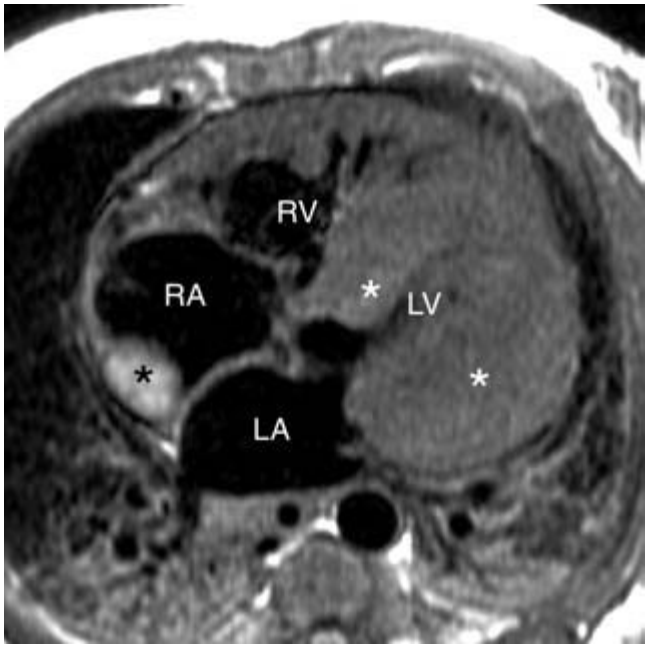


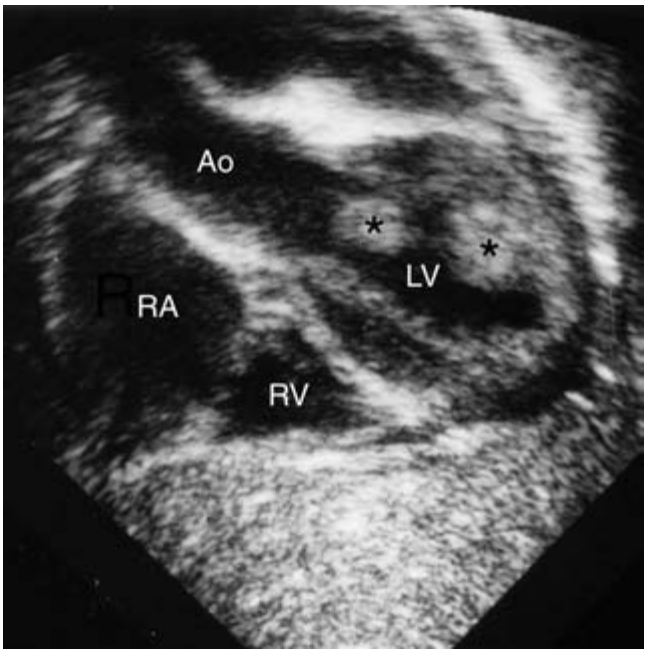
Fig. 40-1 Rhadomyomata in a young neonate. T1-weighted MR image in axial view shows multiple tumors (asterisks). The high signal intensity of the right atrial tumor around the crista terminalis suggests hemorrhage. The patient developed arrhythmia. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

usually multiple. The lesions vary from 1 mm to 10 cm in diameter. They most often occur in the ventricles but can be found in the atria, at the cavoatrial junction and on the epicardial surface.[63,104] Large lesions can obstruct outflow or inflow tracts.[10,11,30,50,54,57,59,60,67,76,78,79,86,87,91,92,98,104] Small lesions can involve the conducting system causing dysrhythmias.[10,30,43,65–67,72,85,91,92,100] The tumors are lobulated, tan-white, and often have a glistening watery cut surface. Hemorrhage and calcification are rare.[104] Sporadic rhabdomyomas more often are larger than those seen with tuberous sclerosis.

Multiple rhabdomyomas have been observed in identical twins,[118] a most unusual occurrence. Molecular genetic advances are likely to shed light on the etiology of cardiac tumors, whether or not associated with the phakomatoses.[121,122]

The tuberous sclerosis complex

Cardiac rhabdomyoma is often associated with the tuberous sclerosis complex (TSC) (Fig. 40-1).[51–103,108–110,114–117] The TSC is an autosomal-dominant disorder with a high mutation rate, characterized by the widespread development of distinctive tumors termed hamartomas. affecting brain, heart, skin, kidneys, and other organs. TSC-determining loci have been mapped to chromosomes 9q34 (TSC1) and 16p13 (TSC2).[51] The TSC1 gene was identified from a 900-kb region containing at least 30 genes. The 8.6-kb TSC1 transcript is widely expressed and encodes a protein of 130 kDa (hamartin) that has homology to a putative yeast protein of unknown function. Thirty-two distinct mutations were identified in TSC1, 30 of which were truncating, and a single mutation (2105delAAAG) was seen in 6 apparently unrelated patients. In 1 of these 6, a somatic mutation in the wild-type allele was found in a TSC-associated renal carcinoma, which suggests that hamartin acts as a tumor. More specifically, the tuberous sclerosis syndrome or complex is characterized by intracranial hamartomas, facial angiofibromas, subungual fibromas, linear epidermal nevi, renal angiomyolipomas, and other hamartomas. The necropsy study published some years ago by Fenoglio reported a 30% incidence of cardiac rhabdomyoma in patients with tuberous sclerosis, and clinically the association



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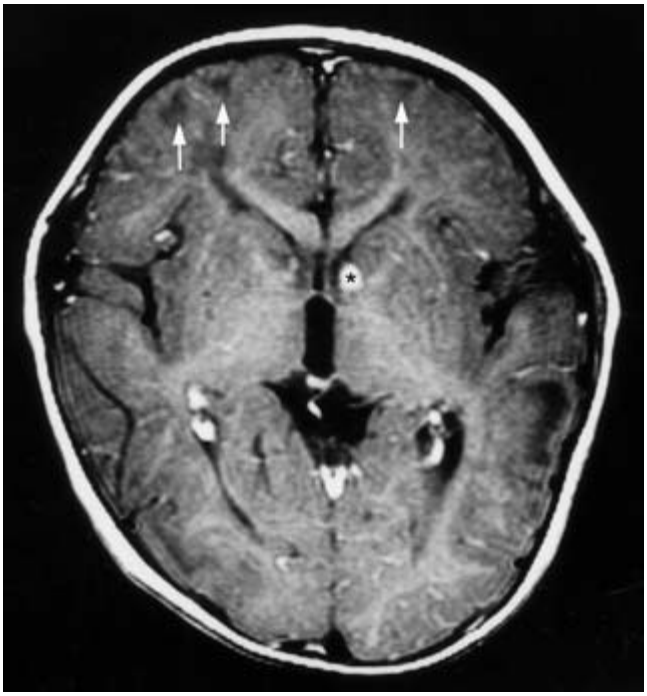

B

Fig. 40-2 Rhabdomyoma with tuberous sclerosis in an 1-year-old infant. **A**. Subcostal echocardiogram shows rhabdomyomas (asterisk) in the left ventricle (LV). **B**. Contrast-enhanced T1-weighted MR image of the brain shows a subependymal tuber (asterisk) along the frontal horn of the left lateral ventricle and multiple subcortical tubers (arrows). Ao, aorta; LV, left ventricle; RA, right atrium; RV, right ventricle.

may be as high as 50%.[63] The cardiac rhabdomyoma tends to be multiple, indeed they are multiple in > 90% of patients, *frequently involving* the interventricular septum, the walls of the heart, appearing as filling defects in the cavities of both ventricles, with a special predilection to involving the left ventricular outflow tract. These tumors may interfere with cardiac filling, and tumors approximating the tricuspid valve have simulated tricuspid atresia and those obstructing the mitral inflow have simulated mitral atresia and the hypoplastic left heart syndrome. Subaortic stenosis has been a common finding in the infant with cardiac rhabdomyomata, with pedunculated tumors in the subaortic vestibule. Superior or inferior caval vein obstruction is well recognized in the baby or young infant with cardiac rhabdomyoma. Patients with cardiac rhabdomyomas may present with almost any type of atrial or ventricular dysrhythmia, including pre-excitation, sinus node dysfunction and heart block. Fetal dysrhythmias or hydrops may be the presenting features in some patients with cardiac rhabdomyoma. Indeed, fetal recognition of multiple cardiac tumors has been considered suggestive of the tuberous sclerosis complex.[45,46,64,69,78,94,95,102,123,124,125] Cardiac rhabdomyomas are often diagnosed in the first year of life, and there is now increasing experience with fetal recognition of these tumors. Rarely, complex congenital heart disease may be associated with multiple cardiac tubers as in the patient with the hypoplastic left heart syndrome reported by Watanabe and colleagues[99] and other forms of congenital heart disease.[109,120] Other associations of the cardiac rhabdomyoma is with the basal cell nevus syndrome.[101] Rarely the fetal expression of cardiac rhabdomyomas is that of diffuse myocardial thickening.[102,115] One would not expect pericardial involvement with cardiac rhabdomyomas because of the origin of this tumor in the cardiac myocyte.

Spontaneous regression of cardiac rhadomyoma

One of the peculiar and puzzling aspects of these tumors is the observation of spontaneous regression.[10,29,30,43,52,58,75,91,92,100,126] This clinical phenomenon has now been extensively documented. We identified 44 patients with cardiac rhabdomyoma at the Hospital for Sick Children over the past 20 years.[91] Partial or complete regression of the rhabdomyomas was identified in 54% of the patients. The mean age at diagnosis for those patients whose rhabdomyomas regressed was 21 ± 30 months and the mean follow-up was 5.6 ± 3.0 years. Findings of tuberous sclerosis were observed in 18 of our 44 patients with rhabdomyoma (40.9%). Farooki and his colleagues reviewed the course of 4 neonates with 12 tumors.[62] All tumor masses except those in the right atrium demonstrated spontaneous regression. Indeed, there are ever increasing reports of spontaneous regression in these tumors. In cataloguing those tumors that tended to regress, Choi and colleagues have shown that complete regression occurred more frequently in younger patients and not surprisingly in those with smaller tumors.[92] Thus surgery is recommended only for those patients with severe hemodynamic compromise or for those with refractory dysrhythmias. One must realize that even with regression of cardiac rhabdomyomas, a substantial number of patients will still be disadvantaged by the cerebral and general organ involvement of tuberous sclerosis. In this regard it may be difficult to give a neurologic prognosis for the affected neonate. Data provided by Nir and associates reviewing the Mayo Clinic experience with cardiac rhabdomyoma showed that these tumors regressed both in number and size in most patients < 4 years of age.[100] Spontaneous regression in the fetus of cardiac rhabdomyoma has also been observed. Progression in size of these tumors secondary to corticotropin therapy has also been noted.[70,112] Corticotropin has been used to treat infantile spasms in these patients.

Those fundamental biological mechanisms governing spontaneous regression of the cardiac rhabdomyoma have not been defined, and clearly those mechanisms promoting selective cardiac apoptosis are intriguing.[76,76A] Wu and colleagues have studied the regression process of cardiac rhabdomyomas.[76] They found that that the cytoplasmic contents of the cardiac rhabdomyoma are degraded via the ubiquitin pathway, and this group observed increased TUNEL positivity, possibly explaining the mechanism of tumor regression or apoptosis. There are fewer data indicating spontaneous regression of cerebral involvement of tuberous sclerosis, and indeed spontaneous regression of cerebral tubers has not been seen. Thus the tragedy for many patients is the reality that spontaneous regression of the cardiac rhabdomyoma does not underscore well-being, as these patients may still be severely disadvantaged by cerebral and renal involvement, with the tendency towards malignancy in these areas. In this regard, Pipitone and colleagues identified nine cases of cardiac rhabdomyoma detected among 5276 fetal echocardiograms recorded over a 10-year period in a single center. The incidence of cardiac rhabdomyoma in this series was 0.17%. The gestational age at diagnosis ranged from 27 to 36 weeks. The most common reason for fetal echocardiography was an abnormal obstetric ultrasound scan (6/9 cases). In no case was there a family history of tuberous sclerosis. In one case, the tumor was single whereas in 8 cases multiple tumors were diagnosed. During prenatal life the majority of tumors were clinically silent. One fetus died of hydrops and arrhythmia. Four children presented with arrhythmia postnatally and one required surgery. At a mean follow-up of 47 months, total or partial regression was observed in 7 patients. Seven patients developed postnatal clinical signs of tuberous sclerosis.[112A] Others have also studied the prenatal and postnatal outcome of cardiac rhabdomyomas, with case reports showing tumor growth during the late stage of gestation.[45,54,69] It is of interest that Guntheroth and colleagues have documented spontaneous regression of myxoma-like tumors of the aortic or pulmonary valves in infants.[126A]

Cause of death in patients with tuberous sclerosis

The Mayo Clinic has reviewed the causes of death in patients with tuberous sclerosis.[105] Reviewing the fate of 355 patients with the tuberous sclerosis complex, their data showed a decreased survival when compared to the general population. The median age of their patients was 26 years, reflecting in part the referral nature of Mayo Clinic practice. They listed the causes of death related to renal abnormalities; brain tumors; cardiovascular involvement; lymphangio-myomatosis; bronchopneumonia; and status epilepticus. In this series, the most common cause of death was renal disease in the form of angiomyolipomas, cysts, or both. Subependymal giant cell astrocytomas occurred in 6% of patients. Pulmonary involvement is uncommon, occurring in < 1% of patients. The pathologic features are similar to those of lymph angiomyomatosis of the lung: cystic changes and focal lymph angiomyomatosis. Relatively few children and fetuses were encompassed in the Mayo Clinic

study and thus the survival curve is likely to be even more abnormal. Certainly patients with the tuberous sclerosis complex should be periodically screened for vascular aneurysms involving the thoracic aorta, the abdominal aorta and carotid artery amongst other sites. Some of these aneurysms have been noted to spontaneously rupture, causing death.[108,116,117] A wide range of cardiac arrhythmias have been documented in patients with cardiac rhabdomyoma, including ventricular arrhythmias and pre-excitiation.[72,83,85] Sudden death has also been attributed to these tumors.[105A]

Cardiac fibroma

The cardiac fibroma is the second most frequent cardiac tumor identified in the neonate and infant after the rhabdomyoma. The cardiac fibroma is a benign congenital tumor that occurs as a discrete bulging mass composed primarily of fibroblasts and collagen.[1–3,6,10,11,18,19,22,30,127–156] This tumor has also been called fibromatosis and fibroelastic hamartoma. The exact nature of the cardiac fibroma is unclear and there is ongoing debate as to whether the cardiac fibroma is a benign neoplasm or hamartoma.[106] This tumor is less common than the rhabdomyoma in the neonate and our institution has recognised less than 10 patients with cardiac fibroma in the past 15 years. Burke and his colleagues reviewed the files of the Armed Forces Institute of Pathology, identifying 23 cases of cardiac fibroma[135] The mean age at the time of diagnosis was 13 years, ranging from 1 day to 56 years. More than one-third of the patients were younger than 1 year of age at the time of diagnosis. This tumor, usually solitary, unlike the rhabdomyoma most often involves the left ventricular free wall or septum (Fig. 40-3). Rarely, more than one tumor is present,[153] and this can make differentiation from the rhabdomyoma more difficult. Involvement of the right ventricular free wall and cavity and the atria is less frequent, but is well described. The cardiac fibroma is not encapsulated and its tissue blends or infiltrates normal myocardium. Cut surface shows a bosselated or whorled pattern. Focal calcification is frequent and there is occasionally cystic degeneration. Both of these features are uncommon in the rhabdomyoma. They average 5 cm in diameter. Large lesions obstruct outflow tracts and compress cardiac chambers. Their growth is confined to the myocardial mass but they can incorporate proximal segments of coronary arteries precluding complete surgical removal. When they originate near or in the right atrioventricular groove, such tumor masses may compress the tricuspid inflow and may promote right-to-left intracardiac shunting in the neonate and young infant. The constituent cells of cardiac fibromas are spindled, monomorphic, and cytologically bland. In neonates and young infants tumors are cellular, may show mitotic activity, and have fibromyxoid stroma with variable numbers of collagen and elastic fibers. Collagen and elastin deposition increases and cellularity decreases with age. The tumor has an infiltrative border, surrounding and entrapping cardiac myocytes.

The tissue characteristics of the fibroma are considerably different than the rhabdomyoma, and thus non-invasive assessment with MR imaging can usually differentiate between fibroma and rhabdomyoma.[154–157] This tumor is benign, but continued slow growth may cause conduction defects, spread to the ventricular free wall, and may result in atrioventricular valve inflow or arterial outflow tract obstruction. Cardiac fibroma has presented in the neonate as severe congestive heart failure. Rarely this tumor may simulate cyanotic heart disease in the newborn because of septal and right ventricular involvement, promoting right-to-left shunting at atrial level. Two of the three neonates seen in our institution in the last decade presented in a state of cardiovascular collapse, were profoundly acidotic, had very weak peripheral pulses, and before application of cardiac ultrasound were considered to have the hypoplastic left heart syndrome or other expressions of diffuse left ventricular outflow tract obstruction. Spontaneous regression of the type seen in the patient with cardiac rhabdomyoma has not been

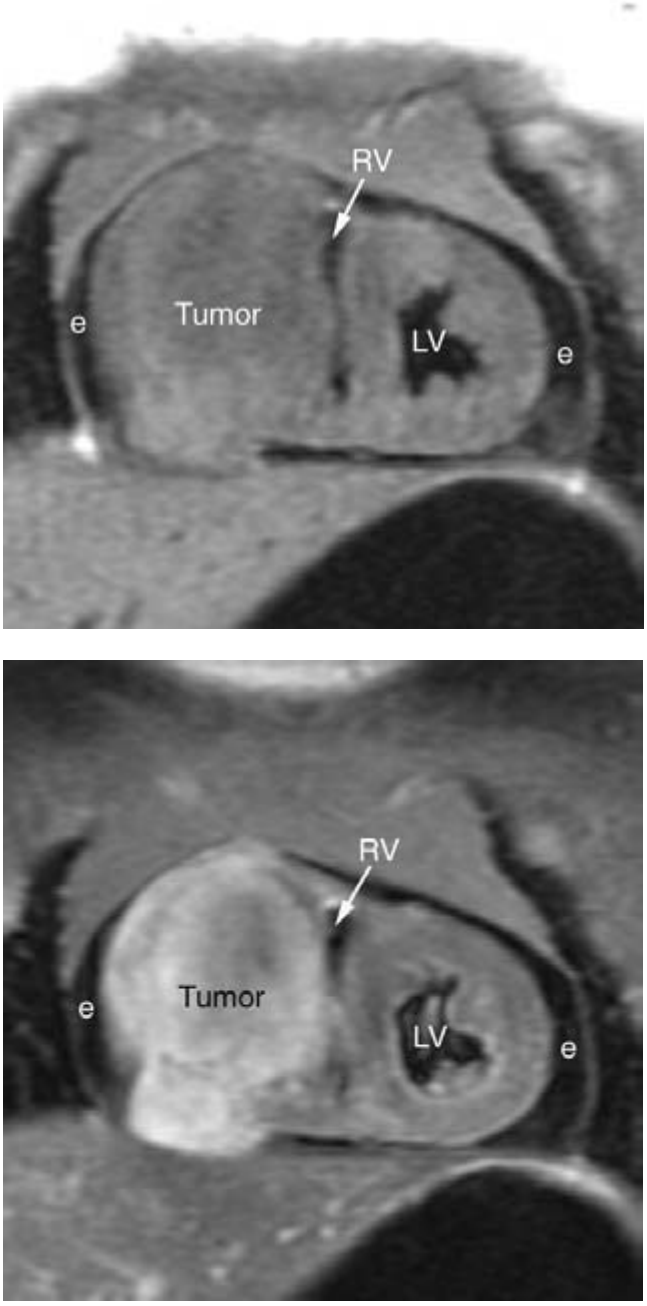

Fig. 40-3 Fibroma involving the right ventricular free wall. **A**. T1-weighted MR image in coronal plane shows a large tumor involving the free wall of the right ventricle (RV). The signal intensity of the tumor is similar to that of myocardium but a little heterogeneous. **B**. Contrast-enhanced T1-weighted MR image with fat saturation shows heterogeneous enhancement of the tumor. e, pericardial effusion; LV, left ventricle.

observed in the patient with cardiac fibroma, and operative intervention is usually required. One must remember that a massively hypertrophied ventricular septum in the newborn is not always neoplastic, but may represent a hypertrophic cardiomyopathy. Ventricular tachycardia and an abnormal cardiac silouette on chest x-ray in the infant and child may be considered presumptive evidence of a cardiac fibroma. The fibroma of the right or left ventricle may be partially or wholly resectable.[129,135,139,141,142,144,148,151,158,159] When the tumor often proves unresectable and cardiac transplantation has been performed in such patients, both in the pediatric patient as well as in the adult.[156,160] We have palliated two infants with a important right ventricular fibroma by partial resection, but we added a bidirectional cavopulmonary connection to provide a stable source of pulmonary blood flow and to unload the right ventricle.[149] Two neonates with huge left ventricular fibromas have undergone transplantation in our institution. Occasionally a neonate with a huge tumor will be asymptomatic and one can cautiously follow these patients.[150] The caveat in "wait and see" approach is of course the potential for sudden cardiac death.[152,161,162] Clonal translocation has been documented in the cardiac fibroma and some suggest that karyotyping should become a routine component of the characterization of cardiac tumors.[163,164]

Finally, myxomas, vascular tumors benign and malignant, teratomas, etc., may of course affect the pediatric patient.

All references can be found at the end of the book. See pp. 820–4 for Chapter 40.

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41A

Robert M. Freedom

Conjoined Twins

How does one begin a chapter on conjoined twins? We are all concerned by the ethical issues that such patients force on their parents and caregivers: "'Do we murder Mary to save Jodie?' An ethical analysis of the separation of the Manchester conjoined twins."[1] Or maybe: "Parents of Siamese twins appeal against separation."[2] And what about the cost to society – "'$1 million' treatment for Siamese twins re-ignites cost debate."[3] And to the heart of the matter: "Two hearts beating as one."[4] The titles of these papers are "catchy," and serve to focus our attention on most of the issues germane to these patients.

There is no doubt about it, conjoined twins are uncommon, with a prevalence suggested between 1:33 000 and 1:165 000 births, with Hansen's estimate of 1:50 000.[5–7] Some years ago, an epidemic of conjoined twinning was suspected in South Africa and Cardiff, although some disputed this report.[8,9] Conjoined twins are classified according to the area of union, the most common site of conjunction being the anterior thoracic and upper abdominal midline, such twins designated as thorapagus or thoracopagi.[5,6] Twins with thoracic union have a high incidence of cardiac anomalies.[5,6] They are considered the product of a single ovum and like separate monozygotic twins, they are of the same sex, presumably have identical genetic constitutions, with similar palmar and plantar epidermal characteristics. Conjoined twins have a striking female predominance (70–95%).[5–7, 10–19] This malformation of monozygotic twinning results when there is incomplete division of the single fertilized egg. The basic defect is an incomplete fission which takes place before the third week of ovulation age. Fortunately very rare, the impact of thoracopagus conjoined twins is not just conjunction of their livers, but of their hearts. From the numerous case reports and review of larger series in the literature of thorapacopagus conjoined twins, the impact of the cardiovascular junction is clearly the most serious, and disturbances in laterality are frequent.[5–7,10–23]

Thoracopagus twins are the most common of conjoined twins, accounting for about 75% of all conjoined twins. They are frequently born prematurely, or are stillborn, but there is increasing prenatal recognition and fetal diagnosis of the associated cardiac malformations.[24–29] The severity of the visceral malformations depends in large part on the extent of the area of union, and the pleural, pericardial, and peritoneal cavities may be common to both twins, or separate. In virtually all cases of thoracopagi, the livers are fused.[5–7,10–29] Somewhat surprising, despite the external symmetry of thoracopagi, their viscera are not necessarily identical, nor mirror-images of one another. Indeed, one twin has been identified with asplenia and lack of organ lateralization, while the other twin has had normally lateralized viscera.[10,21–23]

The cardiovascular systems

As summarized by Gerlis and his colleagues from their extensive examination of conjoined twins, the cardiovascular system in conjoined twins can be described on the basis of the number and nature of the heart(s) and their location within the body.[10] Some conjoined twins had a single heart, but in others partial duplication of cardiac elements forming a single cardiac structure was identified. Gerlis designated this latter arrangement as a compound heart. The situation is made even more complex by the topography of the heart within the twins. The sternum, heart, and spinal columns may be in a single plane, and the heart is then readily assigned to one or the other twin. In some of the twins, however, the heart(s) and sternum are arranged at right angles to the plane between the two spinal columns, and thus neither heart can be assigned to either twin, and these hearts are considered shared. The sternum is partially or wholly absent or deficient in thoracopagus conjunction. Data summarized by Edwards indicates that the pericardial sac was common to both twins in 90% of reported cases, and that fusion of the heart is found in 75%.[12] Three following types of cardiac fusion have been described: pericardial conjunction; atrial fusion with separate ventricles; and atrial and ventricular fusion. Considering the potential and indeed reality for such complex arrangements between the twins, this is probably somewhat of an oversimplification.[5–7,10–29]

The majority of babies with conjoined hearts exhibit complex ventricular anatomy, with one ventricle for both twins; two ventricles (single ventricle for each twin); three ventricles (one ventricle for one twin, and two for the other); and four ventricles. The majority of patients also have complex conotruncal malformations, with complex transposition; pulmonary atresia; truncus variants; hypoplastic left ventricle syndrome, etc. With atrial and ventricular fusion, the circulation is very complex and may be difficult to unravel even at the autopsy table. So-called "figure-of-eight" circulations have been described in babies with atrial and ventricular fusion.[30,31] The cardiac apices usually point in the opposite direction.[5,10,12,13] Rarely, the ventricular masses of conjoined twins may be contiguous, but non-fused, lending themselves to successful separation as in the case reported by McMahon and colleagues.[13A]

Right isomerism and left atrial isomerism have been described in thoracopagus twins, indicative of the tendency of symmetry both in external appearance and in the disposition of viscera so common to thorapagi.[10,21–23] Ursell and Wigger have described a set of thoracopagus twins who did not demonstrate this internal symmetry.[21] In this particular patient, one twin had

asplenia with disturbed laterality of viscera, while the other twin had a normally lateralized visceral arrangement.[21] Of the 6 cases with two conventional hearts in the review of Gerlis, no instance of disturbed laterality was found in both twins despite the finding of right isomerism of the heart of the right-side twin in one case and left isomerism of the heart of the right-side twin in one case.[10,21–23]

The diagnosis of conjoined twins is made with increasing frequency by fetal ultrasound. For the most part, invasive imaging for the investigation of the cardiac abnormalities in conjoined twins has been replaced by a combination of electrocardiography, cross–sectional echocardiographic and magnetic resonance imaging.[24–29,32–44] With complex venous anatomy and the potential for atrial and/or ventricular conjunction, cardiac catheterization with angiography may still be necessary.[32–46] Even in those conjoined twins without primary cardiac conjunction, a complex circulatory arrangement may jeopardize one twin at the expense of the other.[47]

Outcome analysis

Once the prenatal diagnosis of conjoined twins is firmly established, most families decide on termination of pregnancy.[27] Sanders has amply discussed those many factors contributing to successful separation of conjoined twins, and the difficult ethical and philosophical dilemmas posed by these children.[1–3,24,29] There has been some success in the separation of conjoined twins who share a common pericardial sac.[13,14,18,35,48] In one set of conjoined twins, ligation of an arterial duct was performed first, followed by successful separation.[49] Chiu and colleagues reviewed to 1994 the outcome of attempted separation of thoracopagus twins.[49A] In reviewing 47 pairs of surgically separated thoracopagus conjoined twins, in 30 pairs of type A (Leachman's classification, completely separate hearts), 42 patients survived (70%); in 5 pairs of type B (atrial connection only), one patient survived (10%); in 9 pairs of type C (both atrial and ventricular interconnections), none survived. The total survival rate of surgically separated thoracopagus conjoined twins was 47.9%. The survival rate was 38.2% in those operated in the neonatal period ($n = 34$) and 63.6% in those operated over 1 month of age ($n = 44$) ($P = 0.016$). But the most important consideration in terms of successful separation was the site or sites of pericardial or cardiac conjunction. Fishman and colleagues have reported cardiac relocation and chest wall reconstruction after separation of thoracopagus conjoined twins with a single heart. One twin survived.[50]

Finally, and unrelated to either conjoined thoracopagi or ectopia cordis, is that extremely rare condition of an infant with two "half-hearts."[51] This 5-day-old baby was found at autopsy to have two "half-hearts" totally separated from the other and each had a single atrium and ventricle. The two "half-hearts" were enveloped in a common pericardium. There were double truncus and double superior and inferior caval veins. The pulmonary venous drainage was totally anomalous, but there were no splenic abnormalities, and the viscera were normally lateralized. Finally, Anderson has provided documentary and artistic evidence for conjoined twins from 16th century England.[52]

All references can be found at the end of the book. See pp. 824–5 for Chapter 41A.

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41B

Robert M. Freedom

Ectopia Cordis (Exteriorization of the Heart)

Ectopia cordis, so-called exteriorization of the heart, is an exceedingly uncommon condition, and can be considered one of the cardiac malpositions along with dextrocardia, mesocardia, conjoined thoracopagi, and the so-called "topsy-turvy" hearts.[1–4] This condition is characterized by complete or partial displacement of the heart outside the thorax.

Prevalence

Ectopia cordis occurs in *c*. 5.5–7.9 per 1 million live births.[1–4] There is only very rarely a familial tendency,[3A] but a number of patients with ectopia cordis and chromosomal abnormalities have been described.

Morphology

Ectopia cordis can be catalogued into four types: (1) cervical; (2) thoracic; (3) thoracoabdominal; (4) abdominal.[1–4] There is only one well-described case of an abdominal ectopia cordis. The cervical form of ectopia cordis is also a very uncommon form of this already rare disorder, and with rare exception is observed only in severely malformed fetuses. The thoracic and thoracoabdominal forms constitute *c*. 97% of the cases of ectopia cordis.[3]

The classic expression of ectopia cordis is the thoracic form. The thoracic form has an associated sternal defect, deficiency or absence of the parietal pericardium, cephalic orientation of the cardiac apex, an omphalocele, and a small thoracic cavity. The thoracoabdominal form of ectopia cordis has received considerable attention, and this form is usually associated with congenital heart malformations.[1–4] In addition to the usually associated cardiac malformations, this type of ectopia cordis is associated with a distal cleft sternum; an omphalocele-like ventral abdominal defect; a midline anterior diaphragmatic defect; and a free pericardioperitoneal communication, the combination being called Cantrell's pentalogy or pentad.[2]

Associated malformations

Amongst those patients with the thoracic or thoracoabdominal forms of ectopia cordis, many forms of congenital heart disease have been identified, including ventricular septal defect, single ventricle, double-outlet right ventricle, and infundibular atresia.[1–14] The more important extracardiac malformations contributing to poor outcome include a large omphalocele and pulmonary hypoplasia. A number of chromosomal abnormalities have been defined in the patient with ectopia cordis.[15–17] Ventricular diverticulum is well recognized in some patients with ectopia cordis[2,3,5,6,14] (see also Chapter 43).

Outcome

There is increasing experience with fetal diagnosis of thoracic ectopia cordis, but when recognized prenatally, many families decide to terminate the pregnancy.[1,5,18] Of the 5 cases of ectopia diagnosed prenatally in the series reported in 2000 by Hornberger, 4 families elected termination of pregnancy.[18] Humpl and colleagues have reviewed the experience of the Toronto Hospital for Sick Children with ectopia cordis.[5] Between 1978 and 1998, 10 patients with ectopia cordis presented to this institution. Three had normal intracardiac anatomy and the remainder had mild to complex structural heart disease. Associated noncardiac malformations were diagnosed in 6 patients. Prenatal ultrasound diagnosed 6 instances of ectopia cordis in fetuses between 19 and 37 weeks of gestation. These pregnancies were either electively terminated or the infants died shortly after birth. Four other babies with ectopia cordis were referred to our institution and died either at the time of surgery for the cardiac or noncardiac anomalies. Hornberger when in Boston and her colleagues reported on the outcome of 13 infants with ectopia cordis and significant heart malformations seen from 1982 to 1996.[6] Four of these 13 had thoracic ectopia cordis and 9 thoracoabdominal. The diagnosis was made *in utero* in 6, with termination of pregnancy in 2 and death before transfer to the Children's Hospital in one. Of the 10 patients postnatally managed at the Children's Hospital, 4 of 8 with thoracoabdominal ectopia cordis and 1 of 2 with thoracic ectopia cordis survived beyond infancy. Three patients underwent complete repair of the cardiac defects, and 2 underwent single ventricle palliation. None of the 5 survivors had significant extracardiac defects, whereas all 3 who died by 3 weeks of age had both a large omphalocele and pulmonary hypoplasia. Thus as one surveys this substantial series and other case reports in the literature, there have been some surgical successes. but because of the associated cardiac malformations and propensity for infection, survival is still uncommon.[2,5,6,9,14,19–23] However, at least 1 patient with thoracoabdominal ectopia cordis and a univentricular heart underwent a successful three-stage Fontan procedure, a right-modified Blalock–Taussig shunt at the age of 1 month, bidirectional Glenn shunt and pulmonary arterioplasty at 2 years 8 months, and finally a total cavopulmonary connection at 4 years.[24] Another patient with tricuspid atresia, currently with a balanced circulation, has undergone successful repair of ectopia cordis and is scheduled for single ventricle-Fontan palliation.[25] Some have reported excellent outcomes for patients with ectopia cordis and congenital heart disease.[26]

All references can be found at the end of the book. See p. 825 for Chapter 41B.

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41C

Robert M. Freedom

Idiopathic Arterial Calcification of Infancy

Idiopathic arterial calcification of infancy is a very uncommon disorder of unknown etiology that is characterized by diffuse arterial calcification, and with rare exception is fatal in infancy.[1,2] First likely described by Bryant and White in 1891,[3] the earliest major review of this disorder was published by Stryker in 1946.[4] Rosenthal mentioned that by 1966 > 50 patients had been reported,[5] and by the millennium, the number is considerably more. The cause of death in most affected patients is invariably related to severe coronary arterial calcification and the resulting myocardial ischemia and infarction.[1,2,5–15] Rarely, the disorder presents later in childhood as in the 11-year-old girl reported by Sebire and Sheppard.[11A]

Prevalence and genetics

This is a very rare disorder and most even very large centers see only a few cases over many decades. There is a well-known familial predilection and a number of sibships have been reported.[1,2,5,6,10,15–21]

Pathology of idiopathic arterial calcification of infancy

This is a disease that begins and has been recognized in the fetus.[22–28] This disorder involves the coronary arteries, as well as the carotid, renal, retinal and other medium sized arteries.[1,2–21] According to Hoffman, the coronary arteries are involved in 90% of patients and renal, pancreatic and splenic arteries in 50% of patients.[1] It is unclear whether idiopathic arterial calcification is a single pathological process or several that overlap with a similar end result.[1,2] The pathological process is uneven and in the same patient, intimal fibrous proliferation dominates in some sections of muscular arteries, while in others, fragmentation of the internal elastic lamina with deposition of calcium is the more conspicuous finding.[1,2,5–7,19,21] Intimal connective tissue proliferates and occludes the vessels, contributing to coronary, myocardial, and renal ischemia, etc. Rarely, there are findings consistent with an inflammatory arteritis,[29,30] and in other patients intimal proliferation is minimal.[31]

Outcome analysis

This disease has been recognized in the fetus and the affected fetus often demonstrated pleural hemorrhage, hydrops and polyhydramnios.[22–28,32] The diagnosis of idiopathic arterial calcification can be made by palpation of the firm, rigid superficial arteries in the neck and limbs [1,2,5,6] and by imaging of the calcified arteries with plain x-ray, CT scan, and MR imaging.[1,2,5,6,33–36] The majority of affected patients present in infancy with congestive heart failure within the first few months of life, many with findings of myocardial infarction.[1,2,5,5–21] A few patients may present with hypertension, reflecting involvement of the renal arteries.[37,38] Other young infants may present with bowel ischemia, severe hepatic involvement suggesting Reye's syndrome, and infrequently cerebrovascular pathology will dominate the clinical picture.[18]

Survival into adulthood is distinctly uncommon, but this has been reported as has intermediate-term survival.[39–41] In an occasional patient, peripheral vascular insufficiency may dominate the clinical picture.[42] There has been some success with the therapeutic use of bisphosphonates, but this has not been universally effective.[1,2,10,14,17,20,27,39–41,43] Sholler and his colleagues have also reported 3 patients, 1 demonstrating spontaneous regression of calcification.[15]

All references can be found at the end of the book. See pp. 825–6 for Chapter 41C.

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41D

Alejandro R. Peirone, Robert M. Freedom, and Shi-Joon Yoo

Persistent Fifth Aortic Arch

The persistence of the fifth aortic arch is an uncommon congenital heart malformation in humans (Figs 41D-1, 41D-2). In the past, its existence has been a matter of embryologic dispute, because in Mammalia the fifth pharyngeal pouch develops poorly and the associated fifth branchial artery was considered to be similarly indistinct and evanescent by authors such as Balinsky,[1] Arey,[2] Langman,[3] and Duckworth.[4] Yet the descriptions of Huntington[5] and Brown[6] in the cat embryo, and Buell[7] in the chick embryo, led to the conclusion of the definitive existence of the fifth aortic arch in Mammalia. Moreover, in his classic study of the transformation of the aortic-arch system during the development of the human embryo, Congdon,[8] convincingly confirms the occurrence of the fifth aortic arch in man. Two decades later, additional supporting evidence of the existence of the fifth branchial arch was found by Kramer[9] in a 13-mm human embryonic specimen with a well-developed right fifth aortic arch.

In 1969, Van Praagh and Van Praagh[10] first described a case of persistent fifth aortic arch in an autopsy specimen, associated with tricuspid atresia, cor triatriatum, ventricular septal defect, infundibular and valvar pulmonary stenosis and a patent ductus arteriosus. Later, in 1973, Izukawa and colleagues[11] first reported the persistence of a left fifth aortic arch during life. Since then, a fifth aortic arch has been suspected or confirmed in association with numerous congenital heart abnormalities providing systemic to systemic, systemic to pulmonary and pulmonary to systemic arterial connections. The occurrences of a persistent fifth aortic arch in isolation[12,13] and its bilateral persistence[14] have also been described.

Incidence

The incidence of the persistent fifth aortic arch is unknown, greatly due to failure of recognition in many situations, as it has been called "the great pretender." Since a persistent fifth aortic arch presenting as double-lumen aortic arch itself is asymptomatic, some cases occurring as isolated developmental defects, may not be diagnosed. However, Gerlis and colleagues[15] estimated an incidence of *c.* 1 in 330 cases among 2000 congenitally malformed hearts in the combined collections of the Brompton and Killingbeck Hospitals, UK. At the Toronto Hospital for Sick Children seven patients were encountered, all associated with other congenital heart malformations.[11,16,17]

Embryology

The embryology of the aortic arch is best described as a sequential appearance and persistence or dissolution of paired vessels connecting the truncoaortic sac with the paired dorsal aorta, which eventually fuse to form the descending aorta (Fig. 41D-1). Each arch corresponds to a branchial pouch derived from the embryonic foregut, although all are not present at any one time. The first and second brachial arches are first to form and first to disappear. The third branchial arches enter into the formation of the carotid arteries. The segment of the paired ventral aortas between the third and fourth arches represent the right or left common carotid arteries. The fifth pairs of arches regress early but may persist (Fig. 41D-2). In the normal development of the arterial pole of the heart, only two of the six primitive aortic arches, the fourth and sixth, persist to join the ventral and dorsal aorta. The fourth becomes the definitive aortic arch, and the formation of a right or left aortic arch requires regression of the right or left dorsal aortic root respectively. If both persist, double aortic arch is present. The definite right and left pulmonary arteries are formed from the proximal portion of the paired sixth branchial arches. The distal portion of the sixth arches becomes the right and left ductus arteriosus. The persistence of both distal portions of the paired sixth branchial arches leads to the presence of bilateral ductus arteriosus. Early in development, the dorsal aortic roots originate intersegmental arteries that supply the spinal cord and developing somites. The seventh intersegmental artery on each side will migrate between the common carotid arteries and the ductus arteriosus, forming the right and left subclavian arteries.

Associated cardiac malformations

A persistent fifth aortic arch has been involved in a variety of cardiac malformations.[10–57] We have classified its occurrence as providing four different types of connections (Table 41D-1).

Type 1: Systemic to systemic arterial connections

Double-lumen aortic arch (also called "double-barrelled aorta" or "subway") was the first setting in which the persistence of the fifth aortic arch was described and the most frequent type encountered. The fifth arch is situated below the true aortic arch (fourth aortic arch) and extends from the level of the innominate artery proximally to the level of the subclavian artery and ductus arteriosus distally, with ostia at both ends that communicate with the aortic lumen. Embryologically, double-lumen aortic arch appears to result from persistence of both the fifth and the fourth branchial arches. It has been described with either left-[10,11,18,19] or right-sided[15,20–22] aortic arch and in isolation.[13] Associations with common arterial trunk,[15] tricuspid

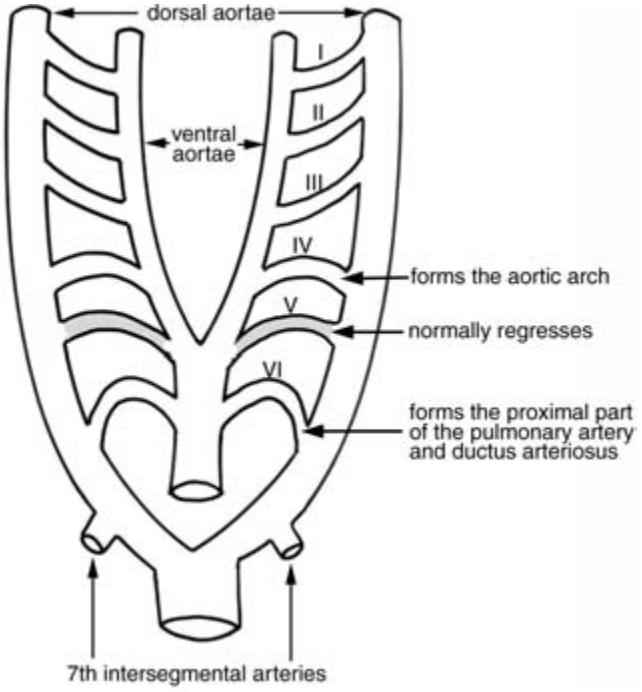


Fig. 41D-1 Development of the aortic arches. The aortic arch arises from the fourth aortic arch (IV) and the ductus arteriosus and proximal pulmonary artery arise from the sixth arch (VI). The persistence of the fifth arch (V) results in various abnormalities as shown in Fig. 41D-2.

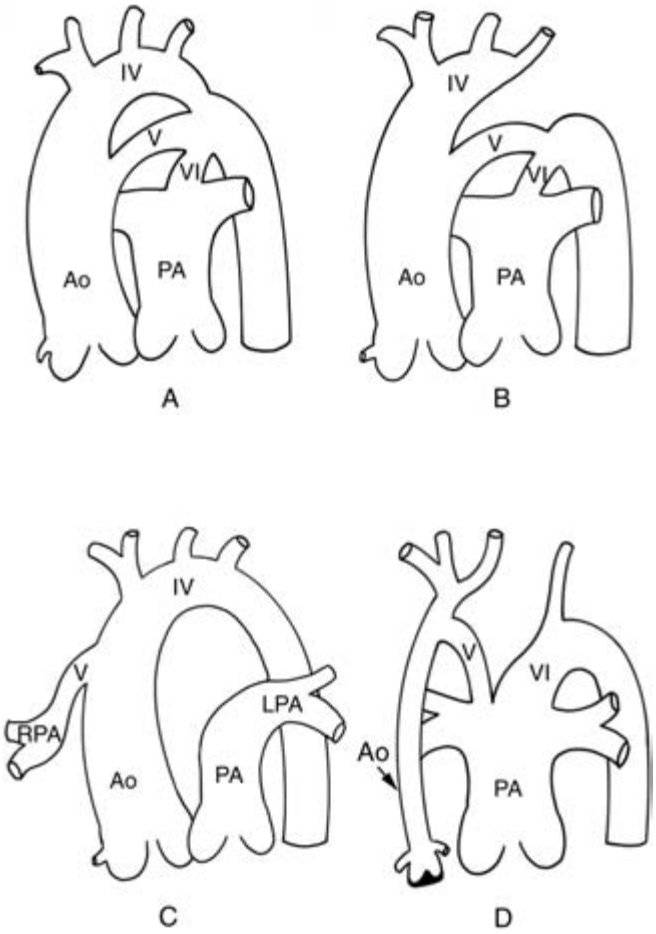


Fig. 41D-2 Examples of persistence of the fifth aortic arch (V). **A**. Double lumen aortic arch. **B**. The fifth aortic arch as the sole aortic arch channel. **C**. Origin of one pulmonary artery from the distal ascending aorta (Ao). **D**. The fifth aortic arch as the sole source of blood flow to the ascending aorta in aortic atresia with interrupted aortic arch. LPA, left pulmonary artery; PA, pulmonary artery; RPA, right pulmonary artery; IV, fourth aortic arch; VI, sixth aortic arch (ductus arteriosus).

atresia,[10,23,24] cor triatriatum,[10,23] pulmonary stenosis,[10,23] pulmonary atresia,[22,24] patent ductus arteriosus,[10,11,18,23] coarctation of aorta,[11,25–35,55,56] bicuspid aortic valve,[11] atresia of the distal part of the fourth arch (interrupted aortic arch),[21,25,26,29,32,33,55,56,57] single right coronary artery,[11] aortopulmonary window,[22] aneurysm of the left subclavian artery,[26] d-transposition of great arteries, ventricular septal defect and pulmonary atresia,[36] tetralogy of Fallot,[20,37,38] stenosis of the origin of the left subclavian artery,[21] double-outlet right ventricle, transposition of great arteries, patent ductus arteriosus and interruption of the fourth aortic arch,[34] bilateral superior caval vein,[22] secundum atrial septal defect,[19] pulmonary sequestration[21] and VATER association[13] have been reported. A patient prenatally exposed to the anticonvulsant drug trimethadione[18] associated with the presence of a double-lumen aortic arch, a patent ductus arteriosus and dislocation of the hip has been described. Chromosomal studies showed a karyotype of 46, XX, 9qh+.

There has been a rather more frequent association between a double-lumen aortic arch with coarctation of aorta and interrupted aortic arch. This might be a coincidental relationship but

Table 41D-1 Types of persistent fifth aortic arch

Type 1 Systemic to systemic arterial connection	Double-lumen aortic arch
	Origin of the subclavian artery as a first branch of the ascending aorta
	Origin of a collateral as first branch of the ascending aorta in pulmonary atresia and ventricular septal defect
Type 2 Systemic to pulmonary arterial connection	Associated with pulmonary atresia or an aortic arch anomaly
	Associated with a large left to right shunt without an associated great vessel anomaly and pulmonary hypertension
	Anomalous origin a branch pulmonary artery from the ascending aorta
Type 3 Pulmonary to systemic arterial connection	Associated with aortic atresia and interruption of the fourth aortic arch
Type 4 Combinations	Bilateral persistent fifth aortic arch

one possible explanation for this faulty development of the aortic arch could be explained by the fact that the normal blood supply to the ascending aorta in patients with this condition is divided between two channels, hence the blood flow to the fourth branchial arch is diminished leading to either coarctation or interruption of the aortic arch. Lim and colleagues reported the case of a 2-month-old girl with a common arterial trunk and coarctation of a persistent fifth aortic arch shown by computed tomography who underwent successful repair.[56A]

The origin of the subclavian artery as a first branch of the ascending aorta would appear to be very uncommon, with a few cases reported in the literature so far.[17–39] It may occur with either a left or a right-sided aortic arch. The first branch arising from the ascending aorta is the subclavian artery on the opposite side of the arch. Embryologically, it could be explained by the persistence of the fifth aortic arch and the disappearance of the ipsilateral fourth branchial arch as well as the segment of the dorsal aorta between the fourth and the fifth arches. Moreover, a cranial deviation of the seventh intersegmental artery on the opposite side of the aortic arch should occur, so the future subclavian artery would originate from the fifth instead of the fourth aortic arch. In this setting, the subclavian artery arises from the ascending aorta as a first branch prior to the ipsilateral common carotid artery. Both, separate and common origins of the left and right common carotid arteries have been encountered.[17,39,40,41] Associations with heterotaxy syndrome, complete atrioventricular canal defect, single right coronary artery, L-transposition of great arteries, double outlet right ventricle, supravalvar and valvar pulmonary stenosis, left superior vena cava, pulmonary atresia and an intact ventricular septum, and patent ductus arteriosus have been reported.[17] A patient with the subclavian artery as the first branch of the aortic arch and Fanconi's anemia has been encountered.[17]

A very unusual case of pulmonary atresia with a ventricular septal defect associated with systemic to systemic arterial connection provided by a fifth aortic arch was reported by Yoo and colleagues.[16] The fifth aortic arch arose from the distal ascending aorta on the opposite side of the aortic arch and was connected to a major aortopulmonary collateral artery, which in turn bifurcated to supply confluent pulmonary arteries as well as intrapulmonary arteries not connected to the pulmonary arteries. A left aberrant subclavian artery from a descending aorta diverticulum was present. A possible embryological explanation includes the regression of the left fourth aortic arch with persistence of the right fourth arch. The left dorsal aorta has been interrupted at two levels: one between the third and fifth arches, and the other, between the fifth arch and the left seventh intersegmental artery. The most distal segment of the left dorsal aorta has persisted and formed the root of the aberrant subclavian artery. A small segment of the dorsal aorta adjacent to the fifth arch has remained patent and it is from this that the collateral arteries extend to both lungs.

Finally, Lee *et al.*[42] reported a patient with microdeletion of chromosome 22q11, isolated infundibuloarterial inversion, right aortic arch and a remnant non-patent systemic to systemic arterial fifth aortic arch.

Type 2: Systemic to pulmonary arterial connections

Systemic to pulmonary arterial connections involving a fifth aortic arch have been reported with either right-[12,35] or left-sided[15,22,43,44] aortic arch. Associations with pulmonary atresia and ventricular septal defect,[22,35,45,46] pulmonary atresia with an intact ventricular septum[48] and right pulmonary artery interruption[46] have been encountered. A rare case where a persistent fifth aortic arch associated with an interrupted fourth aortic arch, a patent ductus arteriosus and a bicuspid aortic valve was reported by Gerlis and colleagues.[15] Three patients with diagnosis of anomalous origin of the left pulmonary artery from the ascending aorta[14,47] associated in all cases with a right aortic arch, a right patent ductus arteriosus and confirmed[14] or suspected DiGeorge syndrome[47] have been reported. Serra and his colleagues[48] described a patient with pulmonary atresia and intact ventricular septum with non-confluent pulmonary arteries, where the right pulmonary artery was supplied through a right-sided patent ductus arteriosus and the left pulmonary artery likely through a fifth aortic arch providing a systemic to pulmonary arterial connection. Freedom *et al.*[43] reported a case with tricuspid and pulmonary atresia, coarctation of aorta, hypoplastic transverse arch and a fifth aortic arch located on the same side as the definitive aorta giving a direct systemic to pulmonary artery connection. Another patient with pulmonary atresia, ventricular septal defect and a persistent fifth aortic arch was described by Macartney *et al*.[35] In this case, the pulmonary blood supply was derived both from several major aortopulmonary collaterals and from a persistent fifth aortic arch.

The majority of cases, in which a persistent fifth aortic arch has a systemic to pulmonary arterial connection, have either been cases of pulmonary atresia or an aortic arch anomaly. Patients with large left to right shunt due to a persistent fifth aortic arch without an associated great vessel anomaly and pulmonary hypertension have also been reported.[12,44]

Type 3: Pulmonary to systemic arterial connections

A persistent fifth aortic arch giving a pulmonary to systemic arterial connection is extremely rare. Four cases with this type of connection have been encountered. In all of them the dominant lesion was aortic atresia with an interrupted aortic arch, and the fifth aortic arch supplied the ascending aorta and the coronary arteries.[15,49,49A,50] Donofrio[49] and De Caro[49A] and colleagues reported one patient each with similar findings: aortic atresia, interrupted aortic arch and an "aortopulmonary fistulous tract" communicating the main pulmonary artery with the ascending aorta. This fistulous tract supplied the ascending aorta and coronary arteries. While the authors did not suggest this fistulous tract to be a fifth aortic arch, in retrospect it likely is this structure. Another patient[50] with aortic atresia, hypoplastic mitral valve and left ventricle, interruption of the aorta proximal to the brachicephalic artery and a persistent fifth aortic arch communicating the hypoplastic ascending aorta and the pulmonary trunk has been encountered. A restrictive left-sided patent ductus arteriosus was also present. Gerlis and colleagues[15] reported another case with aortic atresia, interrupted left aortic arch, aberrant right subclavian artery, bilateral superior vena cava, an inlet ventricular septal defect, a left-sided patent ductus arteriosus and a right-sided fifth aortic arch connecting the right pulmonary artery and the ascending aorta.

Type 4: Combinations

Bilateral persistent fifth aortic arch has been found in a patient with double-lumen aortic arch and anomalous left pulmonary

artery origin from the ascending aorta.[14] In this case, double outlet right ventricle with a subaortic ventricular septal defect, subvalvar and valvar pulmonary stenosis, right aortic arch, and a right-sided patent ductus arteriosus were present. Due to the associated facial anomalies, a conotruncal anomaly was suspected.

In some cases[51] there has been dispute about the presence of a persistent fifth aortic arch versus the persistence of the distal part of the sixth arch as patent ductus arteriosus.[52] Recently, Peirone and colleagues[53] reported a patient with a solitary arterial trunk giving rise to a single coronary artery and branch pulmonary arteries and in which there was absence of the ascending aorta with the totality of the neck vessels arising from the descending aorta. Either a fifth or a distal sixth aortic arch could have provided the connection between the solitary arterial trunk and the descending aorta depending on the level of regression of the ventral aorta. Further confusion exists taking into account that a persistent fifth arch is nearly indistinguishable from a patent ductus arteriosus, with half the expected number of smooth muscle cell layers in the media as documented by Silver and colleagues.[54] Moreover, Freedom *et al.*[43] reported that focal fibrin deposit and hemorrhage extending from the lumen to the media, may be present in a fifth aortic arch resembling an arterial duct that fails to close or reopens after initial closure. Finally, response of a persistent fifth aortic arch to prostaglandin has been observed clinically.[25,43]

Outcome

The management and outcome of a persistent fifth aortic arch depends on the associated cardiac lesions and the other organs affected. There has been an asymptomatic man in whom the diagnosis of a persistent fifth aortic arch associated to a secundum atrial septal defect was made at the age of 31 years.[19] It is important to realize the potential hemodynamic value of a persistent fifth aortic arch. In cases with systemic to systemic arterial connection where frequently coarctation of aorta or interrupted aortic arch are associated, the existence of an alternative source of blood supply is clearly advantageous. Furthermore, in cases with systemic to pulmonary or pulmonary to systemic connections (e.g. pulmonary atresia or aortic atresia and interrupted aortic arch respectively) its existence is crucial. Among the treatment strategies performed for this condition, successful balloon dilation of either coarctation or recoarctation of a persistent fifth aortic arch[21,29,33,56] giving a systemic to systemic arterial connection has been reported. A variety of surgical techniques to repair a double-lumen aortic arch associated with coarctation of aorta or interrupted aortic arch[27,29,30,34,55,56,56A] and pulmonary artery as first branch arising from the ascending aorta[14,47] have been described.

All references can be found at the end of the book. See pp. 826–8 for Chapter 41D.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

41E

Alejandro R. Peirone, Robert M. Freedom, and Shi-Joon Yoo

Superoinferior Ventricles and Hearts with Twisted Atrioventricular Connections

Hearts with a superoinferior ventricle relationship, many with a crossed or more appropriately twisted atrioventricular connection are unusual forms of congenital heart malformations (Figs 41E-1, 41E-2).[1–38] These hearts are characterized in part by an unusual spatial relationship between the two ventricles.[3,6,10,13,22,23,38] Indeed, the topography of the ventricular mass relative to the interventricular septum may depart from normal in a number of conditions. The most readily appreciated situations for this departure are observed in patients with dextrocardia with and without situs inversus and/or atrioventricular discordance.[10,22,23,38] In hearts with atrioventricular discordance, the ventricular mass is often aligned about a ventricular septum occupying a more vertical disposition than normal.[39,40] In other patients the ventricular mass may be oriented about a horizontal ventricular septum, thus defining a superoinferior spatial relationship.[1–38] In the setting of this post-cardiac looping rotational anomaly, the superiorly-positioned ventricle is almost always the morphologically right ventricle and the inferiorly-positioned ventricle the morphologically left ventricle.[1–38,41] The majority of hearts with twisted atrioventricular connections are biventricular, but a few examples of twisted atrioventricular connections in hearts with a double-inlet univentricular atrioventricular connection have been described.[21,42,42A] These hearts include those with a double inlet left or right ventricle. A superoinferior ventricle spatial relationship does not lend itself readily to the prediction of the type of atrioventricular connection.[43–46] Not infrequently despite a concordant atrioventricular connection, the great arteries are levo-positioned relative to one another when the ventricles have a superoinferior ventricular relationship.[10,13,14,22,23,32,38,47–50] In most hearts with a biventricular atrioventricular connection, the atrial and ventricular inlet septa are aligned in a single plane, and the two blood streams from the atria down to the ventricular apices are parallel as seen in the four chamber cross-sectional echocardiogram and angiocardiogram. Some hearts, however, have a varying degree of atrial septal malalignment with a loss of normal parallel connection axes.[38,42,51–54] Externally, these hearts are characterized by an unexpected spatial relationship of the cardiac chambers and great arteries for the given segmental connection. Internally, the blood flow tracts from the atria down to the ventricular apices spiral around each other, and the atrial and ventricular septa show an angulated or curved configuration.[38,42,51–54] Thus the heart appears twisted along its base-to-apex axis (Fig. 41E-1); the spatial orientation of the cardiac chambers and great arteries being governed by the degree of twisting and also by the presence of the frequently found ventricular hypoplasia. In those hearts with a greater degree of twisting, each atrium is connected to the contralateral ventricle, and the two atrioventricular blood streams "criss-cross," actually spiralling almost 180º to each other. Frequently, the ventricles are arranged in a superoinferior or "upstairs-downstairs" fashion, and the ventricular septum tends to be horizontal. The twisting occurs in either a clockwise or counter-clockwise direction. Usually the heart with the ventricular mass exhibiting a right-hand pattern (d-ventricular loop) is twisted in a clockwise direction, while the heart with a ventricular mass of an l-loop configuration is twisted in a counter-clockwise direction. The common directions of twisting place the right ventricular inlet superior and anterior to the inlet of the morphologically left ventricle. Very rarely, the heart appears twisted in a direction opposite to that seen in most hearts with a twisted atrioventricular connection with the right ventricular inlet inferior and posterior to the left ventricular inlet.[38,42,51–54] Thus in some patients with superoinferior ventricles, the atrioventricular connections are crossed, rather than parallel.[12,27–45] Anderson revisiting his earlier concept of the criss-cross heart defined the essence of crossed atrioventricular connections as a rotational abnormality of the ventricular mass so that the relationships of the ventricular chambers are not as anticipated for the given atrioventricular connection.[21] Furthermore he asked "Is a criss-cross an abnormal relation or connection?" It is an abnormal relationship for the type of atrioventricular connection. Stated in another way: one usually anticipates in situs solitus with a concordant atrioventricular connection, a harmonious ventricular relationship and pattern of internal organization: that is a right-sided morphologically right ventricle with a right-hand type of internal organization (so-called ventricular d-loop). But in some hearts with atrial situs solitus, atrioventricular concordance and crossed atrioventricular connections, the type of atrioventricular connection and ventricular relationship are not harmonious: i.e. in a concordant atrioventricular connection, but with crossed atrioventricular connections, the morphologically right ventricle might be leftward and superior with a left-hand pattern of internal organization.[38,55–58] Thus the lesson one learns from those hearts where the atrioventricular connection is not predictive of the ventricular relationship is that one must state both the type of atrioventricular connection and the type of ventricular relationship or situs.

On examination of those hearts with crossing atrioventricular connections, Seo and his colleagues point out those unifying features: a superior and anterior location of the tricuspid valve in the setting of rotational malalignment between the atrial and ventricular septal structures.[28] This malalignment may be lateral, or rotational, or a combination of both.[59] Ando and his

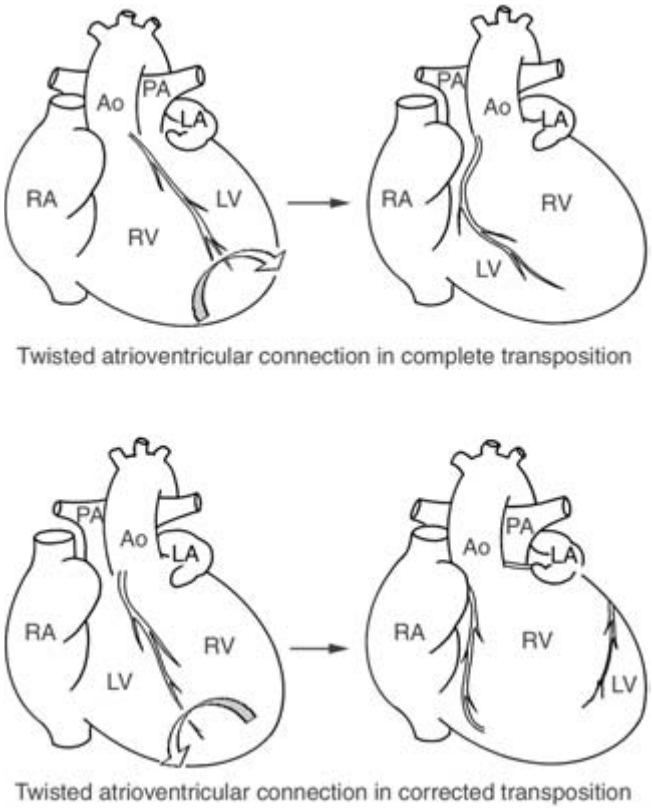
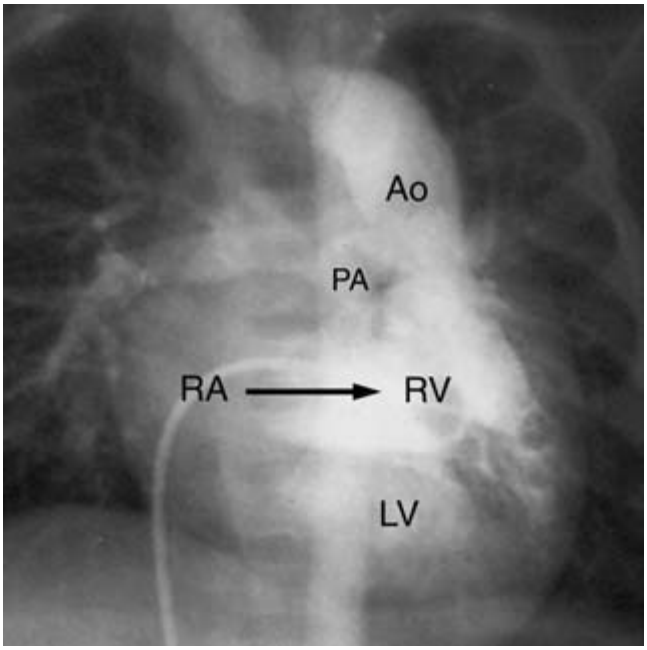


Fig. 41E-1 Twisted atrioventricular connections. When there is concordant atrioventricular connection as in upper panel, twisting is usually in a clockwise direction. When there is discordant atrioventricular connection, twisting is usually in a counter-clockwise direction. Lesser degree of twisting results in superoinferior relationship of the ventricles with the right ventricle being the upper chamber. Greater degree of twisting may result in side-by-side ventricles with complete crossing blood flow at the atrioventricular junction. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

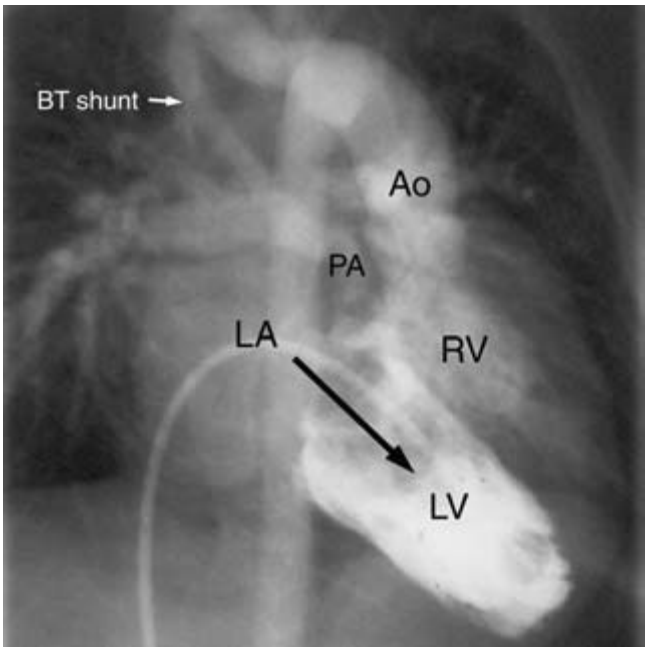
colleagues had previously designated the malalignment as parallel or crossed.[41] Seo also takes issue with the designation criss-cross atrioventricular connection, suggesting that this is not entirely accurate as it is the ventricular inlet tracts that are crossed. He and his colleagues are persuaded that twisted atrioventricular connection, rather than crossed, is a more appropriate designation.[28,51] Using this designation, the two atrial outflows cross at the atrioventricular level. Hearts with most peculiar abnormalities of the base–apex axis, characterized by us as so-called "topsy-turvey" hearts may also have superoinferior ventricles.[38] In this extremely peculiar malposition, the base–apex axis is abnormally rotated by nearly + 180 degrees.

Associated cardiac anomalies in hearts with twisted atrioventricular connection

We have discussed in detail elsewhere those cardiac anomalies commonly found in hearts with twisted atrioventricular connections and superoinferior ventricles.[38] Suffice it to say, the majority of hearts with twisted atrioventricular connections and superoinferior ventricles have an associated ventricular septal defect, pulmonary or less commonly systemic outflow tract obstruction (including aortic atresia), and many have some degree of ventricular hypoplasia, usually affecting the morphologically right ventricle. Abnormalities of ventriculoarterial connection are particularly common with many patients demonstrating a discordant or double-outlet ventriculoarterial connection.[1–37] The atrioventricular junction is frequently abnormal as well with overriding and straddling tricuspid valves and in some patients annular hypoplasia.[1–37] Left juxtaposition of the atrial appendage has been observed in these patients as well.[10,38] In a recent report of 36 patients with atrioventricular discor-



A



B

Fig. 41E-2 Frontal right (**A**) and left (**B**) ventriculograms showing twisted atrioventricular connection and discordant ventriculoarterial connection. The right (RV) and left (LV) ventricles show superoinferior relationship. The atrioventricular blood flow axes (arrows) cross each other. Ao, aorta; BT, Blalock-Taussig; LA, left atrium; PA, pulmonary artery; RA, right atrium.

dance, one patient whose ventriculoarterial connection was double-outlet right ventricle also had crossed atrioventricular connections.[60] A number of these patients have been found to have pre-excitation.[8,27] It is uncommon for the ventricular septum to be intact.[27,29,34] Some patients with superoinferior ventricles and discordant atrioventricular connections have concordant ventriculoarterial connections, so-called isolated atrioventricular discordance, thus making them candidates for atrial repair of the Mustard or Senning type (see also Chapter 26B). Patients with twisted atrioventricular connections and superoinferior ventricles may be candidates for a biventricular repair of various types while others for univentricular palliation.[61–66] It is the important ventricular hypoplasia of the systemic ventricle, straddling atrioventricular valve, intermingling of chordae and papillary muscles that necessitates univentricular palliation.

There is a substantial literature describing the pathological features of these hearts, and their echocardiographic, MR-imaging, and angiographic features.[10,13,14,22,23,32,38,42,51–54,67–76] Fetal diagnosis has been recorded as well.[52,68] Magnetic resonance imaging seems the superior non-invasive imaging modality for the diagnosis of twisted atrioventricular connections.[42,54,75,76]

Surgical procedures

From our experience and that in the literature, patients with superoinferior ventricles and twisted atrioventricular connections can benefit from a variety of surgical procedures.[61–66,77] In general, these can be divided into biventricular repairs and univentricular repairs (Table 41E-1).

From January 1979 to May 2002 at the Toronto Hospital for Sick Children, we assessed 31 children (18 males, 13 boys) with superoinferior ventricles ± twisted atrioventricular connections. Levocardia was noted in 24/31, dextrocardia in 6/31, and mesocardia in 1/31. The situs was solitus in 28/31 inversus in 1/31 and situs ambiguus in 2/31. The basic types of heart could be catalogued as follows:

Table 41E-1 Types of repair for hearts with superoinferior ventricles and twisted atrioventricular connections

Biventricular repair
VSD* closure with/without repair of POTO
Mustard or Senning repair
Arterial switch
Double switch
Univentricular palliation

POTO, pulmonary outflow tract obstruction; VSD, ventricular septal defect.

1 AV–VA concordance: 4/31
2 AV concordance-VA discordance: 8/31
3 AV–VA discordance: 4/31
4 AV discordance-VA concordance (isolated atrioventricular discordance): 2/31
5 AV concordance with DORV: 11/31
6 Topsy-turvy: 2/31 (both with AV–VA concordance and A–P windows).

The atrioventricular junction was abnormal in 21/31 and normal in 10/31.

The aortic arch was left-sided in 27/31, and the aortic arch was right-sided in 4/31. For the group as a whole, univentricular palliation was planned or completed in 23/31 and biventricular repair in 7/31 including two Mustard repairs in the patients with isolated atrioventricular discordance (see Chapter 26B). Heart transplantation was contemplated in 1/31 (diagnosed and listed *in utero*). Fifteen of the 31 patients have died, most in the first decade of the experience, including both of the patients with so-called topsy-turvey hearts.[23,38] The mortality rate was significantly higher in patients undergoing biventricular-type of repair compared with patients having univentricular-type of repair (71% and 43%, respectively). Among the 15 patients with univentricular-type of repair who died, 66% occurred before the completion of the Fontan procedure.

All references can be found at the end of the book. See pp. 828–30 for Chapter 41E.

The Natural and Modified History of Congenital Heart Disease
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41F

Robert M. Freedom

Kartagener's Syndrome

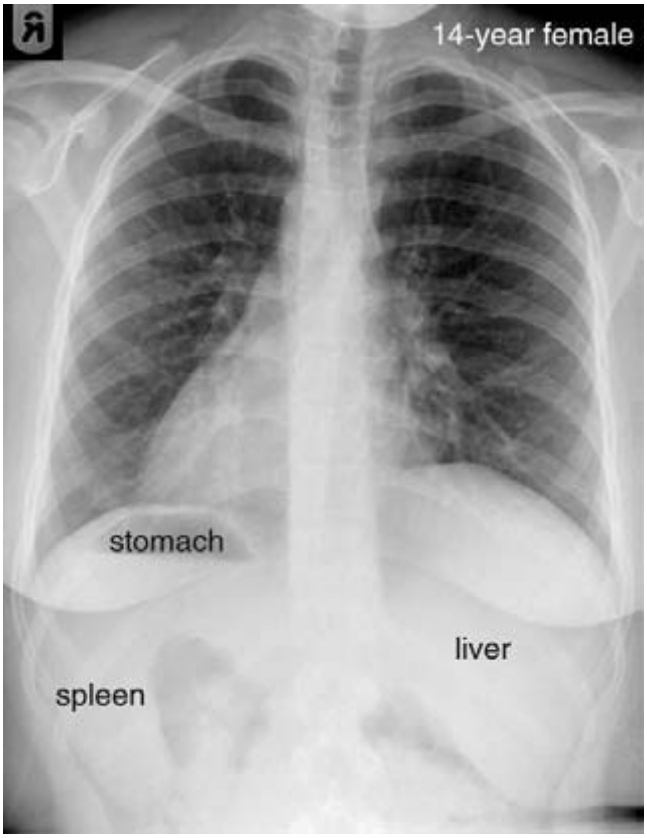
Kartagener first described the clinical triad of dextrocardia with situs inversus totalis, sinusitis, and bronchiectasis (Fig. 41F-1).[1,2] In the first English language report, Adams and Churchill found that 21.7% of patients with situs inversus had bronchiectasis, indicating that this association was not fortuitous.[3] The respiratory difficulties, including recurrent middle ear infections in this syndrome, result from hypomotility or immotility of the tracheobronchial cilia.[3–18] The basic defect is lack of ciliary dynein.[3–18] Males with this disorder are usually infertile, and absence of dynein in the sperm tails accounts for spermatic immotility.[3–19]

Prevalence and genetics

Primary ciliary dyskinesia or immotile cilia syndrome is an autosomal recessive disorder affecting ciliary movement with an incidence of 1 in 20 000–30 000.[3,6,7,10,14–21] Dysmotility to complete immotility of cilia results in a multisystem disease of variable severity with recurrent respiratory tract infections leading to bronchiectasis and male subfertility. Ultrastructural defects are present in ciliated mucosa and spermatozoa. Kartagener syndrome with situs inversus is found in about half of the patients with primary ciliary dyskinesia or immotile cilia syndrome.[3–19] The syndrome has been diagnosed in twins.[22] Guichard and colleagues have found that Kartagener syndrome is a heterogeneous condition that may be associated to axonemal dynein intermediate chain gene mutations.[21,21A]

Outcome analysis

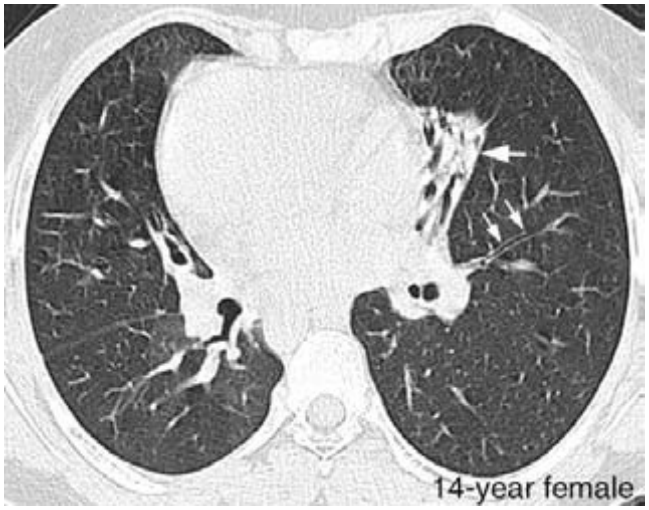
The triad of Kartagener's syndrome has been established in the neonate and as well in a 75-year-old adult.[23–25] "Man's best friend" is not immune from this disorder as Kartagener's syndrome has also been documented in the Dachshund dog.[26] This disorder is most frequently established in childhood, frequently in the investigation of the child or adolescent with recurrent respiratory infections, or in the pediatric patient with recurrent sinusitis and nasal polyps and discharge.[27] It is often in the clinical setting of the investigation for recurrent respiratory infections that frontal chest radiography demonstrates the cardiac malposition.[27] While it is uncommon to establish this diagnosis in the neonate, in at least one neonate the diagnosis of primary ciliary dyskinesia was confirmed by both ultrastructural and functional investigations.[23] The immotile cilia syndrome was suspected in this patient because of respiratory distress, situs inversus, abnormal nasal discharge and a radiograph showing a hyperinflated chest. Others have also made this diagnosis in the neonate and young infant.[24] As pointed out by Peroff, sinusitis varies from mild to severe with nasal polyposis and there may be hypoplasia or agenesis of the sinuses.[27] Similarly, symptoms of bronchiectasis range from mild to very severe.[27] Lobectomy has been required because of massive hemoptysis.[28] Bronchiolitis may dominate the clinical picture in some older patients.[29] Some patients with Kartagener's syndrome have also had rheumatoid arthritis, but it is unclear whether this is just a chance association.[30] When the diagnosis of immotile ciliary syndrome is established early in childhood, vigorous attention

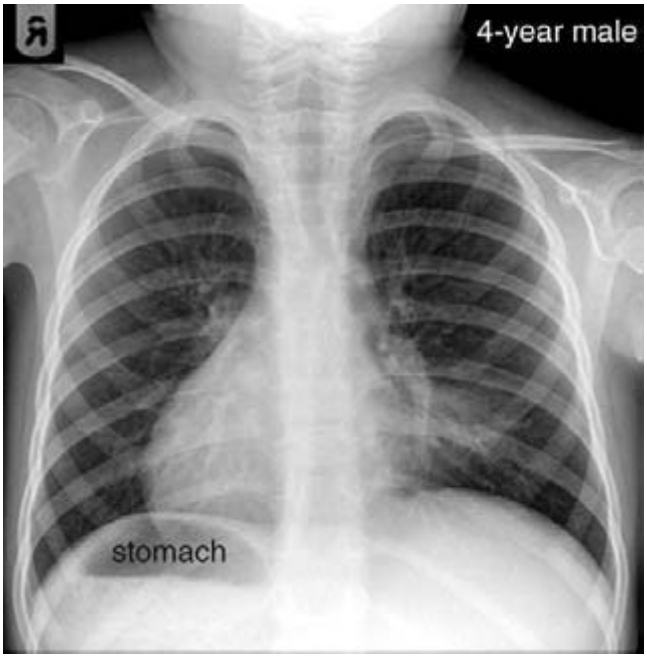


A

Fig. 41F-1 Kartagener's syndrome in siblings. **A**. Plain chest radiogram from a 14-year-old girl shows situs inversus and dextrocardia. The left middle lobe is collapsed. **B**. Lung computed tomograph of the same patient shows bronchiectasis in the collapsed right middle lobe (arrow) and bronchial thickening (arrows). **C**. Plain chest radiogram of the 4-year-old brother shows similar findings.

B





C

Fig. 41F-1 *Continued*

to "pulmonary toilet" significantly reduces the incidence of bronchiectasis.[27] Rarely, as in the patient reported by Gomez de Terreros Caro and colleagues, the diagnosis of Kartagener syndrome is made in the eighth decade of life.[25]

Congenital heart disease can occur in the patient with Kartagener's syndrome, and one tends to assign symptoms to the congenital heart malformation, and ciliary dysfunction may be overlooked.[27,31–35] It has been stated that cardiac defects occur in about one tenth of affected individuals.[31] Congenitally corrected transposition of the great arteries, ventricular septal defect, tetralogy of Fallot and complex forms of univentricular atrioventricular connection have been identified in patients with Kartagener's syndrome.[32–35] Polysplenia and incomplete lateralization of the abdominal viscera have also been seen in these patients.[36,37] Patients with important congenital heart disease have undergone successful cardiac and noncardiac surgery.[38] In the older patient with Kartagener's syndrome, end-stage bronchiectasis has been treated by heart–lung or double-lung transplantation.[39–41]

All references can be found at the end of the book. See pp. 830–1 for Chapter 41F.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

41G

Rachel M. Wald, Robert M. Freedom, Donald Perrin, and Shi-Joon Yoo

Myocardial Noncompaction

Noncompaction of the ventricular myocardium is a rare congenital abnormality characterized by the presence of numerous, excessive prominent trabeculations and deep intertrabecular recesses which communicate with the left ventricular cavity (Fig. 41G-1).[1–5] This particular form of cardiac muscle disease has not yet been classified as a separate and distinct entity by the World Health Organization, but rather it has been categorized as an unclassified cardiomyopathy.[6] Isolated noncompaction of the ventricular myocardium clearly departs in its morphology from typical hypertrophic (see Chapter 21), dilated (see Chapter 46) and restrictive cardiomyopathies.[7] The disease uniformly affects the left ventricle, and less commonly the right ventricle. Myocardial noncompaction has also been called "spongy myocardium," persistent myocardial sinusoids, myocardial dysgenesis, etc.[8–11] While in the past we had used the designation of "spongy myocardium,"[12,13] we acknowledge, as do others, that myocardial noncompaction better characterizes the basic nature of this disorder.[3] Noncompaction of the ventricular myocardium is believed to be a disorder of arrested endomyocardial embryogenesis.[1–5,7] Ventricular noncompaction may occur as a primary disorder, and it is being recognized with increasing frequency.[4,14–18] It is also well known to accompany a variety of congenital cardiac disorders. These include critical aortic stenosis usually of the neonate; pulmonary atresia and intact ventricular septum; some forms of "single" ventricle pathology; anomalous left coronary artery, and the rare variant of an imperforate tricuspid valve or tricuspid stenosis with a congenitally absent pulmonary valve.[12,13,19–31] This latter association has been extensively reviewed by Litovsky and colleagues[31] with most of the reported cases dating from the publication of Marin-Garcia and colleagues three decades ago (see also Chapter 30).[19] Interestingly, left ventricular hypertrabeculation/noncompaction has a peculiar association with neuromuscular abnormalities.[31A] This chapter will concern itself only with the primary form of noncompaction of the left ventricular myocardium.

Incidence and genetics

In a recently published study of the epidemiology of childhood cardiomyopathy in Australia, Nugent and colleagues found an annual incidence of primary cardiomyopathy of 1.24 per 100 000 children less than 10 years of age.[31A] This compares to the 1.13 per 100 000 documented by Lipshultz and colleagues in two regions of the USA.[31B] The Nugent study identified left ventricular noncompaction in 9.2% of their cases. In an echocardiographic study published by Ritter and colleagues some years ago, the frequency of isolated left ventricular myocardial noncompaction was 0.045% in an adult population.[15] Strauss and Lock have provided an interesting editorial to the papers of Nugent and Lipshultz and their respective colleagues.[31C] While left ventricular myocardial noncompaction occurs as a sporadic event, there are a number of reported cases with a familial pattern and a number of cases with typical dysmorphic features and/or chromosomal abnormalities have been recorded.[1,3,4,5,7,14,15–18,32–39] Bleyl and colleagues presented a family with myocardial noncompaction in which 6 affected individuals demonstrated X-linked recessive inheritance of this trait.[37] Affected relatives presented postnatally with left ventricular failure and arrhythmias, In this kindred, genetic linkage analysis localized isolated left ventricular myocardial noncompaction to the Xq28 region in the G4.5 gene, where other myopathies with cardiac involvement have been located. Pauli and colleagues described a dysmorphic 7-year-old girl and complex heart disease including ventricular myocardial non-compaction. She was found to have a distal 5q deletion. Fluorescent *in situ* hybridization showed that this deletion included the locus for the cardiac specific homeobox gene, CSX suggesting that some instances of ventricular myocardial noncompaction may be caused by haploinsufficiency of CSX.[38] Ichida and colleagues mentioned two large families with a high incidence of the disease, suggesting autosomal dominant inheritance.[33] Clearly there appears to be considerable genetic heterogeneity amongst patients with isolated left ventricular myocardial noncompaction.[32] One patient in this survey was noted to have a father with hypertrophic cardiomyopathy, and another patient's brother had a restrictive cardiomyopathy without features of noncompaction.[14] Isolated left ventricular myocardial noncompaction has been identified in the patient with Roifman's syndrome, Noonan's syndrome, Barth syndrome and Melnick-Needles syndrome, amongst others.[3,11,14,16,17,39A,40] The dysmorphic facial appearance commented on by some including Chin and colleagues include a prominent forehead, bilateral strabismus, low-set ears, and micrognathia.[3]

Morphology of isolated left ventricular myocardial noncompaction

During the early stages of intrauterine cardiac development, the loose trabecular network of the sponge-like myocardium undergoes compaction with resolution of the large intertrabecular spaces.[41–43] Formation of a wide inner spongy layer representing the primitive endocardium invaginates into the cardiac jelly. With progression of this process, the outer myocardium

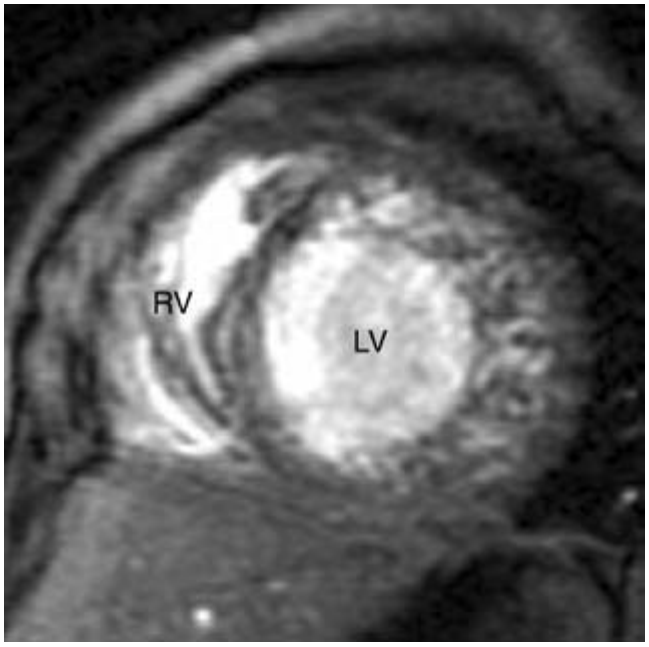


Fig. 41G-1 Myocardial noncompaction. Cine MR image of the ventricles in short axis shows tiny tracks between the fine trabeculations in the thickened myocardium of the free wall of the left ventricle (LV). RV, right ventricle.

becomes compact whereas the inner component differentiates into trabeculae carnae, papillary muscles and chordae tendineae.[41–43] It has been suggested elsewhere that an arrest in this process of normal myocardial development results in noncompaction of the ventricular myocardium,[1–5,7,14–18] a pattern of myocardium normally observed in non-mammalian vertebrates including fish, amphibians and reptiles.[41–43] Histological examination confirms that the so-called spongy appearance of the noncompacted left ventricular myocardium is due to the deep intertrabecular recesses lined by endothelium which extend close to the epicardial surface[3,14–18] (Fig. 41G-2). Increased fibrous and elastic tissue of the endocardium is common, perhaps reflecting as suggested by Chin *et al.* some degree of subendocardial ischemia.[3]

Outcome analysis

There are only a few cases recorded of fetal diagnosis of isolated left ventricular myocardial non-compaction.[44,44A,45] Kohl and colleagues reported a 5-year-old-girl with this condition in whom in retrospect the diagnosis could be made on the fetal study performed at 23 weeks' gestation.[44] More recently Moura and colleagues reported 4 cases of isolated noncompaction recognized in the fetus, 2 of which were familial and 2 sporadic.[45] Three fetuses died and 1 survived.

The diagnosis of isolated left ventricular myocardial noncompaction has evolved from one once only established at the autopsy table to clinical diagnosis based on typical echocardiographic features, MRI imaging and CT findings.[3,4,14–18,33–39,46–54] The diagnosis of isolated left ventricular myocardial noncompaction usually conveys a poor prognosis with clinical features dominated by pump failure, malignant ventricular dysrhythmias, and systemic embolism.[3–5,17,18,33,34,36–39,47–49,55] This latter clinical feature reflects both on the basic morphological features of the disorder which likely predispose to mural thrombi and the reality of progressive deterioration in ventricular function. Sudden death has also been reported.[3,50] A number of catheter studies reveal restrictive physiology with a normal end-diastolic volume, but increased left ventricular filling pressures.[3,4,14,16] There is increasing awareness of this disorder and the echocardiographic features are now fairly well entrenched in the literature.[4] From the increasing number of clinical reports it has become evident that in some patients with isolated left ventricular myocardial noncompaction the clinical course may be more indolent.[4,14–16] This is quite apparent from the nationwide survey conducted by the Japanese and published in 1999.[14] This survey identified 27 patients, with their ages at presentation ranging from 1 week to 15 years (median, 5 years) with the follow-up lasting as long as 17 years, median 6 years. Sixteen of

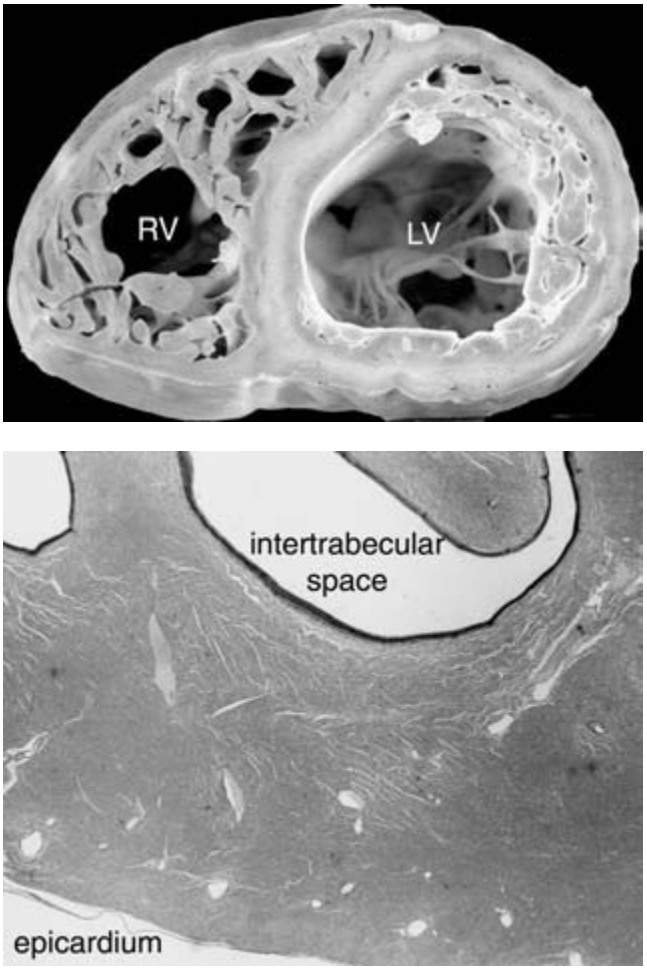


Fig. 41G-2 Explanted native heart from a 3-year-old female with isolated myocardial noncompaction. **A**. Clefts of intertrabecular space in the inner myocardium of the free wall of the left ventricle (LV). Left ventricular endocardium shows thickening and whitish discoloration due to endocardial fibroelastosis. It extends to the tracts and clefts of myocardial non-compaction. **B**. Low power photomicrograph (Movat pentachrome stain) of left ventricular myocardium shows the large, deep intertrabecular spaces within the inner portion of the left ventricular free wall. The subepicardial layer shows normal myocardium with intramural coronary arteries and veins. The intertrabecular spaces are lined by endocardial fibroelastosis. RV, right ventricle.

these patients demonstrated gradually depressed systolic function on echocardiography and 6 showed Doppler evidence of impaired diastolic function. Most of these patients according to the authors have shown no cardiovascular symptoms and have as yet not required medications.[14] While 2 patients died during the follow-up period and 1 patient is a candidate for a heart transplant, the prognosis in this group of patients is certainly better than that reported by Chin *et al.*,[3] acknowledging that the patients in the report of Ichida were identified from a questionnaire sent to 150 hospitals where a pediatric cardiology division exists.[14] Similar to the experience reported by Ichida,[14] the patients reported by Ritter and his colleagues seemingly had a more benign course as well.[15] Reynen *et al.* published the case of a 35-year-old man noted by left ventricular angiocardiography to have isolated left ventricular myocardial noncompaction at 15 years of age remaining asymptomatic until 35 years of age, at which time he presented in florid heart failure.[56] Interestingly, this patient had undergone closure of a secundum atrial septal defect at 6 years of age based on oximetry data. Nine years later because of a heart murmur, left ventricular angiography was performed establishing the diagnosis of noncompaction.[56]

Any number of electrocardiographic abnormalities have been described in patients with isolated left ventricular myocardial noncompaction including diffuse ST–T wave changes, sinus node dysfunction, complete left bundle branch block, Wolff–Parkinson–White syndrome, malignant ventricular arrhythmias, sudden death and complete heart block, amongst others.[3–5,14–18,34,39,47–49,57,58] Left bundle branch block is certainly uncommon in the unoperated pediatric population. In the patient presenting with features of heart failure and cardiomyopathy, one should certainly want to exclude isolated left ventricular myocardial noncompaction. The etiology of myocardial ischemia in these patients is unclear. While the gross coronary circulation has usually been characterized as normal in autopsied specimens, Chin and his colleagues wondered whether intramural perfusion could be adversely affected by the prominent trabeculations and deep intertrabecular recesses.[3] Positron emission tomography was used by Junga and colleagues to evaluate the presence or absence of myocardial ischemia.[59] They found that children with isolated left ventricular myocardial noncompaction had restricted myocardial perfusion and decreased flow reserve in the areas of noncompaction.[59] They wondered whether these perfusion defects in noncompacted areas could be contributory to the myocardial dysfunction and to the genesis of the arrhythmias. Jenni and his colleagues who have had an extensive experience with isolated left ventricular myocardial noncompaction have also documented coronary microcirculatory dysfunction in these patients using positron emission tomography and ^{13}N-ammonia,[60] as has Soler and coworkers using MRI to demonstrate left ventricular subendocardial perfusion deficits.[61A]

A total of 14 cases of left ventricular ventricular noncompaction were seen at the Hospital for Sick Children between September 1988 and January 2001. The male to female gender ratio was 1.33 : 1. The average age at presentation was 3.9 years with a range between 1 day and 14 years of age. This series focused on isolated ventricular noncompaction. It did not exclude minor valvular lesions (such as valvular regurgitation or Ebsteinoid anomalies of the tricuspid valve) or hemodynamically insignificant apical ventricular septal defects. The majority of patients presented with symptoms of congestive heart failure (9/14), 2 patients presented with arrhythmia (WPW and ventricular tachycardia) and no patients presented with thrombotic or embolic events. One patient diagnosed after a screening ECG, ordered because of a strong family history of sudden infant death syndrome and cardiomyopathy, revealed T wave abnormalities. The remaining two cases were diagnosed due to neonatal cyanosis and a neonatal murmur, respectively. Chromosomal abnormalities or syndromal findings were present in at least seven of the patients. These included 2 patients with Barth syndrome, 1 patient with centronuclear myopathy, 1 patient with chromosome 1 deletion and Leber's congenital amaurosis, 1 patient with Roifman syndrome and 2 patients suspected to have "syndromes not yet diagnosed." Half of all males (and no females) had a family history positive for congenital heart disease. Of the 14 patients reviewed, 4 patients progressed to end-stage heart failure and were offered heart transplant. One patient refused transplant and is currently receiving palliative care; he is 3 years of age and has restrictive physiology. Another 22-year-old patient is currently listed for transplant. Two patients received heart transplantation at ages 3 and 11 years, respectively. The latter died suddenly at age 15 due to coronary artery disease. There were no other deaths in our series. Of the remaining 10 patients, 9 patients have evidence of systolic dysfunction and 7 have systolic and diastolic dysfunction on the most recent echocardiogram performed in our hospital. With the exception of 1 patient who was lost to follow-up, all patients have had clinical evaluation within the past year. Over 90% of the patients currently being followed with ventricular noncompaction require anti-failure with or without arrhythmic medical therapy.

Can the course of the disease be modified by therapy? There is little information about this and it is uncertain whether one can make assumptions based on the documented courses and outcomes of patients with a classically dilated or restrictive cardiomyopathy.[4–18,61] Toyono and colleagues have reported the case of a 4-month-old infant with isolated left ventricular noncompaction who was treated with carvedilol.[61] Hemodynamic studies and various types of imaging-including echocardiography, radiographic angiography, magnetic resonance imaging, and single photon emission computed tomography with ^{201}Tl, ^{123}I-beta-methyliodophenylpentadecanoic acid (BMIPP), and ^{123}I-metaiodobenzylguanidine (MIBG) were performed before and 14 months after treatment. In this patient, left ventricular ejection fraction increased from 30% to 57%, and left ventricular end-diastolic volume, end-systolic volume, and end-diastolic pressure showed striking reductions during treatment. Left ventricular mass decreased to about two thirds of the baseline value after treatment. Per cent wall thickening increased after carvedilol in the segments corresponding to noncompacted myocardium. A mismatch between ^{201}Tl and BMIPP uptake in the area of noncompaction observed before carvedilol disappeared after treatment. Impaired sympathetic neuronal function shown by MIBG recovered after treatment. Thus in this single patient carvedilol had beneficial effects on left ventricular function, hypertrophy, and both metabolic and adrenergic abnormalities in isolated left ventricular noncompaction. Thus one would wonder that when a patient is identified in the asymptomatic phase of the disorder, whether they should be anticoagulated, at least using salicylates. Also, whether these patients should be placed on beta blockers, ACE inhibitors, etc., is uncertain, but since most if not all patients with this disorder will eventually deteriorate to the point of requiring

cardiac transplantation,[62,63] these maneuvers may prove beneficial. Finally, there is increasing recognition of isolated myocardial noncompaction, raising the question of rarity or missed diagnosis.[64,65]

In summary, isolated left ventricular myocardial noncompaction is a rare disorder with considerable genetic heterogeneity. This disease may occur as a sporadic event or in a sex-linked pattern of genetic inheritance. It can also be found in females. The clinical course is characterized by ventricular dysfunction, serious cardiac rhythm disturbances and systemic emboli. In some patients it seems the clinical course is fulminant, rapidly concluding in death or the need for a cardiac transplant. In other patients, the clinical course may be quite protracted. The etiology of isolated left ventricular myocardial noncompaction is unknown. Whether the course of the disease when detected in asymptomatic patients can be moderated by afterload reduction, etc., is unknown. Because of the basic morphological features of isolated left ventricular myocardial noncompaction, we would suggest early anticoagulation to prevent mural thrombi and systemic emboli.

All references can be found at the end of the book. See pp. 831–3 for Chapter 41G.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

41H

Robert M. Freedom and Shi-Joon Yoo

Systemic Venous Anomalies Including Divided Right Atrium

Many anomalies of systemic venous anatomy have been observed in patients with or without congenital heart disease.[1] Most of these do not have important clinical implications, but are merely anatomical variations. These include the retroaortic innominate vein among many other variations of systemic venous anatomy.[2–7] Other systemic venous anomalies may be intrinsic components of specific congenital heart malformations, i.e. azygos continuation of the inferior vena cava in patients with left isomerism/polysplenia (see Chapter 34). Yet other systemic venous malformations may be unmasked and recognized only after completion of cardiac surgery.[8–18] These include hepatic vein connection to the coronary sinus or left or pulmonary venous atrium which if not appreciated and dealt with at the time of total cavopulmonary connection will result in postoperative right-to-left shunting and hepatic veno-venous shunting (see Chapter 37), etc. This chapter will consider the following anomalies (Table 41H-1).

Right superior vena cava to left atrium

Right superior vena cava to left atrium (Fig. 41H-1) is one of the rare causes of cyanosis and has been recognized in both the pediatric as well as in the adult patient.[1,19–29] This condition was likely first reported in the English literature by Wood in 1957,[19] and up to 1995, Alday and colleagues identified from the literature at least 15 additional cases.[23] When this occurs in isolation, the development of cyanosis is usually insidious. This disorder may also be responsible for recurring intracerebral abscesses.[26] The diagnosis can be made from contrast echocardiography or from radionuclide imaging.[25] Surgical diversion of the anomalously connected right superior vena cava to the right atrium has been achieved using any of a variety of techniques.[20,30–32] In some patients the right superior vena cava drains into both atria (Fig. 41H-1B).[33] This condition may be a component of total anomalous systemic venous connection, an extremely rare finding (Fig. 41H-1C).[1,19,34–37] Surgical repair of this last condition has been achieved as well.[34–37]

Absent right superior vena cava

Absence of the right superior vena cava is an uncommon condition in the patient with normally lateralized atria.[38–47] In this situation, usually the right superior vena cava is either completely absent or represented by a vestigial fibrous cord (Fig. 41H-2A,B). Drainage of systemic venous blood from the head and neck is usually via the left brachiocephalic vein to the left superior vena cava, coronary sinus and right atrium, or to the left atrium if the coronary sinus is unroofed.[43–46] Lenox and her colleagues identified this malformation in two of 1550 postmortem heart specimens with congenital heart disease,[41] and the Boston Children's Cardiac Registry encountered this condition in 3 of 3226 specimens with congenital heart disease.[43] Among patients with normal situs, Bartram and colleagues found that slightly > 50% had no other form of congenital heart disease.[43] Interestingly, the survey by Bartram found a male : female ratio of 2.3 : 1.[43] One of the more significant features of this condition is that the sinoatrial node is often poorly formed and patients, usually adults, may develop "sick sinus syndrome" requiring pacemaker therapy.[40,43,45,47] Bartram and colleagues list a further six issues that make this diagnosis important (Table 41H-2).[43]

Rarely as in the case reported by Saunders and colleagues, both superior vena cavae are absent.[48] In this patient, blood from the arms, head, and upper torso returned to the right atrium through the azygos vein and the inferior vena cava, mimicking chronic superior vena cava obstruction.

Unroofed coronary sinus

The coronary sinus may be partially or completely unroofed, and in this situation in an otherwise normal heart this defect results in a left-to-right shunt (Fig. 41H-3A,B).[49–68] All-too-commonly, the effect of coronary sinus unroofing is masked by associated congenital cardiac malformations. Raghib and his colleagues were perhaps the earliest to describe the constellation of anomalies now bearing his name (Fig. 41H-3C).[69] These included termination of left superior vena cava in left atrium, atrial septal defect, and absence of coronary sinus. In some patients an unroofed coronary sinus provides an alternative pathway to pulmonary or systemic venous flow in the presence of obstructive lesions in the left or right atrioventricular junction, respectively.[51,62] An unroofed coronary sinus can be easily repaired by patching the defect.[30] In many patients with an unroofed coronary sinus, a left superior vena cava connects directly with the left atrium.[1,19,50–53,56,69] This condition, when isolated, can be treated either surgically or by intervention (Fig. 41H-4).

Left superior vena cava draining to the left atrium

A left superior vena cava connecting directly to the left atrium (Fig. 41H-5) promotes a right-to-left shunt.[1,19,19A,50–53,56,69–82] When the coronary sinus is normally formed and not unroofed, several procedures have been used to treat this condition. These

Table 41H-1 Systemic venous anomalies discussed in this chapter

Right superior vena cava to left atrium
Absent right superior vena cava
Unroofed coronary sinus
Coronary sinus ostial stenosis/atresia
Left superior vena cava draining into the left atrium
Hepatic vein to coronary sinus connection
Hepatic vein to left atrium connection
Persistence of the hepatic venous plexus as the terminal part of the inferior vena cava
Congenital division of the right atrium
Levoatrial cardinal vein

include an intra-atrial baffle; anastomosis of the left superior vena cava to the right superior cava or right atrial appendage; simple ligation; or construction of a left cavopulmonary connection. When the left brachiocephalic vein is of reasonable calibre, the left superior vena cava can be safely ligated with the knowledge that there is not coronary sinus atresia, or this venous channel can be occluded in the catheter laboratory with any of a variety of catheter-delivered devices.[1,19,19A,50–53,56,69–80] In the patient with a small left brachiocephalic vein, this vein can be patch-graft enlarged and then the left superior vena cava can then be ligated.[54] Others, even in the absence of a left brachiocephalic vein, have ligated the left superior vena cava, measuring carefully venous pressure above the level of ligation, acknowledging that this procedure is not always safe.[19,30,82] Collateralization often allows this maneuver to be safely carried out. In other situations the ostium of the left superior vena cava at its point of termination into the left atrium can be baffled into the right atrium.[30,57,76] Patients with adequately-sized pulmonary arteries and low pulmonary artery pressure and vascular resistance can be treated with a cavopulmonary connection.[66,76,77]

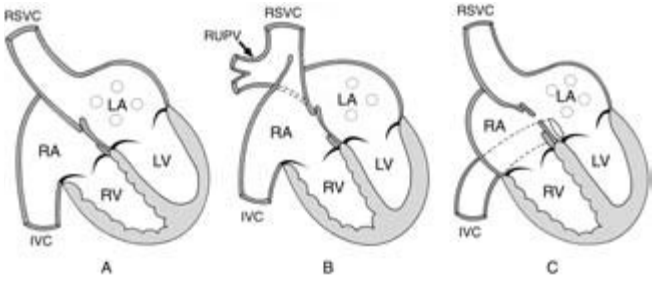


Fig. 41H-1 Variants of abnormal connection of the right superior vena cava to the left atrium. **A**. Connection of the right superior vena cava (RSVC) to the left atrium (LA). **B**. Connection of the right superior vena cava to both atria. **C**. Connection of the right superior vena cava as a part of total anomalous systemic venous connection. IVC, inferior vena cava; LV, left ventricle; RA, right atrium; RUPV, right upper pulmonary vein; RV, right ventricle.

Coronary sinus ostial atresia/stenosis

Coronary sinus ostial atresia (Fig. 41H-6) is a very uncommon congenital abnormality.[1,52,83–94] One of the earliest reports was published in 1943 by Prows [83] and in 2002 Ohta and colleagues stated that only 40 cases had been reported in the world's literature.[94] In patients with an otherwise normal heart, coronary venous return in the presence of coronary sinus ostial atresia is mediated through thebesian-vein like channels, and thus this anomaly should not produce symptoms. Yet in some patients coronary venous blood returns to the right heart via a persistent left superior vena cava. Ligation of this vein during repair of congenital heart malformations in patients with atresia or severe stenosis of the coronary sinus ostium may prove fatal.[1,82,83,86,93] Repair of coronary ostial atresia has been reported by Ohta and colleagues in a patient who did poorly after a total cavopulmonary connection for the hypoplastic left heart syndrome.[94] The effect of coronary sinus atresia precipitated features of a failing Fontan circulation. The coronary sinus was unroofed into the left atrium and the patient subsequently improved. Tateno and colleagues have also reported repair of atresia of orifice of the coronary sinus.[94A] They reported a 5-year-old girl with a coronary arteriovenous fistula, atresia of the ostium of the coronary sinus and a persistent left superior caval vein all documented by aortography. This patient underwent closure of the fistula and membranous atresia of the coronary sinus ostium. The membrane was excised and the orifice enlarged. Subsequent angiocardiography performed 23 days after the operation showed the reconstructed orifice to be patent, but a second postoperative study at 11 years of age showed acquired closure of the coronary sinus orifice.

While the diagnosis of coronary sinus atresia has usually been made by angiography,[1,85,94] Muster and his colleagues and others have suggested that retrograde flow in the left superior

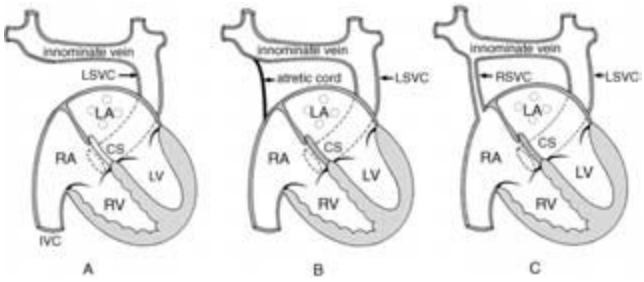


Fig. 41H-2 Absence or hypoplasia of the right superior vena cava. **A**. Complete absence. **B**. Atretic fibrous cord cord. **C**. Hypoplasia. CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; LSVC, left superior vena cava; LV, left ventricle; RA, right atrium; RSVC, right superior vena cava; RV, right ventricle.

Table 41H-2 Issues that make diagnosis of absent right superior vena cava important

Implantation of transvenous pacemaker
Placement of a pulmonary artery catheter for intraoperative or postoperative monitoring without the use of fluoroscopy
Systemic venous cannulation for extracorporeal membrane oxygenation
Systemic venous cannulation for cardiopulmonary bypass
Partial or total cavopulmonary anastomoses
Orthotopic heart transplantation and endomyocardial biopsies

(From Bartram *et al*.[43] with permission.)

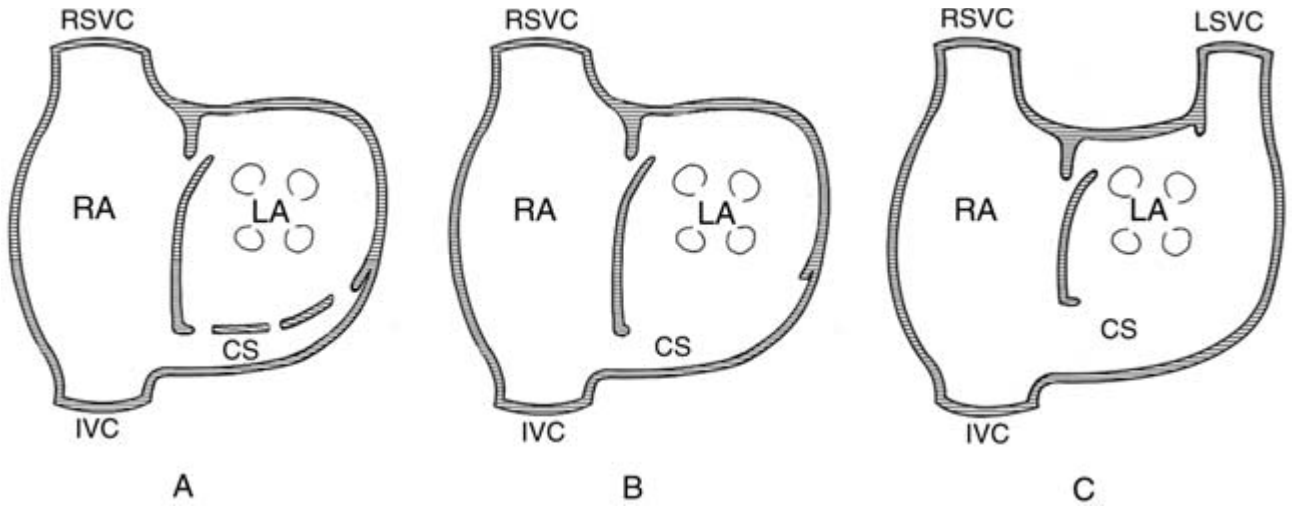
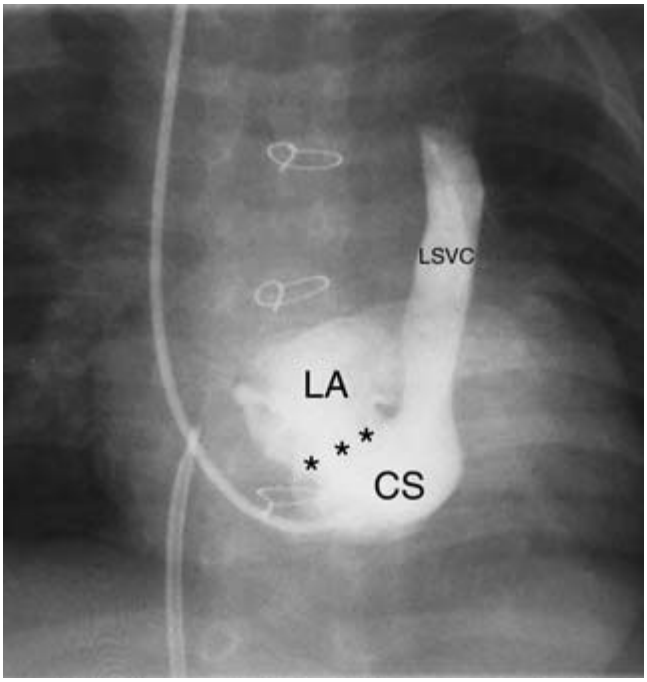


Fig. 41H-3 Variants of unroofed coronary sinus. **A**. Partial unroofing. **B**. Complete unroofing. **C**. Complete unroofing with a persistent left superior vena cava (LSVC) (Raghib defect). CS, coronary sinus; IVC, inferior vena cava; LA, left atrium; RA, right atrium; RSVC, right superior vena cava.

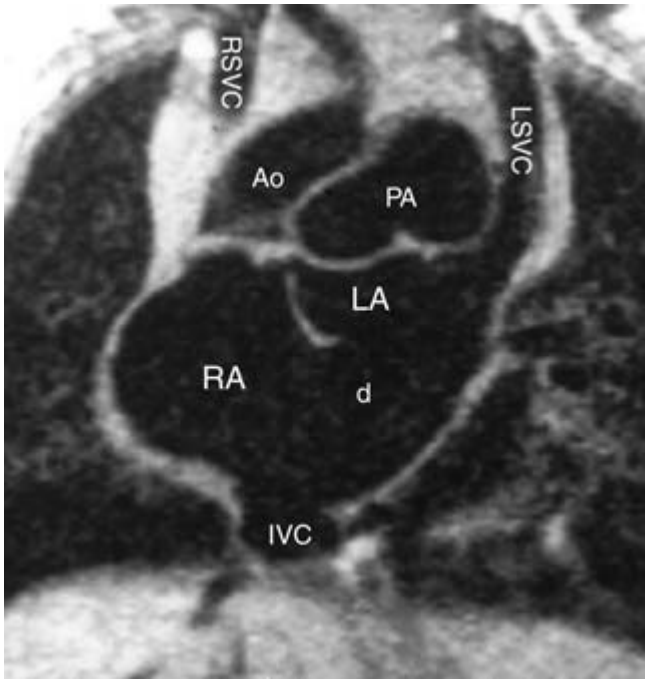
vena cava as assessed by Doppler echocardiography is suggestive of this condition.[82,90,92]

Hepatic vein connection to coronary sinus or left atrium

In patients with unequivocally lateralized atria, these anomalies are rare.[8–16,95] Hepatic vein connection to coronary sinus (Fig. 41H-7) should not produce symptoms or cyanosis in otherwise normal hearts. However, in patients undergoing a Fontan-type procedure, it is routine to construct the atrial anatomy so that the coronary sinus drains to the lower pressure pulmonary venous atrium. If a hepatic venous connection to the coronary sinus is not recognized pre- or intraoperatively, then postoperatively a right-to-left shunt would become apparent, promoting as well a hepatic veno-venous shunt[96,96A] (see Chapter 37). Similar complications would be anticipated in the patient with a hepatic vein connection to left atrium. Nomura and colleagues



A



B

Fig 41H-4 Unroofed coronary sinus. **A**. Injection into the left superior vena cava (LSVC) opacifies the coronary sinus (CS) and shunting of contrast medium into the left atrium (LA) thorough the defect (asterisks) in the party wall between the coronary sinus and left atrium. **B**. MR image in a coronal plane shows complete unroofing of the coronary sinus. As the result, the left superior vena cava connects to the roof of the left atrium and the coronary sinus opening functions as a large atrial septal defect (d). This complex is called coronary sinus defect or Raghib defect. Ao, aorta; IVC, inferior vena cava; PA, pulmonary artery; RSVC, right superior vena cava.

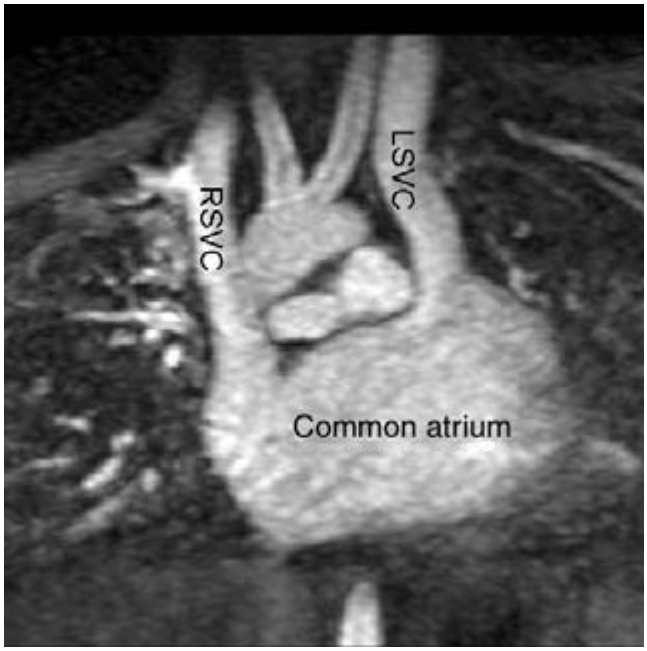


Fig. 41H-5 Bilateral superior venae cavae connected to the roof of common atrium. LSVC, left superior vena cava; RSVC, right superior vena cava.

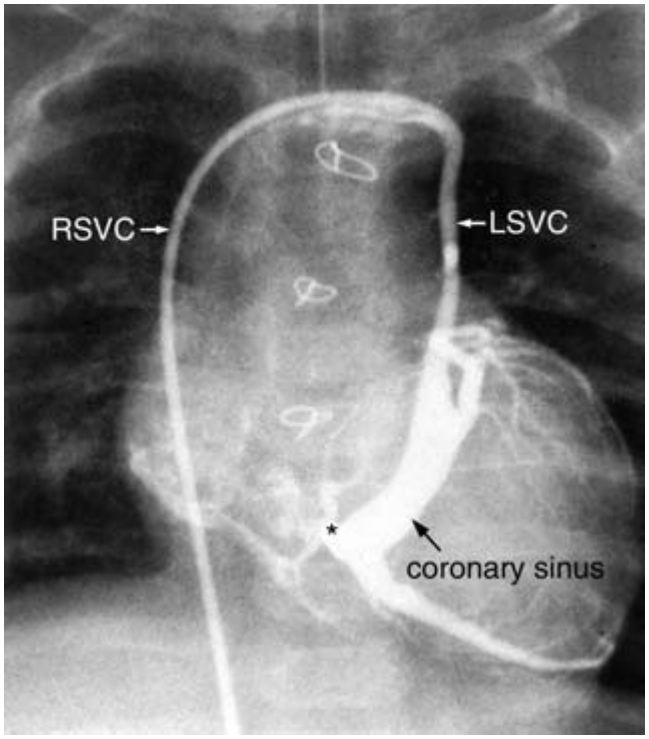


Fig. 41H-6 Stenosis of the coronary sinus ostium (asterisk). LSVC, left superior vena cava; RSVC, right superior vena cava.

have published the interesting case of a patient who became increasingly cyanosed after the Fontan procedure, initially leading to Fontan takedown to a hemi-Fontan as the etiology of the postoperative hypoxemia was incorrectly attributed to high pulmonary vascular resistance. What was later identified was a wide venous channel connecting the left hepatic vein to the left pulmonary vein which in turn connected to the pulmonary venous atrium. Several years later this unusual vascular channel was successfully ligated when the patient underwent a successful fenestrated Fontan procedure.

Furthermore this complication has been observed in patients with heterotaxia after total cavopulmonary connection when hepatic venous connection to the pulmonary venous atrium was not recognized preoperatively.[17] This complication leads to progressive and severe cyanosis following the Fontan operation and the connection must be interrupted either at surgery or by catheter-based intervention.[17A,17B] The dilated intrahepatic channels as shown by Giamberti and colleagues (fig. 2) suggest persistence of the hepatic venous plexus[96A] (see below).

Persistence of the hepatic venous plexus as the terminal part of the inferior caval vein

Persistence of the hepatic venous plexus (Fig. 41H-8), first recognized by Jolly and his colleagues as a relatively isolated anomaly (with an arterial duct and azygos continuation of the inferior vena cava),[97] this condition is now being recognized with increasing frequency.[98–101] Persistence of the primitive hepatic venous plexus has also been observed in the patient with a hypoplastic but patent hepatic segment of the inferior vena cava as well as in the patient with complex congenital heart disease complicating visceroatrial heterotaxia.[98–101] These connections may promote important arterial hypoxemia after a Kawashima operation, and thus their recognition is important in the preoperative investigation of patients with left iso-

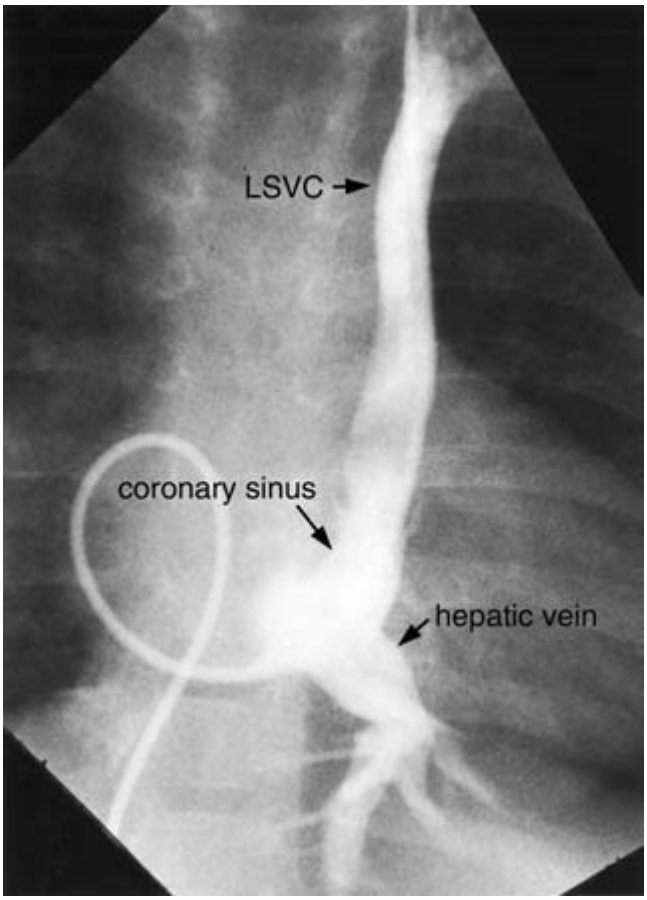


Fig. 41H-7 Anomalous connection of the hepatic vein to the coronary sinus that drains the left superior vena cava (LSVC).

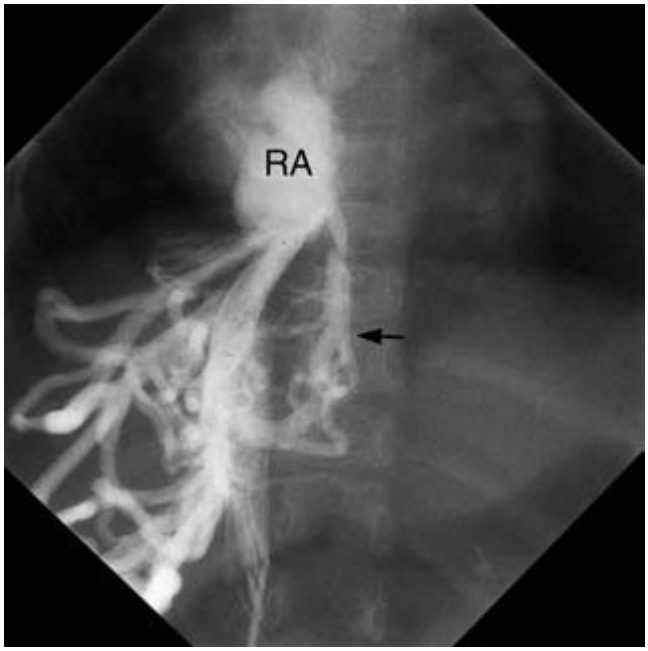


Fig. 41H-8 Persistent hepatic venous plexus (arrow) in a patient with scimitar syndrome. RA, right atrium.

merism/polysplenia[101] (see also Chapter 37). This recognition is facilitated by inferior vena caval angiography performed before palliation with a cavopulmonary shunt or at the catheter study performed before total cavopulmonary bypass.[101] Furthermore, if this condition is not diagnosed preoperatively, its recognition at a postoperative catheter study may lead to the erroneous conclusion that this malformation results as a complication of this surgery.[18,101–104]

Other congenital anomalies of the systemic veins include aneurysmal dilatation of the right or left superior vena cava, hypoplasia of the inferior vena cava, and congenital arteriovenous fistula. We have discussed in detail elsewhere the pathological and morphological features of the persistent venous valve, and its frequent association with hearts characterized by severe right ventricular inflow and outflow tract obstruction.[1,105–119] A divided right atrium can occur in isolation, producing symptoms in the infant or the adult (Fig. 41H-9).[107–120] For symptomatic patients experiencing right heart failure or cyanosis because of right-to-left shunting through a patent foramen ovale or atrial septal defect surgical excision can remedy the situation.[108–113,120] The incomplete regression of the embryonic right valve of the sinus venosus may leave a fenestrated or an unfenestrated membrane in the right atrium that should be considered a normal benign variant of the so-called "Chiari's" network.[105,106,118] This finding was noted in 27 of 1728 transthoracic two-dimensional and Doppler echo-cardiographic studies consecutively performed over a 4-month period.[118] Rarely as in the case published by Inoue and colleagues, a divided right atrium is associated with extensive coronary vein abnormalities.[121] There is also some experience, albeit limited with catheter-based intervention for cor triatriatum dexter.[122] The levoatrial cardinal vein is an uncommon finding, usually, but not invariably identified in patients with mitral atresia and other forms of hypoplastic left heart syndrome connecting the left atrium or left-sided pulmonary vein to the left brachiocephalic vein (Fig. 41H-10).[123–132] Persistence of a levoatrial cardinal vein complicates the completion of a Fontan-type operation, and if not interrupted results in a right-to-left shunt after completion of a total cavopulmonary connection.[133] This vein can be interrupted in the catheter laboratory.[133] Finally, connection of the inferior vena cava to the left atrium is exceedingly rare, if this situation exists at all.[134]

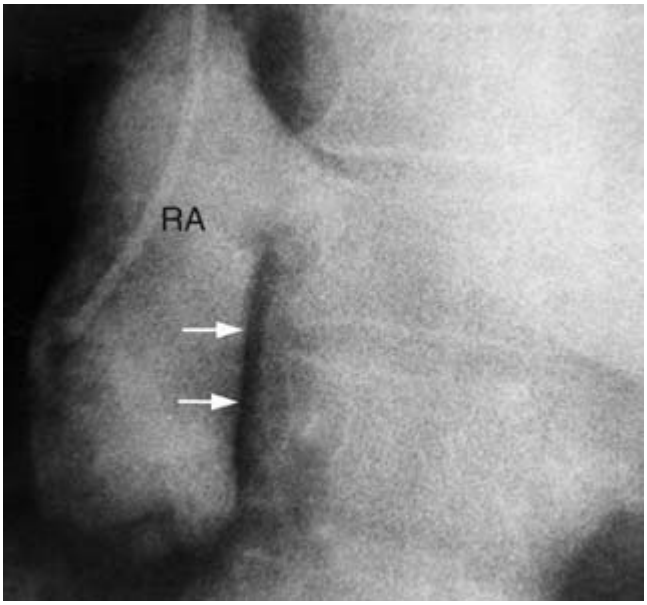


Fig. 41H-9 Divided right atrium. Right atrium (RA) is divided into two parts by the prominent right venous valve (arrows).

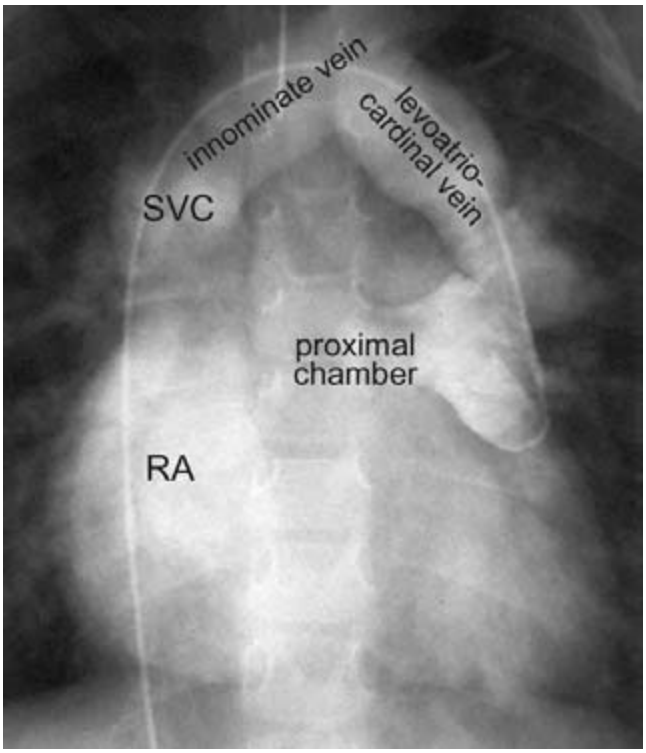


Fig. 41H-10 Levoatriocardinal vein in a patient with cor triatriatum. The levoatriocardinal vein drains the proximal chamber of the left atrium to the innominate vein. RA, right atrium; SVC, superior vena cava.

All references can be found at the end of the book. See pp. 833–6 for Chapter 41H.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

41I

Robert M. Freedom and Shi-Joon Yoo

Isolation of the Subclavian, Innominate, or Left Common Carotid Artery

Isolation of the subclavian, innominate or left common carotid arteries is an uncommon congenital anomaly of the aortic arch system (Figs 41I-1, 41I-2). The embryology, clinical manifestations and imaging algorithms useful in the diagnosis of these uncommon vascular conditions have been discussed elsewhere.[1–8] When either the subclavian artery, the innominate artery or the left common carotid artery is connected inappropriately to the pulmonary artery, isolation of the particular vessel occurs as a result of physiological and anatomic closure of the arterial duct. With closure of the arterial duct, the arch vessel involved is then attached to the pulmonary artery by the ligamentum of the duct, and thus isolated from the systemic circulation.

Embryology

Isolation of the right subclavian artery from the right pulmonary artery with a left aortic arch[1–7] requires regression at two levels in Edwards's hypothetical arch system in this anomaly:[1–3,8] one level, the right arch between the right common carotid and subclavian arteries; the other, the right dorsal aortic root distal to the arterial duct (Fig. 41I-1A). No vascular ring exists in this situation. We have reported bilateral arterial ducts in this situation.[9] For the patient with a right aortic arch and isolation of the left subclavian artery, the left subclavian artery no longer arises from the aorta, but is connected to the left pulmonary artery via a left arterial duct.[1–3,5,10–17] Embryologically there is a regression at two levels in Edwards's hypothetical arch plan:[4] one between the left common carotid and subclavian arteries; and the other, the left dorsal aortic root distal to the left ductus arteriosus (Fig. 41I-1B). Again no ring is formed and cases with bilateral arterial ducts have been reported.[9] Isolation of the right subclavian artery is far less common than isolation of the left subclavian artery.

Isolation of the innominate artery is very uncommon and usually occurs in the setting of a right aortic arch.[18–30] The innominate artery is not connected to the arch.[1–5,18–30] Atresia of the left common carotid and subclavian arteries may also be present. The blood supply to the isolated vessel is via a patent arterial duct or via mediastinal and vertebral pathways. The malformation is the result of interruption of the embryonic arch at two levels: one proximal to the left common carotid artery, the other involves the left dorsal aortic root distal to the left patent ductus arteriosus or ligamentum (Fig. 41I-1C).[3,8,18] The innominate artery is connected to the left pulmonary artery via the left ductus arteriosus or ligamentum. Bilateral arterial ducts have also been described in these patients.[9] Even less common is isolation of the left common carotid artery. Indeed, cases of this anomaly are extremely rare.[31–35] The patients described in the literature exhibited a right aortic arch with an aberrant left subclavian artery which arose from the right sided descending aorta. No vascular ring existed. Embryologically, in the double aortic arch plan of Edwards, interruption of the left arch proximal to the left common carotid artery and between the left ductus arteriosus and subclavian artery could explain the malformation (Fig. 41I-1D).[1–3,8] One would have to assume lack of proximal migration of the left subclavian artery so that the arterial duct enters the left dorsal aortic root proximal to the aberrant subclavian artery.

Associated cardiovascular abnormalities

A wide variety of congenital cardiac abnormalities have been described in association with isolation of the subclavian artery, or isolation of the innominate or left common carotid arteries. These abnormalities can occur in isolation, but they have been observed in patients with atrial and ventricular septal defects, atrioventricular septal defect, tetralogy of Fallot, hypoplastic left heart syndrome, pulmonary atresia and ventricular septal defect; coarctation of the aorta, transposition of the great arteries, interruption of the aortic arch; and aortic atresia with asplenia and heterotaxia.[1,2,4,6,7,9–17,19–35] Isolation of the left subclavian artery has been documented in a patient with Williams–Beuren syndrome.[33] In the setting of bilateral arterial ducts and isolation of the left subclavian artery, bilateral pulmonary artery obstruction has been noted.[15] Finally, there has been some discussion that isolation of the subclavian artery and innominate artery may be associated with chromosome 22q11 deletion.[23,35–39] There is not unanimity of opinion about this association.[37,39]

Outcome analysis

These uncommon vascular anomalies may go undiagnosed for many years, only to be recognized in the adult,[40] or they may be discovered during the investigation of congenital heart malformations. A pulse and blood pressure difference may not be apparent as long as the arterial duct between the pulmonary trunk and systemic artery remains widely patent. Once closure of the arterial duct has occurred, isolation of the subclavian artery may be recognized during the work-up for a weak arterial pulse ipsilateral to the isolated subclavian artery, and/or for a blood difference between the two upper extremities. Some patients will become symptomatic from a subclavian steal syn-

drome, while other patients may exhibit a discolored limb.[41] As with patients who have undergone a classical Blalock–Taussig shunt or left subclavian flap aortoplasty for repair of coarctation, relatively few patients develop clinical symptomatology of a steal. With inadequate arterial collateralization, the limb ipsilateral to the isolated subclavian artery may exhibit inadequate growth, or may be cooler than the contralateral limb. Claudication with exercise or prolonged use may occur if the involved limb is the dominant limb. A 36-year-old woman was investigated for increasing attacks of episodic dizziness, vertigo, and left upper limb claudication spanning 1 year.[41A] She was found to have a right aortic arch with isolation of the left brachiocephalic artery.

Isolation of the subclavian artery may result in a pulmonary artery steal.[17,42] This assumes patency of the arterial duct, and such a phenomenon has been described in the patient with tetralogy of Fallot as well as in the patient with transposition of the great arteries.[17,42] The patient with transposition of the great arteries described by Russell and her colleagues showed unilateral pulmonary edema and severe congestive heart failure secondary to the pulmonary steal.[42] At the time of the arterial switch operation, the isolated left subclavian artery was reanastomosed to the ascending aorta.[42] In this regard, the diagnosis of an isolated subclavian artery has evolved from angiographic imaging [1,2] to the echocardiography laboratory.[38,42,43] Isolation of the subclavian artery may confound cardiac catheterization when for technical or other reasons an approach from the right axillary artery is undertaken. It may further complicate construction of a Blalock–Taussig shunt, either classic or modified.[10,44] There is increasing experience with surgical reimplantation of the isolated subclavian artery.[14–16,38,42,43,45] Jones and coworkers have reported the use of the Gianturco–Grifka vascular occlusion device to close a moderate-sized patent arterial duct associated with isolation of the left subclavian artery.[46] Left vertebral artery "steal" through the moderate-sized patent arterial duct was eliminated by this transcatheter technique. Finally, isolation of the left subclavian artery has been documented in the patient with Williams–Beuren syndrome. In this situation when the pulse is weak, the etiology and therapy differ from the occlusive vascular arteriopathy typical of the Williams–Beuren syndrome (see also Chapter 14B).[47]

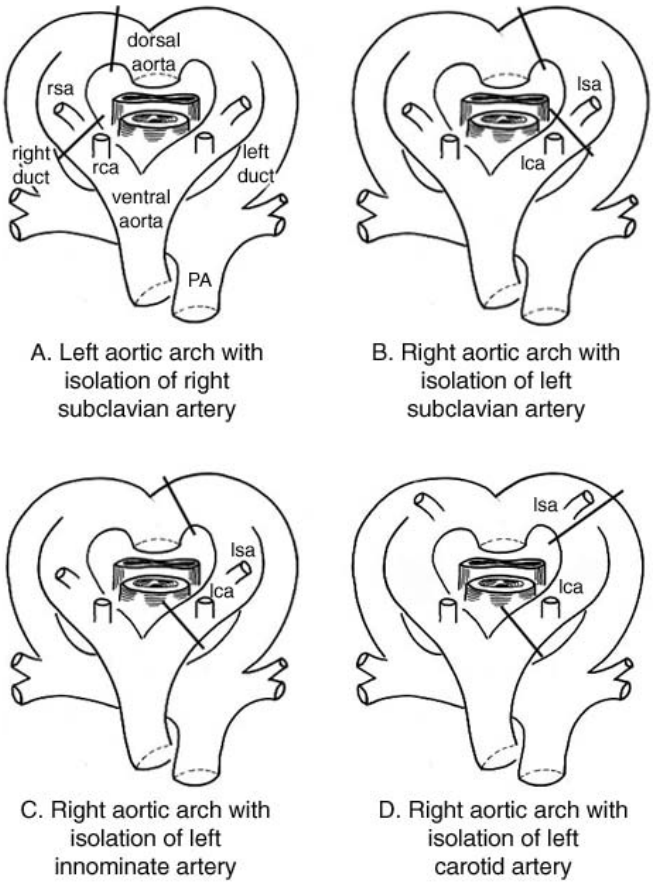


Fig. 41I-1 Various forms of isolation of the subclavian, innominate or carotid artery. The drawings are hypothetical aortic arch models with the sites of regression shown by bars. lca, left common carotid artery; lsa, left subclavian artery; PA, pulmonary artery; rca, right common carotid artery; rsa, right subclavian artery.

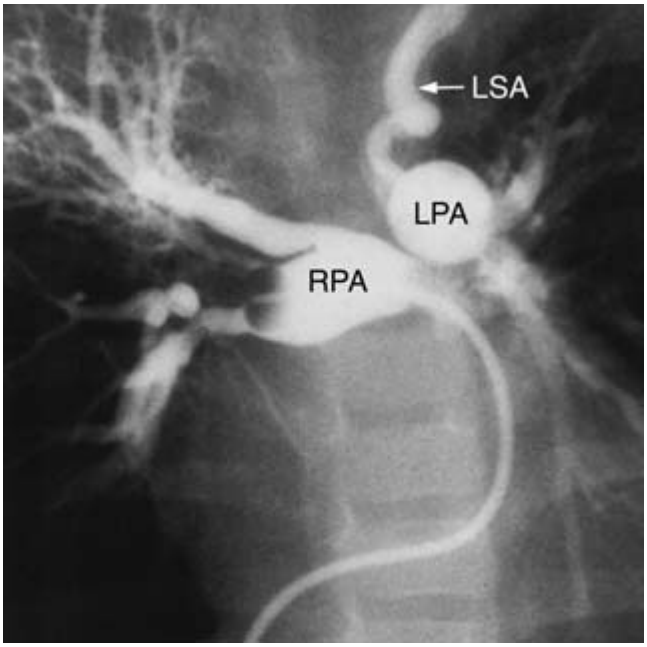


Fig. 41I-2 Origin of the left subclavian artery from the left pulmonary artery in a patient with tetralogy of Fallot. Pulmonary arteriogram shows that the left subclavian artery (LSA) arises from the left pulmonary artery (LPA). RPA, right pulmonary artery.

All references can be found at the end of the book. See pp. 836–8 for Chapter 41I.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

42

William G. Williams and David A. Ashburn

Pulmonary Ventricle to Pulmonary Artery Conduits

Introduction

During an operation to repair pulmonary atresia in 1965, Dr John Kirklin constructed a nonvalved conduit used to connect the right ventricle to the pulmonary artery by wrapping autologous pericardium around a Hegar dilator.[1] In 1966, Mr Donald Ross reported the use of a fresh aortic root allograft (or homograft) as a valved conduit for the same purpose.[2] These two sentinel events expanded the possibilities of repair for patients with complex congenital heart disease. They also initiated a search for the most physiologic and durable prosthetic device – a search that continues > 35 years later.

Conduit types

The conduits used by Drs Kirklin and Ross illustrate the two major types: nonvalved and valved. These two groups are further subdivided on the basis of their composition (Table 42-1). The sterilization process and preservation techniques are important variables that may affect conduit longevity. Sterilizing synthetic devices is simply and effectively accomplished by standard autoclaving, and long-term storage before implantation is similar to other surgical implants. However, tissue devices require more complex processing that may affect durability (Table 42-2). Although having the advantage of longer storage time, cryopreservation of allograft valves has been associated with reduced longevity when compared to those stored in antibiotic/nutrient solution.[3,4]

Indications for insertion

Anatomic lesions

Absence of a connection between the pulmonary ventricle and pulmonary artery (e.g. pulmonary atresia, truncus arteriosus) is an indication for a conduit. The conduit is native tissue if the pulmonary arteries can be sufficiently mobilized to allow a direct connection, although this usually requires an anterior patch to complete the connection. In addition, complex lesions with a component of pulmonary stenosis may require implantation of a conduit as part of a complete repair. For example, a conduit is placed between the right ventricle and pulmonary artery in patients undergoing the Rastelli operation for complete transposition of the great arteries (D-TGA), VSD, and pulmonary stenosis. A conduit may also be interposed between the left ventricle and pulmonary artery during repair of congenitally corrected transposition of the great arteries (L-TGA) when important pulmonary stenosis is present.

Residual lesions of the right ventricular outflow tract (RVOT)

In patients with defects such as tetralogy of Fallot, residual pulmonary insufficiency or stenosis may persist long after intracardiac repair. Patients with resultant right heart failure may benefit from pulmonary valve replacement with improvement in right ventricular function, functional class, and atrial arrhythmias.[5] However, the optimal timing for reintervention remains unknown. Therrien has suggested that patients having repaired tetralogy of Fallot with severe right ventricular dilation before valve replacement may be beyond full recovery of right ventricular function.[6] The inference that earlier valve replacement may preserve right ventricular function is tempered by the present limited durability of the valve.

Pulmonary autograft (Ross) operation

Patients with congenital or acquired aortic valve disease may be candidates for aortic valve replacement using the native pulmonary valve. After the native pulmonary valve and trunk are harvested for use in the aortic position, a conduit (usually an allograft) is inserted to restore continuity between the right ventricle and pulmonary artery.

Use of nonvalved conduits

A valve within the conduit is not always necessary. Because the valve is the primary source of late failure, avoiding a valve may defer subsequent conduit replacement. Patients suitable for a nonvalved conduit must have anatomically well developed, nonstenotic pulmonary arteries. The patient must also have low pulmonary vascular resistance, no anatomic or physiologic obstruction in the left atrium, and good systemic ventricular function.

Conduit reintervention

Most pulmonary devices fail as a result of progressive calcific stenosis, usually with the valve in a fixed, semi-open position.[7] The indications for reintervention for failing pulmonary prosthesis are progressive rise in outflow tact pressure gradient (with right ventricular pressure greater than two-thirds systemic pressure) or, less commonly, pulmonary regurgitation resulting in right heart failure. If the indication for initial valve replacement was right ventricular dilatation due to chronic pulmonary regurgitation, the hemodynamic burden of progressive conduit stenosis may be more poorly tolerated. Stenotic devices may be

improved by balloon dilation and stent placement. Although reintervention will be necessary, stenting may postpone reoperation for a number of months or even years.

Toronto experience

Since our first pulmonary conduit implant in 1966, we have inserted initial conduits into 930 patients. The most common diagnoses in these patients were tetralogy of Fallot, pulmonary atresia, and truncus arteriosus (Table 42-3). Including 32 additional patients referred from elsewhere for conduit replacement, 962 patients underwent a total of 1258 conduit operations. Operative risk for conduit implant and associated intracardiac repair was 16% for the overall experience. Operative risk persistently decreased over time and is currently 5%. The operative risk of replacement of an existing conduit is 4.0% and has not changed appreciably over time.

For the 930 initial implants, the most common devices were allograft valved conduits followed by xenograft valve implants and conduits (Table 42-4). Overall, implant structure included a tubular device containing a valve (609 patients, 66%), a pulmonary valve sutured orthotopically into the native RVOT (295 patients, 32%), or a direct connection using autologous tissue (26 patients, 3%). Only 27 patients had a nonvalved conduit at the initial operation. Patients having a monocusp patch inserted into the RVOT as part of an intracardiac repair are not included in these data.

Table 42-1 Classification of conduits

Non-valved	Valved
Tissue	Tissue
Pericardium	Aortic allograft
Autologous	Pulmonary allograft
Allograft	Xenograft
Xenograft	Stented
Autograft	Unstented
Interposition	Autograft (pericardial)
Direct connection	
Synthetic	Synthetic or composite
Dacron	Xenograft valve in Dacron tube
Polytetrafluoroethelene (PTFE)	Mechanical valve in Dacron tube

Table 42-2 Processing techniques for tissue conduits

Fresh sterile procurement and immediate implantation
Fresh sterile procurement, glutaraldehyde treatment and immediate implantation
Sterile procurement, antibiotic/nutrient storage or cryopreservation
Chemical sterilization
Beta-propriolactone
Glutaraldehyde
Gamma irradiation

Table 42-3 Primary diagnosis of 930 patients undergoing initial pulmonary conduit implant

Diagnosis	*n*	%
Tetralogy of Fallot	208	22
Pulmonary atresia +VSD	167	18
Truncus arteriosus	164	18
D-Transposition of the great arteries	84	9
L-Transposition of the great arteries	82	9
TOF with absent pulmonary valve	67	7
Double outlet right ventricle	63	7
Other	53	6
Pulmonary stenosis	29	3
Pulmonary atresia + IVS	13	1

TOF, Tetralogy of Fallot; IVS, intact ventricular septum.

Table 42-4 Types of connections utilized in 930 patients undergoing initial implant

Device type	Conduit	Direct connection	Valve implant	Total
Hancock porcine	104	–	121	225
Pulmonary allograft	183	–	42	225
Aortic allograft	170	–	12	182
Carpentier–Edwards porcine 76	–	5	81	
Polystan	67	–	–	67
Ionescu–Shiley pericardial	1	–	57	58
Mitroflow pericardial	–	–	34	34
Medtronic intact porcine	–	–	14	14
Monocusp	–	19	–	19
Other	–	7	2	9
Contegra xenograft	4	–	–	4
Tascon porcine	3	–	–	3
Medtronic mosaic porcine	–	–	2	2
Unstented porcine	–	–	2	2
St Jude pericardial	–	–	2	2
Bjork–Shiley mechanical	–	–	1	1
Non–valved conduit	1	–	–	1
Stented porcine	–	–	1	1
Total	609 (66%)	26 (3%)	295 (32%)	930

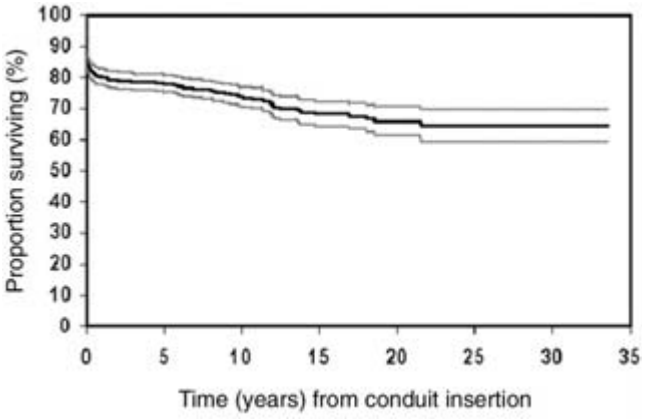


Fig. 42-1 Overall survival of 930 patients undergoing initial implantation of pulmonary conduit. The dark line represents the Kaplan–Meier survival estimate, and light lines enclose the 95% confidence interval.

Long-term function

Assessment of the durability of pulmonary prostheses is complicated by a number of factors. Marked variation in echocardiographic grading of pulmonary valve function exists, and differing definitions of conduit failure make interpretation of outcomes across institutions difficult. In addition, death occurring at some time after pulmonary prosthesis insertion may or may not be related to the function of the device. In either case, loss of the patient affects the assessment of prosthesis longevity. Overall survival amongst our patients is 80%, 74%, and 66% at 1, 10, and 20 years after conduit implant (Fig. 42-1). We have used conduit reoperation as a marker for failure. Although prosthesis function may have been sub-optimal for an undetermined period of time, reoperation represents a definitive end-point that is not especially qualitative. With reoperation as the only end-point (censoring dead patients at the time of death), overall freedom from conduit reoperation is 97%, 57%, and 29% at 1, 10, and 20 years after implantation (Fig. 42-2A). If death is included as an end-point, survival free of reoperation is 93%, 51%, and 23% at 1, 10, and 20 years (Fig. 42-2B). Although seemingly small in this instance, the magnitude of difference in Kaplan–Meier estimates resulting from the method of censoring is dependent upon the proportion of late deaths to reoperations. Long-term outcome data for non-fatal events produced in this manner are entirely dependent upon characteristics of the population that affect patient survival such as age and diagnosis. Therefore, outcome data for pulmonary conduits must be carefully interpreted bearing these considerations in mind.

A more descriptive method of analysing and reporting the outcomes of pulmonary conduits is the use of competing risks methodology.[8] Prosthesis reoperation and death represent two mutually exclusive outcomes and may be viewed as "competing" with one another. A patient who undergoes implantation of a pulmonary conduit is simultaneously at risk for more than one outcome and, at any time, is in one of three categories: reoperation for conduit failure, death before subsequent reoperation, and alive without reoperation. Competing risks determine the prevalence of each state over the follow-up time after implant (Fig. 42-3). At time 0, all patients have received a

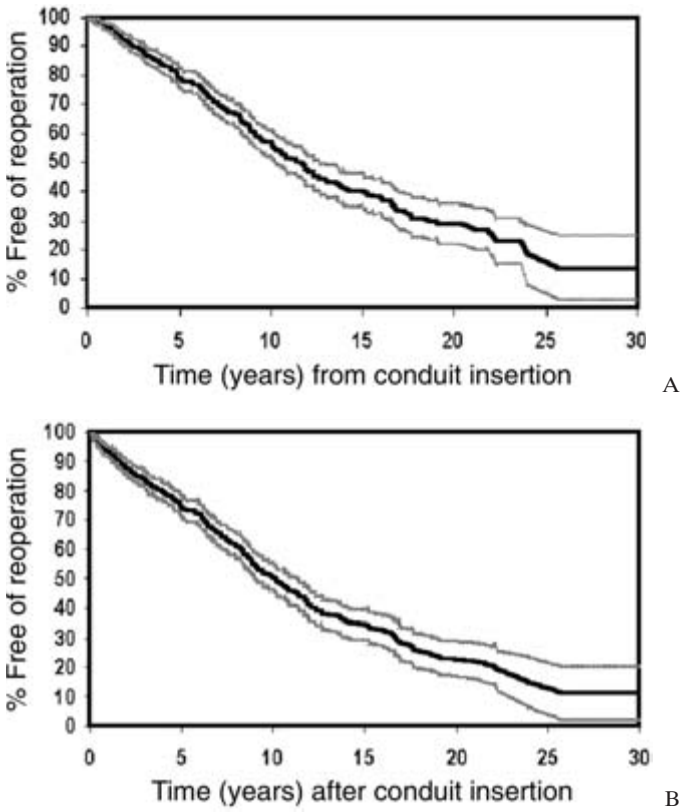


Fig. 42-2 Kaplan–Meier estimates of freedom from reoperation. Dark line, the Kaplan–Meier estimate; thin lines, 95% confidence interval. **A**. Death is not considered an end-point (patients are censored at the time of death). **B**. Death is considered an end-point in addition to reoperation such that survival free of reoperation is represented.

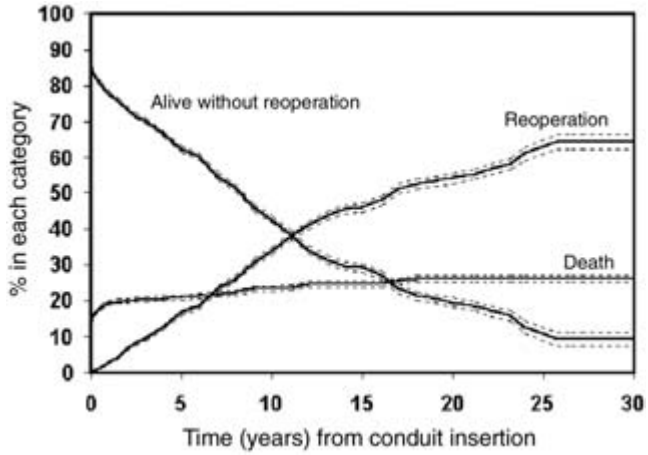


Fig. 42-3 Competing risks analysis of outcomes after initial pulmonary conduit insertion. The percentage of patients in one of three categories (reoperation, death, or alive without either outcome) is represented (vertical axis) at any time after conduit insertion (horizontal axis). At any given point in time, the sum of prevalence of all three states is 100%. For example, at 10 years after implant, 23% of patients have died, 34% have undergone reoperation for conduit failure, and 43% remain alive without reoperation.

conduit and are alive. At any time hereafter, the prevalence of death and conduit reoperation rises. There is an early increase in the prevalence of death corresponding to surgical mortality followed by a lower incidence of late deaths. At the same time, there is a steady increase in the prevalence of patients undergoing reoperation for conduit failure. By 20 years after conduit insertion, 26% of patients have died, 54% of patients have undergone reoperation, and only 20% of patients remain alive without undergoing reoperation. The application of competing risks methodology to the analysis of non-fatal events that compete with death gives the actual prevalence of outcomes expected over time.[9]

Durability following conduit replacement is not well assessed in the literature. In our experience, conduit durability is independent of the sequence of insertion (Fig. 42-4). First, second, third, and even fourth conduits have similar reoperation-free intervals. In a previous analysis, we found that patient age and device size are significant factors affecting long-term pulmonary prosthetic valve durability.[10] One might expect that patients returning for reoperation would be older and more capable of accepting larger devices – conferring improved conduit survival. However, the mean age of patients at initial implants is similar to the age of patients undergoing second or third implants. Successive allograft implantation has been implicated in reducing allograft longevity, potentially owing to a modulated immune response.[4,11] We analysed prosthesis survival in all 271 patients undergoing implantation of a second pulmonary implant. These patients were divided into four groups based on the sequence of allograft insertion: no allograft at first or second operation ($n = 109$), allograft at first operation replaced with non-allograft at second operation ($n = 62$), non-allograft at first operation replaced with allograft at second operation ($n = 64$), and allograft at first and second operation ($n = 36$). By this univariate analysis**,** survival of a second pulmonary device is not affected by the sequence of allograft placement, nor is durability different for patients who have or do not have an allograft (Fig. 42-5).

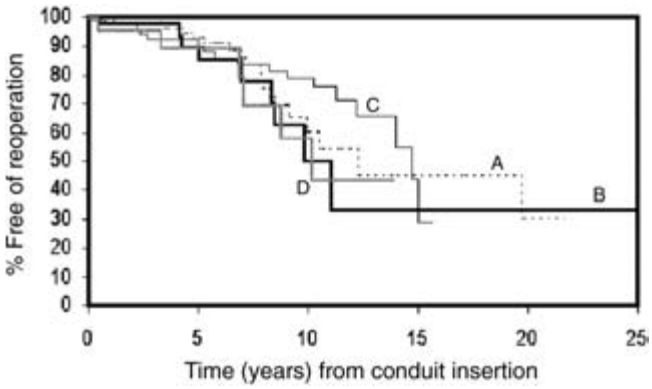


Fig. 42-5 Freedom from reoperation for 271 patients undergoing conduit reoperation (insertion of a second conduit). The patients have been grouped according to allograft sequence: A, non-allograft replaced by non-allograft ($n = 109$); B, allograft replaced by non-allograft ($n = 62$); C, non-allograft replaced by allograft ($n = 64$); D, allograft replaced by allograft ($n = 36$). No important inter-group differences in conduit longevity are observed.

Information from the literature

It is important to realize that patients with an incompetent, or even absent, pulmonary valve can survive without important limitations for many years. Shimazaki and colleagues demonstrated that patients with isolated congenital pulmonary valve incompetence remain asymptomatic for the first 3 decades of life.[12] Symptoms from right heart failure develop in 29% by age 40, beyond which the risk of developing symptoms rapidly increases. It is common to see a similar sequence among patients with pulmonary regurgitation after repair of tetralogy of Fallot who remain well until age 20–30 years. We have demonstrated that patient age and device size are important factors in determining the durability of pulmonary valves, and differences related to the various types of devices are less important.[10] Data from the Mayo Clinic have suggested that pulmonary allografts are more durable than aortic allografts when used in the pulmonary position, particularly for young children. Although allografts are advantageous for their technical ease of implantation, especially in infants, they do not have superior durability as measured by the interval free of reoperation. Stark demonstrated that allografts used at reoperation lasted less well than those implanted at initial operation.[4] We have not observed this trend in our experience as noted above. At reoperation, most obstructed conduits are excised and replaced with another one. As an alternative, the Mayo Clinic group devised a technique of autologous tissue reconstruction in which a xenograft pericardial patch is placed over the roof of the fibrous tissue bed of the explanted conduit.[13] They observed 100% freedom from reoperation for conduit obstruction at 10 years after operation. They purport that the technique simplifies conduit reoperation, provides a sizeable outflow tract, and yields excellent late results with low operative risk.

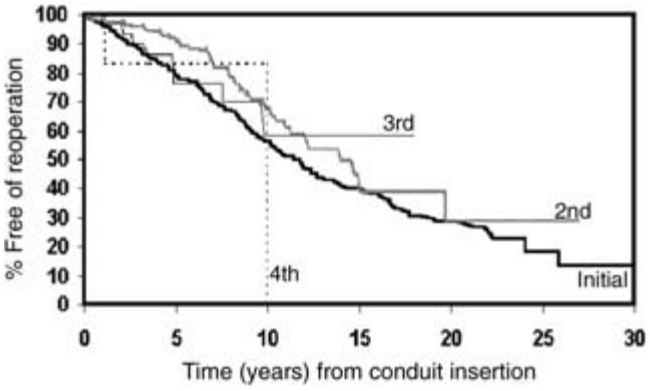


Fig. 42-4 Freedom from conduit reoperation by sequence of implant. There is no meaningful difference in conduit longevity observed for initial ($n = 930$), second ($n = 271$), third ($n = 47$), or fourth ($n = 8$) implants.

The Mayo Clinic published in 2003 its extensive experience addressing the late follow-up of 1095 patients undergoing an operation using pulmonary ventricle to pulmonary artery conduits.[13A] This entire experience included 1270 patients operated between April 1964 and January 2001, but this report concerned the 1095 patients operated before July 1992. The mean age of this group at operation was 9.6 ± 8.2 years. Diagnoses included pulmonary atresia/tetralogy of Fallot (459), transposition of the great arteries (232), common arterial trunk (193), double outlet right ventricle (121), corrected transposition (49), septated univentricular heart (36), and others (5). A porcine valved Dacron conduit was used in 730, homograft in 239, and non-valved

conduit in 126. They reported that early mortality decreased from 23.5% prior to 1980 to 3.7% for the most recent decade. Actuarial survival for early survivors at 10 and 20 years was 77.0 ± 1.5% and 59 ± 2.6%. On multivariate analysis, independent risk factors for late mortality included male gender, older age at operation, diagnosis of tranposition, corrected transposition, truncus, or univentrricular heart and a pulmonary ventricle/systemic ventricle pressure ratio < 0.72 ($P < 0.03$ for all). Freedom from reoperation for conduit failure at 10 and 20 years was 55.5% ± 2.0% and 31.9% ± 2.7%. On multivariate analysis, independent risk factors for conduit failure were homograft conduit, diagnosis of transposition, younger age at operation, and smaller conduit size ($P < 0.03$ for all).

The durability of allograft valves is disappointing, and their potential has not been fully realized in clinical practice. Conversely, preservation of semilunar valve function in transplanted hearts is invariably excellent. In this setting calcific degeneration is extraordinarily rare. Jonas and colleagues compared the histology of explanted allografts to valves retrieved from transplanted hearts at various intervals and observed that their histologic reaction is entirely different.[14] Although collagen is preserved, implanted cryopreserved allografts appear to be metabolically inactive. Lupinetti and associates observed the loss of endothelial cells from aortic and pulmonary allografts resulting from cryopreservation.[15] The viability of allograft cells may affect durability, but most evidence suggests that nonviable grafts have less immune reactivity and better survival.[16,17] Hawkins *et al.* confirmed the immune response generated by allograft insertion in children by demonstrating a measurable rise in panel reactive antibody titres.[18] O'Brien has led a multi-institutional effort in developing enzymatic decellularized xenografts and allografts using a process that preserves only the collagen matrix.[19] When implanted in animals, these experimental valves exhibit cellular and vascular ingrowth and have functioned for up to 1 year. Additionally, these valves have been shown to invoke no immune response as measured by panel reactive antibodies.[20] While this work is promising, the durability of decellularized grafts is presently unknown.

Other alternative valved conduits are being developed. Recent short-term results in which 71 patients with a bovine venous valved conduit were followed for 27 months compare favourably to allografts.[21] Hoerstrup and associates are developing a bio-engineered valved conduit that would obviate the immune reaction and have the potential for growth.[22] Hoerstrup and colleagues have used bio-absorbable polymers seeded with human umbilical cord cells to construct conduits with similar goals.[23] Mechanical valves in the pulmonary position should be mentioned. There are no large series reported, and experience is limited to anecdotal case reports of sudden, usually catastrophic, failure. The need for life-long anticoagulation further precludes serious consideration of pulmonary valve replacement using a mechanical prosthesis.

All references can be found at the end of the book. See p. 838 for Chapter 42.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Ian Adatia

Pulmonary Veno-Occlusive Disease

Introduction

Pulmonary veno-occlusive disease is a rare cause of pulmonary hypertension. At the Evian WHO conference in 1998 pulmonary veno-occlusive disease was classified as a category of pulmonary venous hypertension. Other categories of pulmonary venous hypertension include left-sided atrial or ventricular heart disease, left-sided valvular heart disease and extrinsic compression of central pulmonary veins such as fibrosing mediastinitis and tumors.

Pulmonary veno-occlusive disease causes pulmonary hypertension with pulmonary edema. The patients are often extremely symptomatic at presentation and present a diagnostic dilemma.[1] The disease may be mistaken for primary pulmonary arterial hypertension until lung biopsy or autopsy reveals the correct diagnosis. Pulmonary vascular resistance is elevated secondary to postcapillary idiopathic diffuse fibrous obstruction of the intraparenchymal pulmonary venules and veins. Brown[2] and Heath[3] first used the term pulmonary veno-occlusive disease in 1966 to describe the clinical syndrome of progressive dyspnea, pulmonary edema, pulmonary hypertension and right heart failure without evidence of left heart disease. The pathological findings included diffuse small pulmonary vein muscularisation and obstruction without the typical arterial lesions associated with primary pulmonary arterial hypertensive vasculopathy. Before these descriptions there had been seven other similar cases reported.[2,4]

Pulmonary veno-occlusive disease accounts for about 10% of patients evaluated for primary pulmonary hypertension. The disease is, therefore, rare with an estimated incidence of 0.1–0.2 cases per million. Reported cases have an equal sex ratio, in contrast to primary pulmonary arterial hypertension. The median age at disease onset is 29 years (range 9 days to 68 years) and 30% of reported cases occur in patients < 17 years of age. In children, the sex ratio is 1:1.

Pulmonary veno-occlusive disease may occur in siblings and has been described in brothers[5–7] and brother and sister[8] thus excluding a sex linked transmission. Pulmonary veno-occlusive disease has not been described, as yet, in successive generations. However, at the Toronto Hospital for Sick Children we have seen the daughter (with biopsy proven primary pulmonary arterial hypertension) whose mother died of pulmonary veno-occlusive disease.

Histology

The histological features are typified by complete or partial obliteration of small pulmonary veins and venules by intimal proliferation and the deposition of collagen and reticular fibres (Fig. 43-1). The vein lumen may have the appearance of multiple septations which are thought to represent attempts at vein recanalization. Crescent shaped lesions or irregular thick septa divide the vein lumen into compartments and may extend from pulmonary veins into bronchial veins. There may be secondary thrombosis of the vein.[3,5,9–12] The small pulmonary veins are arterialized with medial hypertrophy. The extrapulmonary veins are usually normal although large intrapulmonary veins may be affected.[3,11,12] The paucity of normal intrapulmonary veins is a hallmark of the disease. The interlobular septa are markedly thickened containing congested lymphatics with many hemosiderin laden macrophages. These are the histological correlates of Kerley B lines and thickened septa visible on chest X-ray (Fig. 43-2) and CT scan (Figs 43-3, 43-4, 43-5) and evidence of post capillary obstruction with passive congestion, focal hemorrhage and hemosiderosis. Venous infarcts may occur adjacent to the interlobular septa.[13] Pulmonary artery morphometry demonstrates marked medial hypertrophy in pre and intra-acinar arteries.[9] However, advanced pulmonary artery changes of fibrinoid necrosis, angiomatoid or plexiform lesions are not found usually.

The diagnosis may not be apparent on lung biopsy, particularly if hematoxylin and eosin stains are used, as the distinction between arterialised vein and artery may be difficult. Movat's stain differentiates internal and external lamina well and helps to define the absence or paucity of normal pulmonary veins. It may be difficult, apart from the degree of venous remodeling to differentiate the changes of pulmonary veno-occlusive disease from mitral stenosis or fibrosing mediastinitis by histology alone.[9] Pulmonary vein intimal fibrosis may be seen in lung resected from young patients with spontaneous pneumothorax and is related to local and chronic inflammation rather than pulmonary venous hypertension.[14]

Pulmonary veno-occlusive disease and associated disease

Malignancy

Approximately 35 reported patients have developed pulmonary veno-occlusive disease in association with malignancy (Hodgkin's lymphoma)[15,16] or treatment of malignancy with chemotherapy,[17–19] radiation[20] or bone marrow transplantation (both allogeneic and autologous).[21–25] Pulmonary veno-occlusive disease has been frequently associated with bone marrow transplantation and high dose chemotherapy particu-

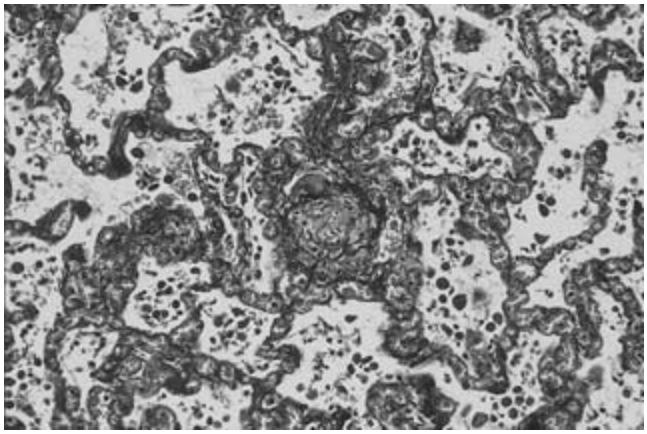


Fig. 43-1 H&E stain pulmonary section in pulmonary veno-occlusive disease demonstrating intraparenchymal pulmonary vein thickening and luminal occlusion.

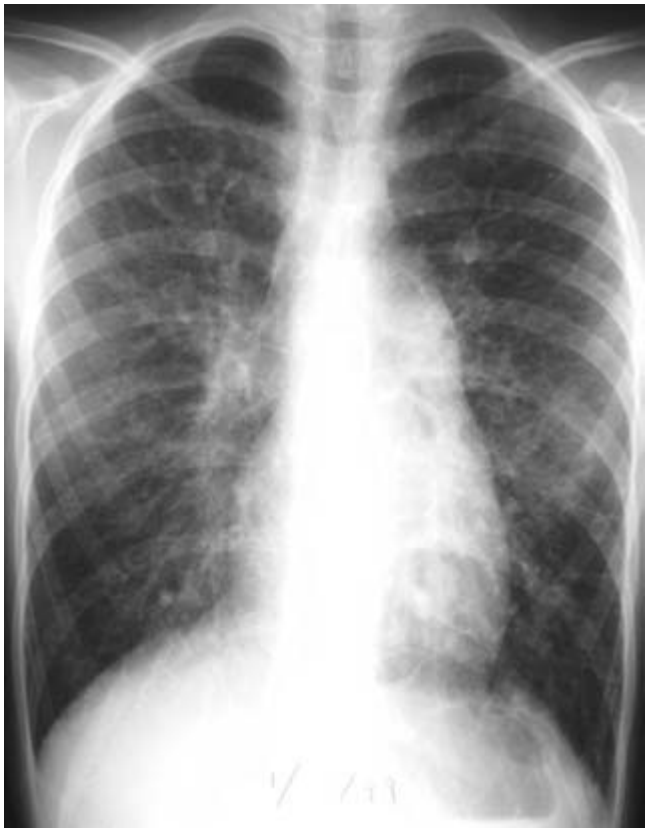
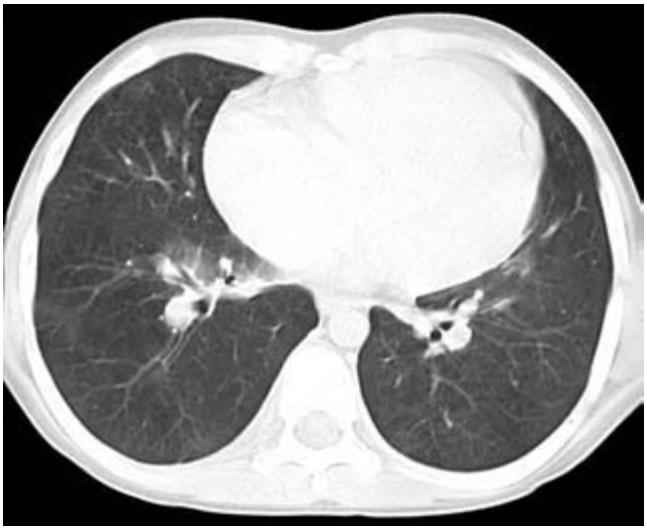


Fig. 43-2 Chest radiogram demonstrating Kerley's B lines, pulmonary edema and hyperinflation in pulmonary veno-occlusive disease.

larly with agents such as bleomycin, BCNU, mitomycin–C.[17] In children it has been reported most often after treatment of acute lymphoblastic leukemia and gliomas. In adults it has been described during treatment of cerebral glioma, melanoma,[26] lung cancer treated with gemcitabine,[27] cervical[19] and gastric carcinoma.[28] Interestingly, although hepatic veno-occlusive disease also complicates cancer therapy and may be caused by monocrotaline (Jamaican "bush tea"), the latter



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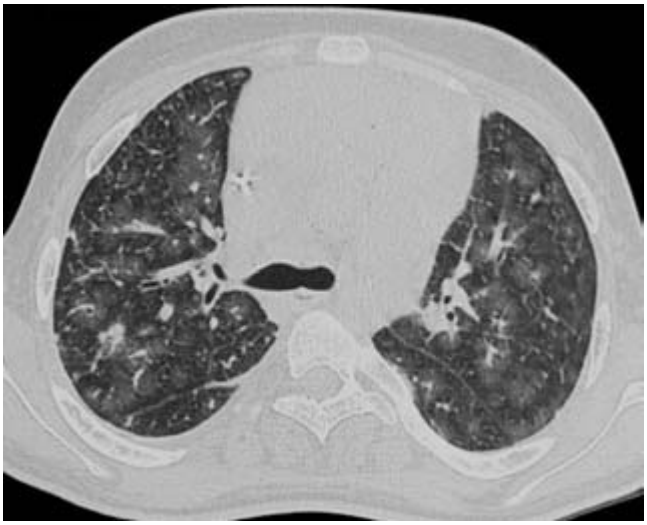

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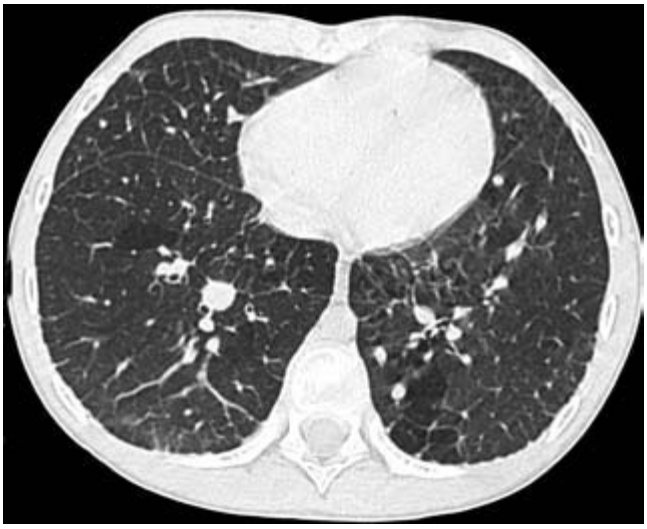


43.5

Figs 43-3, 43-4, 43-5 High resolution thin slice CT images demonstrating a ground glass "mosaic" pattern of uneven pulmonary edema with thickened interlobular septal lines and dilated lymphatics in histologically confirmed pulmonary veno-occlusive disease.

produces, in animal models, pulmonary arteriolar hypertension.[29] The association between hepatic and pulmonary veno-occlusive disease remains tenuous. There is one report of the development of pulmonary veno-occlusive disease occurring after resolution of hepatic veno-occlusive disease during cancer therapy.[21] However, pulmonary veno-occlusive disease occurs in association with interstitial pneumonitis during treatment of malignancy and the presence of pulmonary veno-occlusive disease may not be apparent until resolution of the pneumonitis after steroid therapy.[22,30] Pulmonary veno-occlusive disease has been reported with microangiopathic hemolytic anemia and chemotherapy for gastric adenocarcinoma[28] as well as after a second bone marrow transplantation for acute lymphoblastic leukemia.[24]

Autoimmune disease

Pulmonary veno-occlusive disease has been associated with the Felty's syndrome,[31] systemic lupus erythematosis,[32] CREST variant of scleroderma[33] syndrome, immune complex deposition, Raynaud's phenomenon,[34–37] following renal transplantation in a child for membranoproliferative glomerulonephritis,[38] hepatic cirrhosis (due to chronic active hepatitis) and celiac's disease.[7]

Despite the reports of pulmonary veno-occlusive disease with autoimmune disease and positive serology a direct link to immune mediated vascular lesions is lacking. Corrin *et al*.[39] demonstrated immune complexes in the alveolar wall but Hasleton *et al*.[7] could not find evidence of immune complex deposition in the vascualture of affected patients.

Other reported associations are with human immunodeficiency virus,[40,41] oral contraceptive use,[42] pregnancy,[43] preceding viral infection[44,12,45] and toxoplasmosis.[46]

Associations with congenital heart disease

Pulmonary veno-occlusive disease has been associated rarely with congenital heart disease other than patency of the foramen ovale. Biopsy proven pulmonary veno-occlusive disease has been described in a patient with pulmonary hypertension 5 years after aortic coarctation repair and resection of subaortic stenosis.[47] Pulmonary veno-occlusive disease has developed in the contralateral lung of a woman 4 years after left pneumonectomy for congenital unilateral pulmonary venous atresia.[48] Lang *et al.* described left sided pulmonary veno-occlusive disease in a patient with congenital unilateral absence of the right pulmonary artery.[49] In addition pulmonary veno-occlusive disease has been described in a patient with hypertrophic cardiomyopathy.[50]

Clinical features

The majority of patients present with dyspnea or syncope on exertion. The severity of symptoms is often out of keeping with the presenting clinical examination or resting hemodynamics. Other reported symptoms include orthopnea, paroxysmal nocturnal dyspnea, chest pain. Hemoptysis is rare, although presentation as life threatening pulmonary hemorrhage[51] and sudden infant death[52] are described. Physical examination reveals signs of pulmonary hypertension. Approximately one third of patients in the literature have displayed cyanosis at presentation. Clubbing was present in 5/11 patients in a recent series[53] yet only described in 3 prior cases.[54,30,55] Three reports comment on the absence of clubbing despite cyanosis.[45,3,12] Cyanosis and clubbing are unusual features of primary pulmonary arteriolar hypertension and their presence may alert one to the diagnosis of pulmonary veno-occlusive disease.

Chest X-ray

The chest X-ray demonstrates signs of pulmonary edema in 70% of reported cases. Kerley B lines (Fig. 43-2) are characteristic and represent septal thickening seen by CT scan. The distribution of pulmonary edema may be either diffuse or patchy and unlike mitral stenosis there is absence of upper zone pulmonary vein dilation and lower zone vasoconstriction. Pulmonary edema and septal lines may not be evident at presentation and may develop rapidly.[56] The right ventricle, right atrium and central pulmonary arteries are enlarged but the peripheral lung fields are not oligemic in contrast with primary arteriolar pulmonary hypertension or Eisenmenger's syndrome.[56]

The electrocardiogram

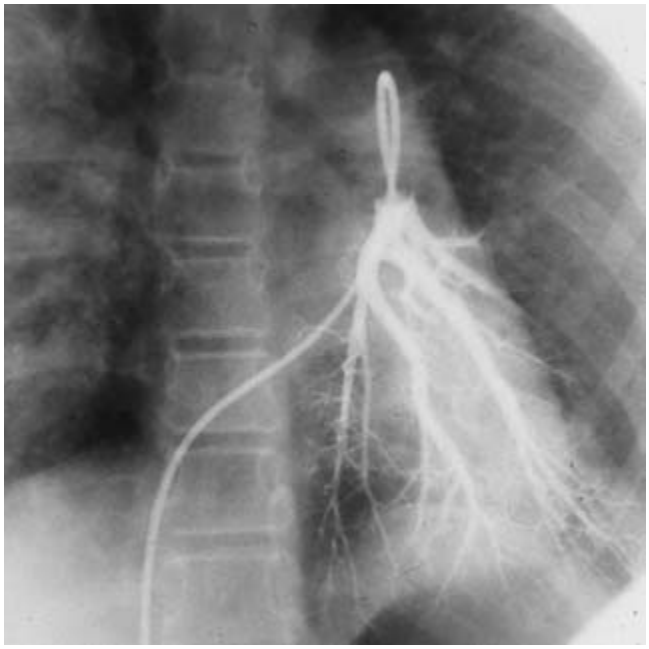
There are no characteristic ECG features of pulmonary veno-occlusive disease. The presence of right atrial enlargement, right ventricular hypertrophy with or without strain and right axis deviation do not aid in the differentiation from other causes of right ventricular hypertension.[2] The ECG may be within normal limits, even in the presence of dyspnea on exertion, but progresses rapidly.[36,57]

Echocardiography

Echocardiography is extremely useful in the diagnosis of all forms of pulmonary hypertension. However, there are no unique features of pulmonary veno-occlusive disease. Echocardiography can, however, rule out other causes of pulmonary hypertension with pulmonary edema such as extraparenchymal pulmonary vein compression, ostial pulmonary vein stenosis, cor triatriatum, supramitral stenosing ring, mitral valve stenosis, left atrial myxoma, cardiomyopathy and shunt lesions.

Cardiac catheterisation and angiography

The pulmonary artery pressures are elevated with median reported systolic and diastolic pressures of 75/36 mmHg (range 120/80–43/21) and mean pressure median of 56 mmHg (range 34–100). Right atrial pressures may be normal or elevated depending upon severity of disease and the presence of right heart failure. The characteristic hemodynamic feature is the variability of the pulmonary artery occlusion or "wedge" pressure. The pressure may be high, low or normal in the same patient depending on catheter position.[36] The pulmonary artery "wedge" pressure reflects left atrial pressure if there is an uninterrupted column of blood between pulmonary artery distal to the occluding balloon, or catheter tip, and the left atrium.[58] Pulmonary veno-occlusive disease is a patchy disease and "wedge" pressures will be normal (or reflective of left atrial pressure) if the catheter is "wedged" in a pulmonary artery proximal to unobstructed venules. However, if the catheter is "wedged" proximal to stenosed venules or completely occluded pulmonary venules the obtained pressure will not reflect left atrial



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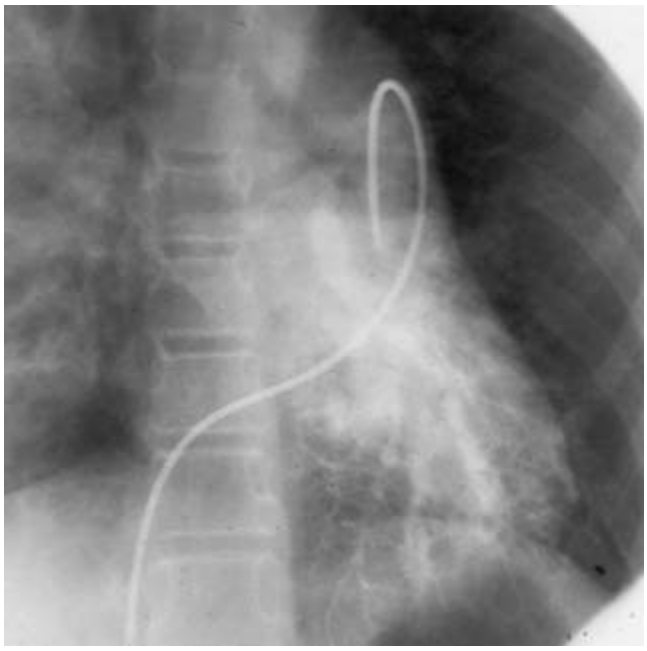

43.7

Figs 43-6, 43-7 Pulmonary artery wedge angiogram in pulmonary veno-occlusive disease. The peripheral pulmonary arteries are less tortuous with more peripheral haze than in pulmonary arterial disease.

pressure. In the former case the "wedge" pressure will be elevated and in the latter low.[58] If the catheter is "wedged" and flushed in this position there is an unusually rapid rise in pressure which falls slowly as the saline fails to clear because of the intervening obstructed venules.[54,59] The pulmonary artery wedge pressure is usually < 18 mmHg.[53]

In most cases of pulmonary veno-occlusive disease it is difficult to make the diagnosis unequivocally by angiography alone. Figures 43-6**,** 43-7**,** and 43-8 represent an exceptional patient. The described abnormalities include a delayed and patchy transit time of contrast from pulmonary artery to appearance in the left atrium.[56,60] The pulmonary artery may in extreme cases remain well opacified even after contrast appears in the aorta.[60] Pulmonary angiography may help to exclude chronic thromboembolic disease or peripheral pulmonary artery stenoses as a cause of proximal pulmonary artery hypertension. However, Katz *et al.* described pulmonary veno-occlusive disease presenting with pulmonary artery thrombosis.[43]

CT scan

High resolution chest CT scan may offer useful information and may help to differentiate pulmonary veno-occlusive disease from primary pulmonary arterial hypertension (Figs 43**-**3**,** 43**-**4**,** 43**-**5). The CT scan appearances that have been described include diffuse multifocal groundglass opacities, a mosaic pattern of attenuation with patchy areas of increased or decreased attenuation due to regional differences in perfusion, smooth (but occasionally nodular)[61] septal interlobular thickening, centrilobular nodules, mediastinal hilar adenopathy (in the absence of malignant disease) and pleural effusions.[61–64] Other CT findings, enlarged central pulmonary arteries with normal size airways, normal central pulmonary veins, right atrial and ventricular enlargement are present but do not help to differentiate pulmonary arterial from pulmonary veno-occlusive disease. However, demonstration of a normal left atrium and extrapulmonary veins excludes left heart inflow obstruction as a cause of pulmonary venous hypertension. Early disease may not show all of these features.[63] Mediastinal lymphadenopathy is an inconstant finding that has been described in approximately 8 patients without malignancy.[37,53,54,65,66] Mediastinal lymphadeopathy was not detected by CT scan in 8 patients reported by Swensen *et al.*[63] It may be difficult to differentiate pulmonary veno-occlusive disease from infiltrative lung disease

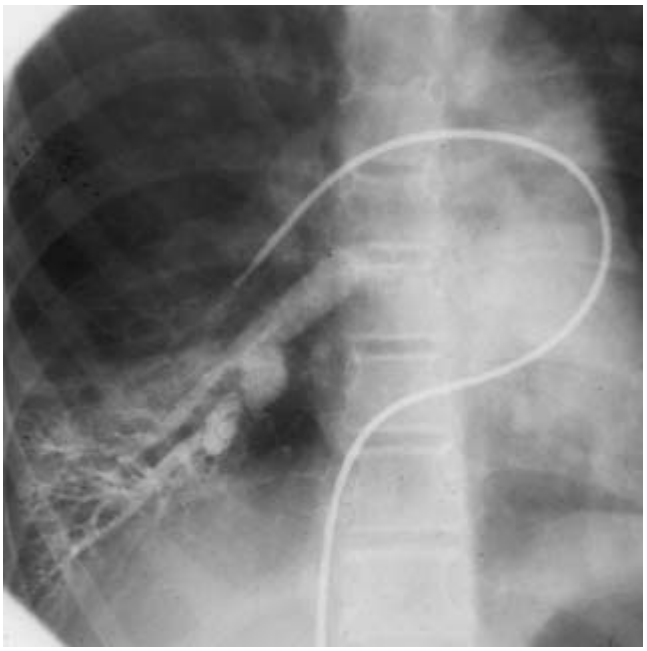

Fig. 43-8 The intraparenchymal pulmonary venous phase is distinctly abnormal with "bleeding" of the veins and delayed contrast clearance. The pulmonary venous connection with the left atrium is unobstructed.

by CT scan and mosaic attenuation due to vascular disease may be identified correctly in only a third of cases.[67]

V/Q Scan

Nuclear lung perfusion scan may demonstrate a segmental contour pattern,[68] small inhomogeneous sub-segmental matched or mismatched defects,[53] multiple mismatched segmental perfusion defects suggestive of thromboemboli[53,66] or nonspecific soft, fluffy inequalities of perfusion.[69] Lung perfusion scans may be entirely normal in 60% of cases.[53]

Pulmonary function tests

A severe impairment of single breath carbon monoxide diffusing capacity (D_{LCO}) especially with normal lung volumes and spirometry is an extremely useful test result in the differential diagnosis of primary pulmonary hypertension.[70] D_{LCO} has been reported in *c.* 40 patients with pulmonary veno-occlusive disease with a median D_{LCO} of 55% of predicted range (14–102%).[3,7,13,18,20,22,23,27,30,32,33,38,41,46,53,71–73] Approximately 50% of these patients have a severe reduction of D_{LCO} that is below 50% of predicted. In comparison patients with arterial pulmonary hypertension have D_{LCO} that is mildly reduced (69–70% predicted)[74] or normal.[75] Patients with pulmonary fibrosis and pulmonary hypertension will demonstrate a marked reduction in vital and total lung capacity, as well as, D_{LCO}.

Pulmonary function testing may yield mild restrictive, obstructive or combined patterns in a minority of patients with pulmonary veno-occlusive disease.[53]

Bronchoscopy

Bronchoscopy is not a routine test in the evaluation of pulmonary veno-occlusive disease. Nevertheless, the report by Matthews and Buchanan[71] is interesting for the insights it provides into the pathophysiology of pulmonary veno-occlusive disease and the interaction between airway and vasculature. They describe a sharp demarcation between normal main bronchi and intensely hyperemic lobar and segmental bronchi. They point out that the bronchial veins that drain the trachea and main bronchi return to the systemic venous circulation whereas bronchial veins draining lobar, segmental and peripheral bronchi return to pulmonary veins. In pulmonary veno-occlusive disease these bronchial veins become congested and enlarged. In severe cases the bronchial veins may act as a an alternative pathway from precapillary to postcapillary circulation and permit deoxygenated pulmonary arteriolar blood to bypass totally obstructed pulmonary venules in one lung segment to another. This may account in part for hypoxemia in patients with pulmonary veno-occlusive disease as disease progresses.

Differential diagnosis

It may be difficult to differentiate pulmonary veno-occluisve disease from primary pulmonary artery hypertension or chronic thromboembolic disease.[1] However, once the patient is recognised to have pulmonary hypertension with pulmonary edema, and cardiac conditions with elevated left atrial pressure are excluded further confirmation of the diagnosis requires lung biopsy. In children pulmonary veno-occlusive disease masquerades as interstitial lung disease especially if the CT scan is interpreted in isolation. Indeed in the review of Sondheimer 9/92 children who were thought to have interstitial lung disease had pulmoary veno-occlusive disease.[76] Other diseases which produce pulmonary venous obstruction and have been confused with pulmonary veno-occlusive disease include pulmonary capillary hemangiomatosis,[77] sarcoidosis,[78] Langerhans' cell granulomatosis,[79] left atrial tumour,[80] sclerosing mediastinitis,[9] pulmonary lymphangiomatosis. A syndrome of venulitis affecting pulmonary and systemic veins has been described.[81,82]

Treatment and outcome

The survival of patients after the diagnosis of pulmonary veno-occlusive disease is poor. Survival is generally supposed to be < 2 years from diagnosis[1] with a recent series of 11 patients reporting a 72% mortality in 1 year.[53] Survival of seven years without specific therapy has been reported.[36]

Pulmonary edema, which may be fatal, has been reported after prostacyclin infusion.[73,53] There is speculation that the dose of vasodilator may influence whether or not pulmonary edema is precipitated.[83] Nevertheless, symptomatic improvement and prolonged survival have been reported with prostacyclin, prazosin, dipyridamole and calcium-channel blockers.[26,53,54,84]

Pulmonary veno-occlusive disease related to cancer therapy may respond to steroids and warfarin.[23]

Most would recommend early listing for lung transplantation,[9,20,53,66,62] a cautious trial of vasodilator therapy, anticoagulation[2,54] and perhaps a short course of steroids.[1,21,54] A single prolonged response to azothioprine in a woman with associated autoimmune disease has been described.[35]

Since 1994 we have diagnosed three children with pulmonary veno-occlusive disease in the Toronto childhood pulmonary hypertension clinic. Two patients derived important symptomatic benefit from vasodilator therapy. One patient treated with diltiazem and subsequently intravenous prostacyclin survived 6 years from diagnosis and died awaiting transplantation. Another with rapidly progressive disease received initial benefit from continuous domiciliary nitric oxide inhalation but died 6 months after diagnosis. Another underwent bilateral lung transplantation 1 year after diagnosis but died from the sequelae of recurrent rejection within 1 year of transplantation.

Conclusion

Pulmonary veno-occlusive disease remains difficult to diagnose and treat. Differentiation from primary arteriolar pulmonary hypertension is challenging in those cases that do not demonstrate all the classic features of the disease. The disease may progress rapidly and at presentation early listing for lung transplantation seems to offer the best hope for prolonged survival.

All references can be found at the end of the book. See pp. 838–40 for Chapter 43.

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Ian Adatia

Pulmonary Vascular Disease

Introduction

Pulmonary arterial hypertension is a devastating disease. The histological sequential changes are smooth muscle hypertrophy of the arterial wall, intimal proliferation, *in situ* thrombosis, small vessel occlusion and the formation of plexiform lesions. The cross-sectional area of the pulmonary vascular bed is diminished severely by small vessel obliteration. The progressive and sustained elevation in pulmonary vascular resistance leads to right heart insufficiency. After the onset of symptoms, the clinical course is unremitting with progressive right heart failure until death. Children suffer as badly as adults.[1] Until the last decade, conventional therapy was limited to digoxin, diuretics, calcium channel blockers and warfarin anticoagulation.[2,3] However, recent advances in vascular biology and molecular genetics have been translated rapidly into clinically relevant treatments.

The spectrum of pulmonary hypertension

Pulmonary hypertension is defined as a mean pulmonary artery pressure above 25 or 30 mmHg with exercise. At the Evian conference in 1998, the classification of pulmonary hypertension was revised to reflect clinical patterns of disease.[4,5] Primary pulmonary hypertension, which may be familial or sporadic, refers to pulmonary hypertension for which no cause can be identified. It is a form of pulmonary arterial hypertension. Other causes of pulmonary arterial hypertension include collagen vascular disease, congenital systemic to pulmonary shunts (Eisenmenger's), portal hypertension, HIV infection, exposure to drugs notably anorexigens (fenfluramine) and persistent pulmonary hypertension of the newborn. Pulmonary hypertension may be caused by pulmonary venous abnormalities (e.g. pulmonary veno-occlusive disease, left-sided heart disease) or associated with respiratory diseases and hypoxemia (e.g. alveolar capillary dysplasia, upper airway obstruction), chronic thrombotic or embolic disease (e.g. sickle cell disease) and finally disease directly affecting the pulmonary vasculature such as schistosomiasis and sarcoidosis.

The genetics of primary pulmonary hypertension

Familial vs. sporadic disease

Remarkable advances in the understanding of the genetics of primary pulmonary hypertension have emerged from the first clinical observations of familial pulmonary hypertension, 70 years ago, to the identification of the genetic mutations encoding bone morphogenetic protein receptor 2 (BMPR2).[6–8] The first report of the familial occurrence of primary pulmonary hypertension appears to have been in 1927.[9] Clarke *et al.*[9] described the clinical and autopsy findings of primary pulmonary hypertension in sisters (aged 5 and 8 years). They credited the suggestion of an "inherited aetiological factor" to Kidd in 1904.[9] However, Dresdale *et al*.[10] were the first to document familial transmission of the disease from one generation to the next. They described a woman and her son, who died from primary pulmonary hypertension aged 43 and 21 years old, respectively. The mother had, in addition, lost a brother ("at a young age") and sister (aged 31 years) from right heart failure, presumably owing to primary pulmonary hypertension. These early clinical observations describe many of the now established features of the inheritance of familial primary pulmonary hypertension including vertical transmission, genetic anticipation and the curious observation that within a family, affected males are clinically symptomatic and die younger than females.

The incidence of familial primary pulmonary hypertension would appear to be 1 to 2 cases per million with 6% of the cases in the NIH Registry fulfilling the criteria for the disease,[11] although subsequent observations suggest this is an underestimate with at least 50 affected families in the US.[12] Familial primary pulmonary hypertension differs from nonfamilial or sporadic forms of the disease with an earlier diagnosis after the onset of symptoms. Familial primary pulmonary hypertension is otherwise clinically indistinguishable from the sporadic form with a female to male ratio of 2:1 in adults but not children in whom the ratio is 1.3:1.

Familial primary pulmonary hypertension is transmitted vertically and in one family as many as five successive generations have been affected.[12] It may be transmitted from male to male and we have documented in the Toronto Childhood Pulmonary Hypertension Clinic the transmission of primary pulmonary hypertension from unaffected father to two daughters, each with a different mother. This mode of transmission excludes X linkage and is highly suggestive of an autosomal dominant gene. However, despite fulfilling criteria for autosomal dominant transmission, not all offspring are affected and not all carriers of the gene manifest the disease. Autosomal dominance with variable and lower penetration in males may explain the female preponderance of adults who carry the gene and manifest the disease.[13] Alternatively, the disease may affect males more severely at a younger age thus limiting the males who survive to adulthood. In addition fewer males are born to families who carry the gene, supposedly owing to selective wastage of the male fetus.[13]

The observation that within families with primary pulmonary hypertension successive generations are more severely affected at a younger age is termed genetic anticipation. Trinucleotide repeat amplification has been demonstrated in other diseases (e.g. fragile X syndrome) which show genetic anticipation, but not in primary pulmonary hypertension.

An association with major histocompatibility complexes in childhood familial hypertension suggests an autoimmune disease,[14] although antinuclear factors are usually negative in children.

Histology of familial, sporadic and Eisenmenger's vasculopathy

The histological features of familial pulmonary hypertensive arteriopathy appear to be heterogeneous and there is frequent coexistence of thrombotic and plexiform lesions within and among families.[15] Until the seminal publication of Lee *et al*.,[16] familial primary pulmonary hypertension appeared indistinguishable histologically from both sporadic primary pulmonary hypertension, and Eisenmenger's complex. Lee *et al*.[16] have demonstrated that the plexiform lesions of patients with familial primary pulmonary hypertension contain monoclonal proliferating endothelial cells in contrast to the polyclonal endothelial cell proliferation in secondary pulmonary hypertension (owing to congenital cardiac shunts). This is the first report of monoclonality of endothelial cells in a non-neoplastic vascular disease. The presence of monoclonal endothelial cell proliferation in primary pulmonary hypertension suggests that somatic gene alteration, similar to that present in a neoplastic process, may permit a clonal expansion of pulmonary endothelial cells.

Other histological subgroups of primary pulmonary hypertension include pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis: both may be familial but the inheritance seems to be distinct from the arteriopathy.[17]

Chromosome 2q33 and bone morphogenetic protein receptor 2

Independently, two groups have linked familial primary pulmonary hypertension with definitive logarithm of odds (LOD) scores to chromosome 2q33.[6–8] The detection of the haplotype associated with disease in a presumed to be unaffected sibling has led to the diagnosis of pulmonary hypertension.[18] Asymptomatic carriers may demonstrate an abnormal pulmonary vascular response to exercise.[19] Genetic testing offers the opportunity to at risk family members of close observation and early treatment if disease develops. However, more than just genotype is required for clinical disease to develop and interaction with environmental or other genetic traits is important. Thus, identification of haplotype insufficiency may provoke more anxiety than benefit.

Fifty per cent of familial and 25% of sporadic cases of primary pulmonary hypertension are caused by mutations in the gene encoding bone morphogenetic protein receptor 2 (BMPR2). Over 25 different mutations have been identified. A specific mutation is transmitted within a family.[20] BMPR2 is part of the transforming growth factor beta (TGF-β) pathway.[20–22] The TGF-(signaling pathway) is important in maintaining vascular and endothelial cell integrity. TGF-(inhibits vascular endothelial cell proliferation in culture), which may be pertinent to the observation that the plexiform lesion in patients with primary pulmonary hypertension represent abnormally proliferating monoclonal endothelial cells.[16] Mutations of a TGF-(type 1 receptor gene), activin-receptor-like kinase 1 (ALK1), and endoglin, an accessory protein of the TGF-(receptor complex), are present in hereditary hemorrhagic telangiectasia.[23] Patients with hereditary hemorrhagic telangiectasia may develop pulmonary arteriovenous malformations but very rarely pulmonary hypertension.[24] In fact patients with pulmonary arteriovenous malformations usually have low pulmonary artery pressures and resistances. However, Trembath *et al*. evaluated five kindreds with hereditary hemorrhagic telangiectasia and identified 10 patients with pulmonary hypertension (2 of 10 had pulmonary arteriovenous malformations) and mutations in ALK1.[25] This suggests that mutations in the TGF-(pathway) are associated with diverse vascular effects including abnormal dilatation, proliferation and small vessel occlusion. Interestingly, pulmonary artery smooth muscle cells from patients with primary pulmonary hypertension exhibit abnormal growth responses to TGF-β.[26] Gene transfer of vascular endothelial growth factor VEGF attenuates monocrotaline induced pulmonary hypertension mice and illustrates the potential impact of gene therapy.[27]

In summary, familial primary pulmonary hypertension is transmitted as an autosomal dominant gene with incomplete penetrance. From generation to generation there is genetic anticipation and a preponderance of affected adult females with a reduction in male progeny. The discovery of the genetic mutations of BMPR2 on chromosome 2q33 in 25% of sporadic and 50% of families with primary pulmonary hypertension will focus research efforts towards early detection of disease in asymptomatic carriers, better understanding of the triggers that result in clinical disease in the genetically predisposed and targeting the gene therapeutically.

Primary pulmonary arterial hypertension – clinical features

The etiology of primary pulmonary arterial hypertension is unknown. It tends to affect predominantly young people and its course is relentlessly fatal although isolated cases of spontaneous regression have been documented.[28,29] Children despite their young age often present with advanced disease[1,30] and median survival was 4 years[1] with a 37% survival at 1 year and 12.5% at 2.5 years.[30] Children present with similar pulmonary artery pressures to adults but a higher cardiac index. Right ventricular function is an important determinant of survival and a right atrial pressure of < 7.5 mmHg suggests a better outcome.[1] Similarly, a low mixed venous saturation does not bode well (< 63%) in either adults or children.[3,30,31] Children are more likely to respond to vasodilator therapy than adults (41% vs. 26%)[1] and may have a greater hemodynamic response.[32,33] In some studies hemodynamic response to vasodilators augurs a longer survival[30,33] but not all.[1] Despite this the histological profile of lung biopsy from children with primary pulmonary hypertension suggests increased vasoconstriction with more medial hypertrophy but fewer plexiform lesions and intimal fibrosis.[34]

Pulmonary hypertension in the absence of an intracardiac shunt is a difficult diagnosis to make in childhood and there may be a substantial delay from onset of symptoms to diagnosis. Common symptoms are dyspnea (often diagnosed as "asthma"), syncope or near syncope, generalized seizures, failure to thrive,

palpitations or cyanosis with exercise and leg edema. Exercise intolerance is almost always present. Chest pain is a rare presenting complaint in children (5.5%) as opposed to adults. Nevertheless, myocardial ischemia may be evident in children particularly when pressures rise above systemic and with exercise.

The chest radiograph provides valuable evidence of pulmonary hypertension with cardiac enlargement and characteristic enlargement of the proximal pulmonary arteries with distal pruning (Fig. 44-1). Pulmonary edema usually suggests pulmonary venous hypertension.

The electrocardiogram shows right atrial and ventricular hypertrophy with a strain pattern in 70–80% of patients.

Echocardiography is diagnostic of elevated right ventricular pressure and will provide evidence of a normal mitral valve and pulmonary veins. Other causes of right ventricular hypertension due to sub, valvar or supravalvar pulmonary stenosis are readily apparent. Small proximal pulmonary arteries with continuous distal color Doppler flow indicate multiple peripheral pulmonary artery obstructions. Intracardiac and extracardiac shunts can be excluded. Contrast saline echocardiography with visualization of the four chambers and descending aorta is useful to exclude right to left shunts and the appearance of microbubbles in the descending aorta may help to delineate a patent ductus arteriosus with reversed shunting.

Lung perfusion scanning is less likely to yield the diagnosis of chronic pulmonary emboli than in adults. Exceptions are children with ventriculo-atrial shunts or long-term intravenous lines who may develop pulmonary hypertension secondary to thromboemboli.[35] Nuclear perfusion scans are of value if single lung transplantation is to be considered in which case the lung with the poorest perfusion should be sacrificed. Cardiac catheterization and angiography are important in the evaluation and are discussed more fully below.

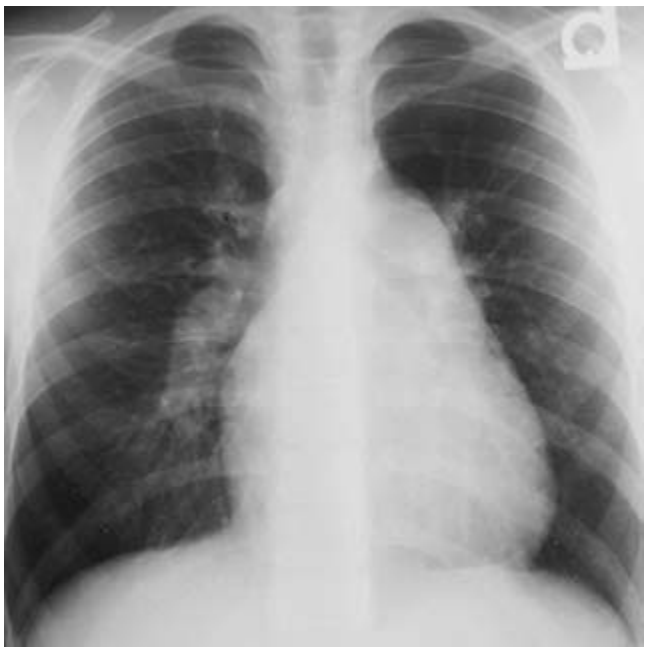

Fig. 44-1 Chest radiogram in primary pulmonary artery hypertension demonstrating right sided enlargement and dilated proximal pulmonary arteries with marked paucity of peripheral vessels.

Calcium channel blockers

In 1992, Rich *et al*.[2] demonstrated in 64 patients with primary pulmonary hypertension that high dose calcium channel blockade reduced pulmonary artery pressure and resistance by > 20% in 26% of patients. These patients were maintained on oral nifedipine or diltiazem with a 94% survival at 5 years and evidence of reduced regression of right ventricular hypertrophy and increased exercise tolerance and quality of life. Patients who responded with a fall in pulmonary vascular resistance but not pulmonary artery pressure did not experience a reduction in symptoms with long-term therapy. It is of note that calcium channel blockers may exacerbate right ventricular failure and need to be administered with caution.[36] Calcium channel blocker therapy is effective in only a minority of patients and has been superseded by newer agents.

Vasoactive mediators and pharmacological treatments

Prostacyclin is an endogenous vasoactive mediator, which promotes vasodilation, inhibits platelet aggregation and vascular smooth muscle proliferation. Thromboxane mediates opposite and generally deleterious effects in pulmonary vascular disease. The ratio of prostacyclin to thromboxane production is reduced in primary pulmonary hypertension,[37] the Eisenmenger complex and children with left to right intracardiac shunts but returns to normal after successful operative closure.[38]

Long-term prostacyclin infusion

Higenbottam *et al*. reported the beneficial effects of long-term prostacyclin in patients with primary pulmonary hypertension[39,40] Prolonged prostacyclin infusion was associated with an improvement in patient well-being, exercise tolerance and survival. This has subsequently been confirmed by other groups.[41,42] The results of long-term prostacyclin in patients awaiting heart–lung transplantation have been compared with historical controls. Survival at 1 year was improved and prostacyclin reduced mortality by 66%. Interestingly at 2 years there was no improvement over conventional therapy except in patients with more advanced disease (low mixed venous oxygen saturation and evidence of right ventricular dysfunction). In these patients long-term benefit was unrelated to the effects observed during acute administration raising the possibility that prolonged prostacyclin infusion works through mechanisms other than vasodilation such as inhibition of platelet aggregation and remodeling of the vascular wall.

Side-effects such as headache, cutaneous flushing and abdominal pain are seen usually transient and settle over 24 h but may reappear when the dose is increased.

Complications are related to the indwelling venous line, and delivery pump failure with two episodes of sepsis per patient per year. Dyspnea and syncope may occur during interruption of the infusion. The requirements for prostacyclin tend to increase with time[43] and dose titration to a normal cardiac index is required.[44] Nevertheless, prolonged intravenous prostacyclin therapy has a considerable impact with survival at 1, 2, and 3 years of 88%, 76%, and 63% which is significantly better than 59%, 46%, and 35% compared to historical controls. Baseline

predictors of survival include exercise tolerance, NYHA functional class, right atrial pressure and acute vasodilator response to adenosine or inhaled nitric oxide. After 1 year of therapy additional predictors of survival are cardiac index and mean pulmonary artery pressure.[44]

Continuous intravenously delivered prostacyclin improves exercise tolerance, pulmonary vascular hemodynamics and survival in pulmonary hypertension.[39,41,45,46] This therapy has revolutionized the chronic treatment of pulmonary hypertension. However, the drawbacks to continuous intravenous prostacyclin are the need for and complications of prolonged central venous access, the side-effects of the drug, and delivery system malfunction. Dangerous rebound effects occur if the infusion is interrupted. These problems are particularly cumbersome in the treatment of children and require the parents to acquire the skills of a critical care nurse, if the therapy is to succeed. Unsurprisingly many patients are reluctant to embark on such therapy. The development of alternative treatments is desperately needed. One approach has been to explore different delivery techniques for prostacyclin. These include the development of oral analogues, the aerosolisation of prostacyclin and the use of subcutaneously delivered prostacyclin. Beraprost is an orally active analogue of prostacyclin that has been shown to have beneficial short-term as well as long-term effects in pulmonary hypertension.[47,48] Functional class and 6-min walk improved by 63 metros after the addition of Beraprost to conventional therapy.[48] The improvement was similar to that observed after treatment with intravenously delivered prostacyclin and sustained over one year of therapy. However, there was only a small decrease in systolic pulmonary artery pressure and pulmonary vascular resistance was not measured. The side-effects of prostacyclin including facial flushing, arthralgia, muscle pain and nausea or diarrhea were common but clearly the catheter related morbidity was avoided.

There have been studies evaluating the effect of aerosolized prostacyclin, usually iloprost, in pulmonary hypertension. Inhaled iloprost is as effective as inhaled nitric oxide acutely, but there is no additive response to both agents.[49,50] Inhaled iloprost improves exercise capacity in severe pulmonary hypertension.[51–53] The findings are encouraging but do suggest that combination with an oral agent such as bosentan or sildenafil is likely to be the favored approach.[54]

Inhaled nitric oxide

Inhaled nitric oxide remains the acute pulmonary vasodilator of choice because it is selective for the pulmonary vascular bed, improves intrapulmonary shunt fraction and has a short half-life.[55] It is ideally suited for use in the cardiac catheterisation laboratory or in mechanically ventilated patients on the critical care unit with persistent pulmonary hypertension of the newborn or after cardiac surgery.[56–59] However, seemingly unjustified price increases driven by commercial exploitation of a natural gas may threaten the continued and widespread use of inhaled nitric oxide. Promising preliminary data are accumulating, using ingenious delivery systems, as experience is acquired with the chronic administration of inhaled nitric oxide to ambulatory patients. It suggests a beneficial reduction in pulmonary vascular resistance and improvement in patient symptoms with prolonged nitric oxide administration in both adults and children.[60–63] The drawbacks appear to be the need for continuous delivery and rebound pulmonary hypertension. Interestingly, a recent report suggests that although oxidative stress, as mirrored by increased lipid peroxidation, is elevated in patients suffering from pulmonary hypertension, inhaled nitric oxide does not increase peroxy nitrites further.[64]

Sildenafil

Sildenafil is a selective inhibitor of type V phosphodiesterase. Type V phosphodiesterase breaks down cyclic GMP and limits cGMP mediated nitric oxide vasodilation. The effects of phosphodiesterase inhibition are best known in the penile vascular bed, hence its use in the treatment of erectile dysfunction. However, there are high concentrations of the type V enzyme in the pulmonary vasculature. Preliminary reports suggest that sildenafil may have useful effects in pulmonary hypertension particularly in attenuating rebound pulmonary hypertension after discontinuing inhaled nitric oxide and in the chronic therapy of pulmonary hypertension.[65–68] Orally administered sildenafil abolishes hypoxic pulmonary vasoconstriction in humans.[69] Sildenafil is well tolerated and available as an oral preparation which makes it an attractive option to prostacyclin particularly for patients whose symptoms do not warrant continuous intravenous infusion. Sildenafil may prove to be a useful adjunctive therapy with nebulized prostacyclin or continuous inhalation of nitric oxide to prevent rebound pulmonary hypertension associated with inadvertent discontinuation or between inhalations of prostacyclin or analoges. Sildenafil produces acute and relatively selective pulmonary vasodilation and this appears to be maintained long term.[54,66–70] There may be synergistic or additive effects with prostacyclin resulting from elevation of both cAMP and cGMP.[54] Interestingly intrapulmonary shunting can be reduced with nebulised sildenafil, at least, in animal models.[71] and oral sildenafil appears to decrease intrapulmonary shunting in patients with lung fibrosis and secondary pulmonary hypertension.[72,73] Oral sildenafil would appear to be a selective pulmonary vasodilator in contrast to other intravenous or oral vasodilator.[72]

Endothelin receptor blockade

Endothelin is a powerful vasoconstrictor of certain vascular beds and promotes smooth muscle proliferation. There is accumulating evidence to suggest that abnormally high circulating endothelin levels may be deleterious in pulmonary vascular disorders. Increased endothelin levels, accompanied by reduced nitric oxide synthesis, have been implicated in the pathophysiology of pulmonary hypertension following cardiopulmonary bypass, persistent pulmonary hypertension of the newborn and Eisenmenger's syndrome.[58,74–78] Furthermore, continuous prostacyclin therapy in patients with primary pulmonary hypertension appears to improve pulmonary clearance of endothelin, *pari passu* with hemodynamic and clinical parameters.[79] The effects of endothelin are mediated through two receptor types ET_A and ET_B. ET_A is present on vascular smooth muscle cells and mediates vasoconstriction and proliferation, while ET_B is the predominant receptor type found on endothelial cells. When endothelin binds to ET_B receptors it promotes vasorelaxation through nitric oxide and prostacyclin release. This explains both the paradox of early work in which infusions of endothelin in normal mammals produce pulmonary vasodilation even in doses that produce systemic vasoconstriction and the importance of the endothelial cell in maintaining pulmonary vascular

homeostasis.[80] Thus it appears that in the damaged pulmonary vascular bed it is the ET_A receptor that predominates. It remains unsolved whether the appropriate pharmacological target should be the ET_A or ET_B receptor.[81] Nonselective ET receptor blockade may reduce the beneficial effects of ET_B (i.e. nitric oxide and prostacyclin release and endothelin clearance). Thus far, the most promising ET receptor blocker is the dual ET receptor blocker, bosentan. Intravenous bosentan reduces pulmonary artery pressure and resistance, but not selectively in patients with primary pulmonary hypertension.[82] Despite the non selective effects of intravenous bosentan, orally administered bosentan in two placebo-controlled studies improved exercise capacity, hemodynamics and symptoms over 16–20 weeks in patients with primary or pulmonary hypertension secondary to scleroderma.[83,84] The drug was well tolerated and free of side-effects apart from a dose dependent increase in liver enzymes. Elevations in hepatic enzymes reversed within 2–6 weeks of discontinuing bosentan.

Anticoagulation

A retrospective review of patients followed over a 15-year period suggested that patients who received warfarin had improved survival over those not receiving therapy.[3] There is histological evidence supporting the role of vessel thrombosis in primary pulmonary hypertension.[85] A substantial improvement in outcome has been demonstrated in patients who do not respond to calcium channel blockade and 1-, 2-, and 3-year survival is increased from 52%, 31%, and 31%, respectively, to 91%, 62%, and 47%.[2]

Other potential therapeutic agents

Abnormalities in potassium channels[86] and the extracellular matrix have been implicated in the pathobiology of pulmonary hypertension. However, despite demonstration of dramatic reversal of monocrotaline induced vascular changes in the rat by inhibition of matrix metalloproteinase and tenascin-C by serine elastase inhibitors these observations have not led, as yet, to therapeutic strategies applicable to human disease.[87–89]

Blade atrial septostomy

Cognizant of the fact that patients with the Eisenmenger reaction and pulmonary hypertensive patients with a patent foramen ovale tend to live longer than patients with primary pulmonary hypertension without intracardiac shunts.[90–92] Nihill,[93] Kerstein[94] and Sandoval[95] have reported blade septostomy in patients with advanced pulmonary hypertension. Animal studies[96] and experience with fenestrated Fontan operations have demonstrated that an interatrial communication allows decompression of a failing hypertensive right side with maintenance of cardiac output at the expense of a fall in systemic oxygen saturation but with an improvement in systemic oxygen delivery and reduction in symptoms of right sided failure. Blade atrial septostomy increases cardiac output (2.3 ± 0.6 to 4.3 ± 1.7 L/min/m^2) and systemic oxygen transport (450 ± 107 to 757 ± 325 mLO_2/min/m^2) despite a fall in systemic oxygen saturation (from 97.6 ± 2 to 91.0 ± 6.9%).[94] Survival at 1, 2, and 3 years was 80%, 73%, and 65% with significant improvement based on survival curves predicted from the equation developed by the NIH primary pulmonary hypertension registry data.[97] Blade atrial septostomy may benefit patients with recurrent syncope despite maximal medical therapy. However, it is not without risk. There is an early mortality, the patients require volume loading, elevation of hematocrit and inotropic support in the peri-procedural period.[94] Sandoval *et al*. suggested that graded, repeated balloon dilation of the septostomy might be the preferred approach.[95]

Lung transplantation

Despite advances in the understanding of pulmonary hypertension, lung transplantation is the last resort for patients who fail medical therapy for pulmonary vascular disease. The number of children who have received lung transplantation remains small. Nevertheless, Armitage *et al*.[98] suggest that actuarial 1-year survival in children is 73% and 90% for children with congenital heart disease. Armitage *et al*.[98] identified four issues they consider critical to the survival of children after lung transplantation. These were cytomegalovirus infection (23%), obliterative bronchiolitis (25%), post transplant lymphoproliferative disease (15%) and bronchial stenoses (9%). Ten year survival for lung transplantation in children is 30–40%.[99]

The timing of organ transplantation remains controversial. However, the success of medical therapy suggests that listing should no longer occur as soon as the diagnosis is made but rather wait a period of drug therapy. However, serious consideration of lung transplantation should occur with the onset of right ventricular failure or NYHA class IV status when mean survival time is < 6 months.[100] Absence of response to acute vasodilator therapy, suprasystemic pulmonary artery pressures, syncope or low cardiac output are signals of severe disease and should prompt careful assessment by the transplant team. Survival curves for children based on hemodynamics have been generated. The simplest devised by Clabby *et al.* suggests that if the right atrial mean pressure times the pulmonary vascular resistance index is < 160 survival will be better without lung transplantation.[1,101,102]

Summary

There have been remarkable advances in our understanding of the pathobiology of pulmonary hypertension. A region on chromosome 2 encoding bone morphogenetic receptor type 2 has been identified to underlie familial and many cases of sporadic primary pulmonary arterial hypertension. The vasoactive mediators, discovered and defined by vascular biologists, have been translated into promising treatments of human disease.

Prostacyclin, endothelin receptor blockers, sildenafil and nitric oxide have been applied therapeutically to limit, and occasionally reverse, the inexorable damage to the pulmonary circulation initiated by recently identified genetic and environmental triggers of pulmonary arterial hypertension.

Pulmonary hypertension secondary to congenital heart disease

Introduction

The functional and structural status of the pulmonary vascular bed plays a pivotal role in the presentation and outcome of the child with congenital and acquired cardiovascular disease. Assessment of the degree of pulmonary vasoconstriction rela-

tive to fixed pulmonary vascular obstruction is important in the management of the child with evidence of an elevated pulmonary vascular resistance. Recent advances in vascular biology have highlighted the essential role of the endothelium in the modulation of vessel tone in both the systemic and pulmonary circulations and abnormalities of endothelial function are considered important in the vascular pathology of a number of circulatory diseases.

Pulmonary hypertension and congenital heart disease

At birth the pulmonary artery pressure is close to the systemic pressure.[103] Within the first hours and days of life pulmonary artery pressure decreases rapidly due to a combination of vessel wall remodeling, functional maturation of the endothelial cell, differentiation of smooth muscle cell, recruitment of lung vessels and release of vasoactive mediators.[103–108] If successful transition of the pulmonary circulation occurs the pulmonary artery mean pressure falls to 10–20 mmHg and is similar to adult levels in the first three weeks of life.[109] In young children total pulmonary vascular resistance indexed is similar to adults.[110] Yet despite this physiological adaptation with reduction in pulmonary vascular resistance the ultrastructural appearance of smooth muscle cells does not closely resemble that of the adult until about 2 years of age.[111] This may account for the lability of the neonatal pulmonary vasculature. The normal development of the pulmonary vascular bed is altered in neonates with a large left to right shunt and pulmonary hypertension[105,112] and if the defect remains uncorrected can progress to obliterative pulmonary vascular obstructive disease. There is, however, great variability in this rate of progression. The type of congenital abnormality and the age of the patient are the two most important factors, which determine the onset of pulmonary vascular disease. For example, the progression of pulmonary vascular disease is slow in most children with an atrial septal defect in whom there is an increase in pulmonary blood flow without an increase in pressure. Only rarely will an atrial septal defect in childhood be associated with accelerated pulmonary vascular change.[113] Children with a large unrestrictive ventricular septal defect with both increased pulmonary flow and pressure develop pulmonary vascular changes more rapidly and should undergo correction by the first year of life.[112] Pulmonary vascular changes are accelerated in patients with transposition of the great arteries, especially if complicated by a ventricular septal defect, and severe obstructive intimal proliferation may be present at 6 months of age.[114,115] Even with the current policy of early neonatal repair there are reports of severe and fatal pulmonary vascular disease occurring after the arterial switch operation.[116]

Pulmonary artery pressure and vascular resistance may be elevated secondary to high pulmonary venous pressure due to elevated end diastolic left ventricular pressure, mitral stenosis or pulmonary vein obstruction. Typically patients with a high pulmonary venous pressure demonstrate marked vasoreactivity and if the underlying abnormality is corrected will respond favorably to vasodilator therapy and regression of the pulmonary vascular changes.[117] In general children with congenital mitral stenosis respond similarly.[118] However, on occasion presumably because the pulmonary vascular has always been exposed to high pressures unlike the situation in acquired disease the pulmonary vascular disease may be fixed.[55]

Heath and Edwards have described the classical progression of the pulmonary vasculature in subjects with congenital left to right shunt lesions.[119] They classified the progression from grade 1, medial hypertrophy with extension of smooth muscle into normally non-muscular arteries through to grade 6, the stage of necrotizing arteritis. Rabinovitch has described a more recent classification, which is clinically useful in the assessment of operability and is based on a quantitative morphometric analysis after the injection of a barium gelatin mixture into the lung tissue. Grade A is the appearance of muscle more peripherally than usual with or without medial hypertrophy of normally muscular vessels. Grade B is distal extension of muscle plus medial wall thickness 1.5–2 times normal (B mild) or more than two times normal (B severe). Grade C is grade B plus decreased density of peripheral arteries relative to alveoli with a < 50% decrease in density of peripheral arteries being grade C mild and a reduction of > 50% grade C severe. These grades have been correlated with both pulmonary artery wedge angiography[120] and pulmonary artery pressure and resistance.[121] Balloon occlusion pulmonary artery wedge angiography[120] allows the quantification of the pulmonary vascular disease by analysis of the rate of tapering of vessels over which the luminal diameter decreases from 2.5 to 1.5 mm, background haze and on deflation of the balloon the pulmonary recirculation time (Figs 44-2, 44-3, 44-4). It also provides excellent visualization of the pulmonary veins.

Endothelial cell dysfunction and its role in the pathophysiology of pulmonary hypertension

The endothelium situated between vascular smooth muscle and the vessel lumen is ideally located to influence vascular tone. Pulmonary endothelial cells when exposed to high shear stress from birth demonstrate structural abnormalities.[122] Functional abnormalities are thought to precede morphological damage raising the possibility that vasoactive mediators produced by the endothelium may contribute to the evolution of pulmonary vas-

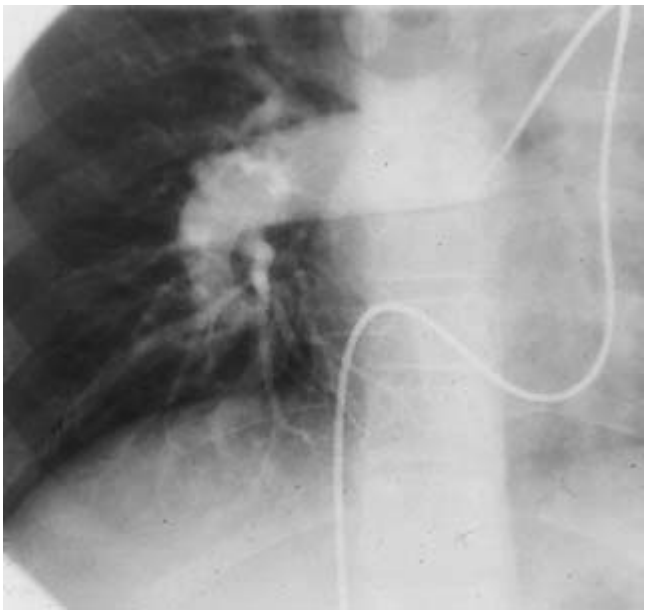

Fig. 44-2 Right pulmonary arteriogram demonstrating markedly enlarged proximal pulmonary artery that is typical of advanced pulmonary arterial hypertension.

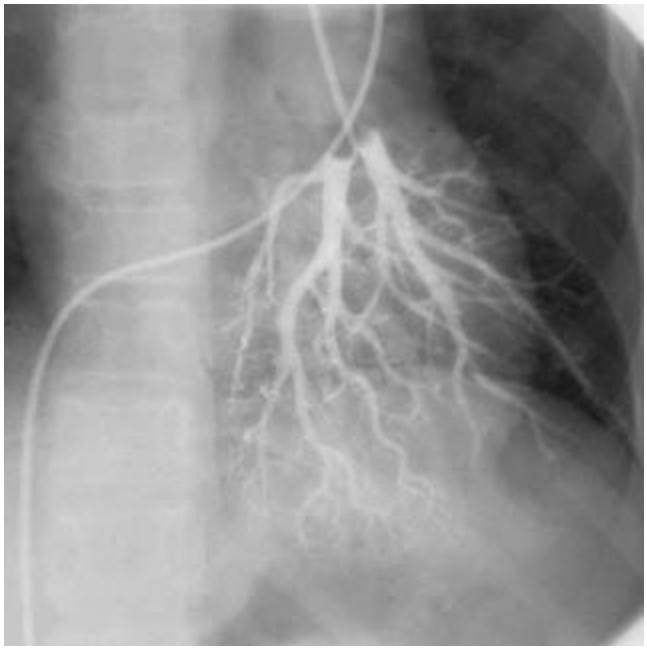

Fig. 44-3 Left pulmonary artery balloon occlusion angiogram demonstrating tortous and "pruned" distal vessels with rapid tapering.

cular disease. The endothelium produces both vasodilators and vasoconstrictors and modulates the adhesion and aggregation of platelets. Thus the changes of pulmonary hypertensive disease including vasoconstriction, smooth muscle hypertrophy and vessel obliteration and could be mediated through an imbalance in the production of endothelial derived mediators subsequent to endothelial injury.

Thromboxane A2 and prostacyclin are both products of the arachidonic acid cascade but have opposing actions on smooth muscle and platelet aggregation. Thromboxane A2 is synthesized by activated platelets and by endothelial cells. It is a vasoconstrictor and proaggregatory. Prostacyclin is synthesized by pulmonary arterial endothelial cells but inhibits platelet aggregation (pGI2), relaxes vascular smooth muscle cells and inhibits their proliferation. Abnormal biosynthesis of prostacyclin and thromboxane with the balance favoring thromboxane A2 has been demonstrated in primary pulmonary hypertension,[37] and in young adults with fixed pulmonary vascular disease.[38] In young children with pulmonary hypertensive congenital heart disease and potentially reversible pulmonary vascular disease an abnormal ratio of thromboxane A2 to prostacyclin excretion is reversed following corrective surgery.[38,123]

Assessment

The rationale for the invasive assessment of pulmonary vascular resistance and the use of pharmacological agents to lower the pulmonary vascular resistance is based on the assumption that in the early stages of pulmonary vascular disease vasoconstriction precedes fixed luminal obstruction and that the institution of prolonged vasodilator therapy will at least retard the progress of the disease. Furthermore symptoms and decreased exercise tolerance are related to right ventricular function. Thus a decrease in right ventricular afterload by reducing pulmonary vascular resistance or allowing decompression of the right side through an atrial septal defect may improve the patient's lifestyle.

The assessment of pulmonary vascular resistance is not without difficulty, both theoretical and practical. The relationship between pressure and flow in the pulmonary circulation is complex. The resistance to flow is a function of the number, luminal area and length or the architecture of the vascular bed. In addition, pulmonary flow, left atrial pressure, pulmonary vascular tone, and critical closing pressure are important.

A measure of resistance to flow through the lung can be provided for by analogy with that used in an electrical circuit.

Pulmonary arteriolar resistance index **(**PARI) is calculated from PARI = mean PAp-LAp/Qp. PAp is the mean pulmonary artery pressure (mmHg) LAp is left atrial pressure and Qp is pulmonary blood flow in L/min per m^2. The latter is usually indexed for body surface area in children. Resistance units are expressed as Woods units (U/m^2) or multiplied by 80 to convert the value to dyn/s per cm^{-5}.

Thus a change in pulmonary arteriolar resistance index in response to administration of a vasodilator should reveal the vasoconstrictive component and potential for improvement with continued therapy. Indeed, there is a correlation with intimal area on lung biopsy and response to vasodilator.[124]

There are spontaneous variations in pulmonary arteriolar resistance index and over 6–8 hours in patients with pulmonary hypertension the variation was 6–13% and for pulmonary artery pressure 8%.[125,126] The response to vasodilator drugs is currently defined as follows.

- Responders experience a reduction in pulmonary vascular resistance ≥ 20% associated with reduction in mean pulmonary artery pressure ≥ 20 % and no change or an increase in cardiac index.
- Nonresponders: the reduction in pulmonary vascular resistance is ≥ 20% without significant reduction in mean pulmonary artery pressure.

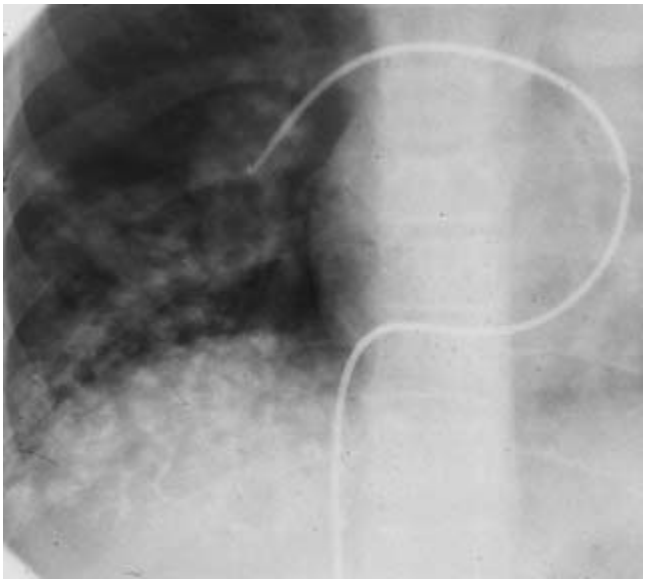

Fig. 44-4 Right pulmonary artery balloon occlusion angiogram late phase shows the patchy and diminished background haze often referred to as "puddling" of contrast.

- Unfavorable responders: symptomatic hypotension (or mean blood pressure fall of > 20%) with a reduction in cardiac index or an elevation in right atrial pressure.

Assessment of pulmonary vascular reactivity in young children is a challenging and demanding process.

Agents used for short-term testing

The ideal agent for short-term testing of pulmonary vascular responsiveness as recently suggested by Rubin,[31] would have better pulmonary dilating effects than systemic, a short half-life, and minimal adverse effects and be both easily and quickly administered, and predict reliably the effect of long-term administration of orally active agents.

Nitric oxide is simple to deliver either by mask or ventilator and as a trial of vasoreactivity over 15 min remains free of side-effects that might be encountered during long-term administration such as methemoglobinemia or nitrogen dioxide toxicity. Indeed no patient developed significant methemoglobinemia after a trial of nitric oxide nor was a level of nitrogen dioxide above 1 ppm registered during the administration. Thus nitric oxide gas fulfills many of the ideal characteristics, as recently suggested by Rubin required of a drug to test the acute responsiveness of the pulmonary circulation.[31] It has better pulmonary dilating effects than systemic, it has a short half-life, minimal adverse effects and it can be both easily and quickly administered. Whether it is able to predict reliably the effect of long-term administration of orally active agents awaits confirmation.

Treatment of acute pulmonary hypertensive crisis

Following surgery to correct congenital heart disease the pulmonary vascular bed may remain labile and susceptible to intense life threatening vasoconstriction.[127–130] The histological correlate of such hemodynamic changes has been described[112] and is due to strategically placed intimal proliferation in arteries accompanying terminal bronchi with a near normal appearance of peripheral intra-acinar arteries. Cardiopulmonary bypass may damage the endothelium,[131–133] attenuate the release of nitric oxide[134] or increase the thromboxane A2 to prostacyclin ratio[123] and increase the vulnerability of such patients to pulmonary vasoconstriction. The management of postoperative pulmonary artery hypertension is important because such patients have reversible pulmonary vascular changes. A successful strategy involves the adequate monitoring of pulmonary artery pressure, extending paralysis and anesthesia to blunt the stress response, which contributes to pulmonary vasoconstriction,[135] hyperventilation or alkalosis and more recently the judicious use of inhaled nitric oxide gas. Inhaled nitric oxide with its rapid onset of action and selectivity for the pulmonary circulation may become the treatment of choice for postoperative pulmonary hypertension and a number of reports asserting its efficacy have been published recently.[134,136–138]

Eisenmenger syndrome

In 1897 Victor Eisenmenger described the autopsy findings in a 32-year-old man with a large VSD and pulmonary hypertension.[139] However, Paul Wood in 1958 defined the disease in a masterly account, which remains relevant to our understanding of the clinical syndrome today.[140,141] Paul Wood used the term Eisenmenger syndrome to describe patients with pulmonary hypertension at systemic level, due to a high pulmonary vascular resistance (> 800 dyn/s per cm^{-5} or 10 Wood U/m^2) with a reversed or bidirectional shunt at aortopulmonary, ventricular or atrial level.[140,141] The term Eisenmenger complex refers specifically to patients in whom the fundamental lesion is a VSD.

Childhood Eisenmenger's syndrome is becoming increasingly rare. However, a glimpse into the severity of the problem that existed before early diagnosis and surgical correction of congenital heart defects were routinely available, can be gleaned from a cohort of patients aged 2 months to 16 years (median age 5.5 years) from Papua New Guinea between 1978 and 1994. The incidence of pulmonary vascular disease that precluded surgical repair of a shunt lesion was 21%.[142]

Clinical features

The clinical features of Eisenmenger syndrome are related to cyanosis, polycythemia, right heart failure (exacerbated by atrioventricular valve, and semilunar valve regurgitation) and pulmonary artery dilation. Patients with complex disease truncus arteriosus, atrioventricular septal defect, univentricular connection and transposition are symptomatic at a younger age and have poorer outcome. Patients with trisomy 21 also fare less well. In general symptoms are slowly progressive with age and become more prominent in late adolescence and adulthood. Effort intolerance is almost invariably present.

Cyanosis is at first present with exercise but becomes constant as the disease progresses and reflects in most cases the severity of the right to left shunt. The mean arterial oxygen saturation is saturation 83.6 ± 7.7% at presentation[143] Clubbing is invariable once cyanosis becomes persistent and may progress to hypertrophic osteoarthropathy with arthralgia and joint effusions.

Hematological abnormalities ensue from the hypoxemia, which results in erythrocytosis. Elevations in hemoglobin improve oxygen carrying capacity and patients are not usually symptomatic from the hyperviscosity syndrome until the hemoglobin level rises above 18–20 g/L. Symptoms attributed to hyperviscosity include headache, dizziness and visual disturbance including rarely central retinal vein occlusion.[144] Iron deficiency together with erythrocytosis aggravates the hyperviscosity and is a risk factor for cerebrovascular hemorrhage and stroke. Thrombocytopenia, prolonged bleeding times, abnormal PT and PTT with deficient clotting factors and abnormal fibrinolysis have been described and contribute to a bleeding diathesis and prolonged bleeding after surgical and dental procedures.

Hemoptysis (20.2%) may be due to intrapulmonary bleeding, ruptured bronchial artery or rupture of a pulmonary artery aneurysm from progressive central pulmonary artery dilation.

Pulmonary embolism and *in situ* thrombosis within dilated pulmonary arteries may also lead to hemoptysis (13.2%).[143,145]

Hyperuricemia is common due to increased production and decreased renal clearance of uric acid. Gout is less common affecting 13–23% of patients.[143,145]

Cholelithiasis and cholecystitis (15%) may occur from increased bilirubin in bile secretions secondary to high erythrocyte turnover.

Renal dysfunction with proteinuria (65%) may progress to the nephrotic syndrome and elevated serum creatinine is an independent risk factor for reduced survival.[143]

Cerebral complications include stroke (7.9%), cerebral abscess (3.7%) and occur at a mean age of 31.4 ± 15.7 and 24.1 ± 4.9 years respectively.[143]

Arrhythmias include isolated supraventricular ectopics and ventricular ectopics (42%), atrial flutter and fibrillation (35.5%).

In 22% of patients syncope or presyncope was related to ventricular tachycardia.[143]

Endocarditis (3.7%) may complicate outcome.[143]

Hoarseness and cough due to laryngeal nerve compression by dilated pulmonary arteries has been reported. Likewise, dilated pulmonary arteries may compress the left coronary artery with angina.[143,146–148]

Sudden death occurs in 30% of patients. Although the presence of a shunt and a "primed" ventricle since fetal life confers a survival benefit over patients with primary pulmonary hypertension as described by Hopkins and Waggoner,[92] the development of cardiac failure and death from the sequelae is common (40–50%). Cardiac failure is more common in complex Eisenmenger's and is due to AV valve, and/or semilunar valve stenosis and regurgitation.

Clinical outcome

Patients with the Eisenmenger syndrome require expert supervision.[149] All patients who present as adults with Eisenmenger syndrome escaped detection in childhood. However, the few studies, which include children, suggest that symptomatic children may deteriorate quickly and face all of the difficulties reported in young adults including sudden death, cardiac failure and hemoptysis.[150,151] It is the role of the pediatric cardiologist to emphasize lifestyle practices and therapies that appear to result in improved survival. It is paramount and the absolute responsibility of the pediatric cardiologist that the graduate from pediatric care be referred to a clinic for adults with congenital heart disease and provide a transcript of all the information relating to the patient. It is of note that 20% of deaths in an Eisenmenger cohort were associated with avoidable medical error.[149] Thus noncardiac surgery accounts for 23.5% of deaths.[143] Venesection should be performed sparingly for symptoms of polycythemia and in 20% of patients venesection leads to iron deficiency anemia which increases the risk of hemoptysis, stroke bleeding and adverse outcome.[143,145,152] In addition patients should receive counseling about the risks of pregnancy, high altitude, estrogens and anesthesia.[149] The use of vasodilators and anticoagulants need to be tailored to each patient by a physician experienced in the management of these patients as the balance between pulmonary vascular and systemic vascular resistance and the risks of bleeding and thrombosis are complex.

Oxygen therapy

An early study which was not randomized and included a heterogeneous group of patients seemed to indicate that oxygen therapy was beneficial in the Eisenmenger syndrome as all treated patients survived and 5 of 6 patients who did not receive oxygen treatment died.[153] However, these results have not been confirmed in a more recent study. Sandoval *et al*. based on the observation that the supine position resulted in desaturation in Eisenmenger patients undertook a 2-year randomized study of oxygen therapy in established Eisenmenger patients aged 20–50 years living at altitude. There was no change in hematology, exercise capacity or quality of life. The mean survival time was 20.7 months in both groups. The only factor associated with adverse outcome was a low MCV underscoring the harm that may ensue from venesection and the importance of treating iron deficiency. In addition oxygen delivered by nasal cannulae predisposes to epistaxis.[145]

Outcome

Survival of the patient with Eisenmenger syndrome is quite variable and risk factors include trisomy 21, complex underlying disease (worse for truncus, atrioventricular septal defect, univentricular hearts), anemia, pregnancy, sustained arryhthmias and elevated creatinine and need for noncardiac surgery.[145,143] In series that contain children the average age at death is 29 years with a 56% probability of surviving 10 years for a 20-year-old patient.[150] Whereas in adult clinics median survival at 18 yearss is 53 years with average age at death of 37 years ± 13.3.[154] Oya *et al.* report survival of 98% at 1 year, 77% at 5 years, 58% at 10 years and found that right atrial pressure and a cardiac index < 2.9 to be independent risk factors for death.[155] Patients with a simple VSD survive longer (42% at 25 years) with survival at 1, 2, and 3 years of 97%, 89%, and 77%.[91] Five-year survival for simple VSD is 91%, with truncus 67% and 34% for patients with single ventricle.[145]

Saha *et al.* report actuarial survivals at 5 years of 87%, at 10 years of 80%, and at 15 years of 77%.[156] Factors associated with poor prognosis included syncope at presentation, right atrial mean pressure above 8 mmHg and arterial oxygen saturation below 85%.[156]

Quality of life as reflected by employment in adult patients is variable with 53–57% (nontrisomy 21) holding full-time jobs.[143,145,150] However only 30% with complex disease enjoyed full-time employment vs. 89% with a VSD.

Pregnancy

In the 1960s pregnancy in women with Eisenmenger's syndrome carried a 27% mortality.[157] The risk of adverse outcome for mother and fetus remain high. The outcome of 84 pregnancies reported from six different centers was as follows: spontaneous abortion or stillbirth occurred in 25%, therapeutic abortion in 27%, premature or low birthweight baby in 26%, maternal death in 16% and maternal deterioration (including stroke, post partum hemorrhage, rapid decline in pulmonary vascular status) 54%.[143,145,150,151,155,156]

Therapeutic options for Eisenmenger's syndrome

Despite remarkable advances in the understanding of pulmonary vascular disease and advances in treatment for primary pulmonary arterial hypertension patients with established Eisenmenger's syndrome remain therapeutic orphans. However, demonstration of residual reactivity in these patients[55,158] is cause for cautious optimism that they will be included in future studies. However, recent observations on the regression of advanced pulmonary vascular disease in animal models[89,88] and the availability of oral therapies have stimulated renewed interest in devising treatment strategies for Eisenmenger's syndrome.

Rosenzweig *et al.* have used chronic infusions of prostacyclin to treat symptomatic Eisenmenger's and demonstrated an improvement in exercise tolerance and oxygen delivery but not arterial oxygen saturation.[159]

Although, surgical techniques for established Eisenmenger's syndrome with preparatory pulmonary artery banding and subsequent surgical closure of ventricular septal defect have been revisited (following an initial report in 1971 by Azzolina)[160] and stimulated considerable debate,[161–164] definitive follow-up data are awaited. Regression of medial hypertrophy and intimal proliferation is documented well after pulmonary pressure unloading in animals and humans.[165–167] It is unclear if advanced intimal fibrosis, fibrinoid necrosis or plexiform lesions regress after pulmonary artery banding. It is interesting to note that pulmonary vascular resistance may decrease after ductal ligation, despite plexiform arteriopathy on lung biopsy.[168]

The use of a double patch to close ventricular septal defects with hinge and fenestration to permit right to left but not left to right shunting has been reported in 18 patients with only one late death.[169] Baseline pulmonary vascular resistance was 11.4 Wood units (unindexed) and all patients were desaturated albeit with predominant left to right shunts. Pulmonary vascular reactivity results were not reported. It is, therefore, difficult to assess the degree of pulmonary vascular disease present in the patients reported by Novick *et al*.[169]

Lung transplantation and heart and lung transplantation

Thoracic organ transplantation is required only rarely for the child with Eisenmenger's syndrome, Nevertheless, according to Mendeloff *et al.* the outcomes are similar in children and adults with pulmonary hypertension secondary to congenital heart disease. Hospital mortality is 23% (16% required ECMO support) with a 5-year survival of 57%.[170]

Lung transplantation alone is possible for patients with ASD or PDA.[171] Conversely for Eisenmenger VSD survival is better with heart lung transplant rather than lung transplantation and VSD closure.[172] Patients with Eisenmenger syndrome wait on the list longer and the time when transplantation relative to remaining on the waiting list is less clear than for primary pulmonary hypertension.[173] Estimated survival for children with pulmonary hypertension and congenital heart disease is 88%, 88%, and 77% at 1, 2, and 5 years after cardiac catheterization.[101] In general if the product of mean right atrial pressure and indexed pulmonary vascular resistance is < 160, then survival is better without organ transplant.[101]

Heart and lung transplantation offers better survival than lung transplantation for most patients with Eisenmenger syndrome. Early mortality rates for adults after heart and lung transplantation are 16% for Eisenmenger syndrome vs. 13% for non-Eisenmenger. The 1-, 5- and 10-year survival rates are 73%, 51%, 28% for Eisenmenger compared with 74%, 48%, 26% for non-Eisenmenger.[174]

Summary

Patients with Eisenmenger syndrome have few therapeutic options. The hope must lie in early diagnosis and repair of congenital heart disease with appropriate and timely postoperative use of therapeutic agents that show promise in primary pulmonary arterial hypertension. The care of Eisenmenger patients should be cohorted in a clinic with experienced personnel who are willing to promote clinical trials of drugs that may improve the considerable morbidity associated with unrepaired and reversed central shunts.

All references can be found at the end of the book. See pp. 840–4 for Chapter 44.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Desmond Bohn and Ian Adatia

Outcomes of Extracorporeal Membrane Oxygenation and Ventricular Assist for Congenital Heart Disease

Introduction

The first attempts at mechanical support of the circulation began with the pioneering work on cardiopulmonary bypass for open heart surgery in the 1950s, although this did not become widely used until the 1960s. The development of the membrane lung in the 1970s was a major advance in extracorporeal technology as it extended the safe period of cardiopulmonary bypass which, until then, had been limited by complications associated with the use of bubble oxygenators. It was only a matter of time before this technology was transferred from the cardiac surgery operating theatre to the intensive care unit. In 1971 the first case report was published of an adult patient with severe hypoxic respiratory failure (AHRF) who was successfully treated with extracorporeal membrane oxygenation (ECMO).[1] This was followed by case reports which included pediatric patients who had developed AHRF following repair of congenital heart defects. However, ECMO was largely abandoned in adult medicine following the publication of a trial showing no difference in survival in patients with AHRF treated with ECMO versus conventional ventilation.[2]

The first successful use of extracorporeal cardiac support in congenital heart disease is credited to Baffes *et al*.[3] who used it during palliative closed cardiac procedures as an emergency form of circulatory support, although these were of relatively short duration. Soeter *et al*.[4] in 1973 reported on the successful use of ECMO to support a child with cardiorespiratory failure following repair of tetralogy of Fallot. While the use of ECMO in congenital heart disease was sporadic at this time, there was increasing experience in applying the technique for the treatment of newborn infants with AHRF, pioneered by Bartlett and colleagues in Ann Arbor.[5] Through the 1970s and 1980s neonatal ECMO programmes were set up across North America and the Extracorporeal Life Support Organization (ELSO) was founded and a registry developed on outcomes following extracorporeal support. Over this period there were major advances in extracorporeal technology with the development of compact roller pump systems and small silicone membrane oxygenators suitable for neonatal use. To date over 16 000 term or near term infants with AHRF have been treated with ECMO with an 80% overall survival. The numbers of operational ECMO centers peaked in the early 1990s and since 1992 there has been a downward trend in the numbers of neonates placed on ECMO. This is probably due to a number of factors including the increased use of alternative ventilation strategies such as inhaled nitric oxide, high frequency oscillatory ventilation and a change in ventilation practice which recognizes that hyperventilation in persistent pulmonary hypertension of the newborn causes injury to the lung without changing the outcome. Over the same period there has been a major increase in the use of extracorporeal technology to support children with circulatory failure following repair of congenital heart disease,[6] as a bridge to heart and heart–lung transplantation[7] and in diseases of cardiac muscle (cardiomyopathy and myocarditis).[8] There have also been major new developments in circulatory assist devices so that other options apart from ECMO are now available for use in children with congenital and acquired heart disease. The chapter will describe the options available, the application of the technique and the outcomes.

Options for mechanical circulatory support

There are two options currently available for mechanical support in acute myocardial failure in children: a pumping device with an oxygenator (ECMO) or a ventricular assist device (VAD) to support either the left ventricle (LVAD), right ventricle (RVAD) or both ventricles (BIVAD) without an oxygenator. Ventricular assist devices can be extracorporeal (Biomedicus Centrifugal Pump) or paracorporeal (Berlin Heart, Thoratec) or implantable (Heart Mate).

The most extensive experience in children has been with the use of ECMO in the support of children with cardio-respiratory failure. The advantages of this technique are familiarity, the opportunity to avoid opening the sternum by using neck or groin vessels for cannulation, the provision of biventricular support with two peripheral cannulation sites and the presence of an oxygenator when hypoxemia complicates the clinical picture. The disadvantages are the presence of the oxygenator leads to increased destruction of platelets and greater heparin requirements resulting in bleeding, which may be particularly problematic if there has been a recent cardiotomy. There also may be inadequate unloading of the left heart which may necessitate a balloon or blade atrial septostomy or opening the sternum to place a left atrial vent. Although most centers use a roller pump system for ECMO, others prefer to use a centrifigal pump which allows for the flexibility to use either the ECMO or VAD option.[9] Using a VAD has the advantages of automatically unloading the left heart by draining the left side and since there is no oxygenator in the circuit, less anticoagulation requirements and destruction of platelets and fewer circuit related complications. The principal disadvantage is that cannulae have to be placed within the chest which may result in significant bleeding and the risk of infection.

Mechanical support systems

Roller pumps

The roller pump is the most commonly used in pediatric life support. In this system venous return is gravity dependent and therefore the pump has to be below the level of the patient. Venous return (inflow) is regulated by a distensible bladder, controlled by a servoregulatory mechanism attached to a spring loaded switching device. Interruption of venous inflow turns the pump off to prevent air entrainment. Forward flow is generated by compression of the circuit tubing between the roller heads and a back plate in the pump head housing. Volume is displaced as the roller heads travel the length of tubing within the pump head, known as the "raceway." The output of the pump is dependent on the diameter of the tubing, the rotations of the rollers per minute and the degree of occlusion. This is the gap between the roller and the back plate which, if significant, will allow backward flow of blood during rotation. The technical complications that can be seen with this system are blow out of the arterial circuit with occlusion of the distal arterial line and "raceway" rupture at the site of contact between the pump head and the circuit tubing.

A newer innovation in roller pump technology has been the development of the AREC (M pump) system which is non-occlusive. A silicone chamber is stretched over the outside of a three-pronged roller pump head. The pumping chamber fills passively by venous return and is less gravity dependent than the conventional roller pump system and the possibility of raceway rupture is eliminated.[10,11]

Centrifugal pumps

The centrifugal pump is gravity independent, venous inflow being driven by negative pressure generated at the pump head. The design principle is a constrained vortex produced by a series of cones rapidly spinning along a vertical axis. The mechanical energy comes from an electrical drive and coupled magnets. Line pressure is negative between the patient and pump head and care must be taken that this does not exceed –20 mmHg in order to prevent hemolysis. Excessive negative pressure can occur due to unfavorable venous cannula position, thrombus in the inflow or inadequate filling pressures in the patient. Venous line pressure is positive between the pump head and oxygenator. Flow is non-pulsatile and can be increased by increasing the rotational speed of the pump head. A reduction in venous return will reduce pump output which can be corrected either by increasing vascular volume or addressing the venous cannula position. Increasing the pump speed (rpm) in this situation without addressing problems of venous return will generate higher negative pressures in the inflow and increased hemolysis. This system operates most efficiently when the rpms are lowest for any given flow.

Oxygenators

There are two types of oxygenators currently in use for cardiac support, namely the membrane oxygenator or the hollow fibre types. The majority of the experience has been with the former. The design is based on a rolled spiral silicone membrane perfused with blood on one side and gas on the other. The transfer of gas to the blood phase depends on the partial pressure differences between the two, sweep gas flow, thickness and surface area of the membrane. Membranes are rated according to maximum allowable blood flow which, if exceeded, can lead to membrane rupture. Carbon dioxide clearance can be achieved by increasing the sweep gas flow. Differences in temperature between the blood and gas phase lead to water condensation in the gas compartment of the membrane which can result in decreased CO_2 clearance, as can clot formation on the blood side. The PaO_2 of the blood exiting the membrane is dependent on the FiO_2 of the sweep gas and the thickness of blood film.[12]

Membrane oxygenators are a source of considerable resistance to blood flow in the ECMO circuit. The pre- and post-membrane line pressures are monitored and an increase in the pressure drop (venous–arterial) may indicate thrombus formation within the membrane. A reduction in the pre- and post-membrane pressure difference may be due to kinking of the arterial line (increase in arterial line pressure), obstruction of the venous cannula (decrease in venous line pressure), an open bridge between the venous and arterial side of the circuit or, in the case of a roller pump, non-occlusion of the pump head.

A more recent innovation has been the introduction of the hollow fibre oxygenator. This consists of woven capillary tubes of microporous polypropylene. The internal resistance of these membranes is low and their gas exchange efficiency is very high. These attractive features are counterbalanced by their tendency to leak plasma which results in foaming after short intervals of use. They are frequently used in combination with heparin bonded circuits but the leakage problem makes them suitable only for short-term use.

Circuit components

The tubing commonly used in ECMO and other ventricular-assist circuits is polyvinyl with a diameter of either 1/4, 1/2, or 3/4 inch depending on the patient's size and circuit flows. The size of the tubing connectors and stop cocks used in the circuits depends on the tubing diameter, but constitute a source of increasing resistance and a site of potential thrombus formation within the circuit. A more recent innovation has been the introduction of heparin bonded circuits (Carmeda) which may decrease the need for heparin therapy. A circuit that bypasses the oxygenator, known as the bridge, directly connects the venous with the arterial line. This is opened when the arterial and venous cannulae have to be clamped either during an emergency or during the weaning process. During the normal ECMO run, the bridge is partially occluded with a U clamp, allowing for a minimal blood flow across the bridge in order to prevent stasis leading to thrombus formation.

Circulation of blood outside the body causes cooling. A heat exchanger is placed into the post membrane to reheat the blood temperature to 37ºC. These devices are controlled by a water bath, the temperature of which can also be lowered in situations where hypothermia may be required. The heat exchanger also incorporates a bubble-trap to collect any gas bubbles that escape from the membrane.

Circuit priming

Prior to initiation of mechanical support the circuit needs to be primed with fluid. First the circuit is flushed with CO_2 to eliminate any air. Line suction is applied to the gas ports of the membrane to bring the blood and gas phase of the membrane into

intimate contact. An electrolyte solution is added to the circuit in step-by-step fashion being careful to eliminate all air from the circuit. Albumin is then added to the prime in order to coat the blood contact side which helps to prevent platelet adhesion and activation. This solution is then replaced by a prime consisting of fresh frozen plasma and red blood cells, to which heparin is added. Bicarbonate or THAM is then added in order to normalize the pH and calcium to neutralize the effect of citrate. The prime is then circulated and the electrolyte and ionized calcium concentration measured prior to connection.

Some institutions now maintain a pre-primed ECMO or blood circuit for the institution of emergency mechanical support.[13] In this situation, the circuit is primed only with an electrolyte solution. Depending on the urgency of the situation, the circulatory support may be instituted with a clear prime, with the subsequent adjustment of the hematocrit, with the addition of red cells or hemofiltration to remove fluid.

Cannulation: sites and technique (ECMO and LVAD)

For the institution of ECMO most neonates and small children (<10 kg) are cannulated via the carotid artery and internal jugular vein as the femoral vessels are too small to accept adequate size cannulae. Older children, adolesents and adults are cannulated via the femoral vessels due to concerns of cerebral ischemia that may result from carotid cannulation.

The placement of cannulae in the neck vessels for ECMO is via an oblique incision in the right side of the neck with the venous cannula advanced so that the tip is in the mid right atrium and the tip of the arterial cannula at the junction of the innominate artery and the aorta arch. For femoral cannulation the venous cannula is advanced so that the tip is at the IVC right atrial junction and the arterial cannula is advanced so that the tip is at the aortic arch. When the trans-sternal approach is used for ECMO the venous cannula is placed directly into the right atrium with a left atrial vent and the arterial cannula is placed in the aortic arch. When LVAD is used the venous drainage cannula is placed through the left atrium or superior pulmonary vein.

Anticoagulation

During mechanical support a delicate balance has to be achieved between sufficient anticoagulation to prevent clotting within the circuit while minimizing hemorrhagic complications, which may be particularly problematic in the post-cardiotomy patients. Insufficient anticoagulation can also produce a DIC-type picture and further hemorrhage. The standard method for monitoring coagulation during mechanical support is the activated clotted time (ACT). The objective is to maintain the ACT usually in the range of 160–180 s. This is achieved by the infusion of standard heparin, in a dose of 20–30 U/kg/h. In situations where excessive bleeding occurs, the options are to reduce the heparin dose and run the ACTs in the lower range (160 s). There is also the option of using the anti-fibrinolyic drug aminocaproic acid (Amicar), for which there is extensive experience in the neonatal respiratory failure population.[14] The presence of an oxygenator in the circuit increases the need for heparin, which is one of the advantages that the LVAD system may have over ECMO. Some centers run the LVAD system without heparin in the post-cardiotomy situations where there is uncontrolled hemorrhage.

Patient management on mechanical support

Mechanical circulatory support is usually initiated at flow rates of 80–150 ml/kg/min depending on age, flows being higher in infants than in older children. The objective should be to achieve flows that provide adequate cerebral oxygenation and tissue perfusion with the preservation of end organ function. Objective markers of these would include a mixed venous saturation greater than 70%, a normal pH and lactate. One of the major objectives in mechanical support is to prevent ongoing myocardial injury. Therefore, care must be taken to avoid the heart overdistention which can occur with inadequate venous drainage. This will be evident by a high left-atrial pressure and the development of pulmonary edema on the chest x-ray. We have used echocardiography to assess the need for atrial decompression particularly after neck cannulation in the older child. Left atrial and left ventricular volume and function may be assessed serially and provide useful information to time left atrial decompression before pulmonary edema or hemorrhage become clinically manifest. If the sternum has not been opened percutaneous transcatheter left atrial decompression can be performed either in the cardiac catheterization laboratory or at the bedside. If transfer to the cardiac catheterization laboratory is an option, static balloon dilation of the atrial septum or blade septostomy can be performed after transeptal needle puncture (Fig. 45-1). Alternatively (especially if transfer to the catheterization laboratory is not feasible or urgent left atrial decompression is required) we have undertaken echocardiographically guided transeptal needle puncture. We have placed a long transvenous femoral sheath over the guidewire into the left atrium to decompress and monitor left atrial pressure as described by Ettedgui *et al*. and Ward *et al*.[15,16]

Clearly in the presence of a patent but restrictive foramen ovale then traditional echocardiographic bedside balloon atrial septostomy may be performed to good effect.[17,18]

Once bypass is established, a decision has to be made on the appropriate pulmonary management. In situations where LVAD is used full ventilatory support has to be maintained. The rules regarding ventilation settings on ECMO for cardiac support are different to those that apply in respiratory support and have to take into consideration the underlying heart function. A flat-line on the arterial trace indicates no cardiac contraction and therefore, the distal and proximal aorta, including the coronary arteries, will be perfused partly by fully saturated blood from the aortic cannula. The preservation of cardiac ejection, as is evidenced by arterial wave form, indicates there is opening and closure of the aortic valve. In this situation the coronary arteries are partially perfused by blood being ejected from the left ventricle.[19] It is therefore important that this blood be fully oxygenated by ventilating the lungs, so that any ongoing ischemic injury is minimized.

Another important factor in minimizing any ongoing myocardial injury is the maintenance of minimal afterload. The best marker of the effectiveness of this is the monitoring of the arterial pressure, which tends to rise with high-flow mechanical support.[20] This can be treated with intravenous vasodilator therapy in the form of phenoxybenzamine or nitroprusside with the objective of achieving an age appropriate mean arterial

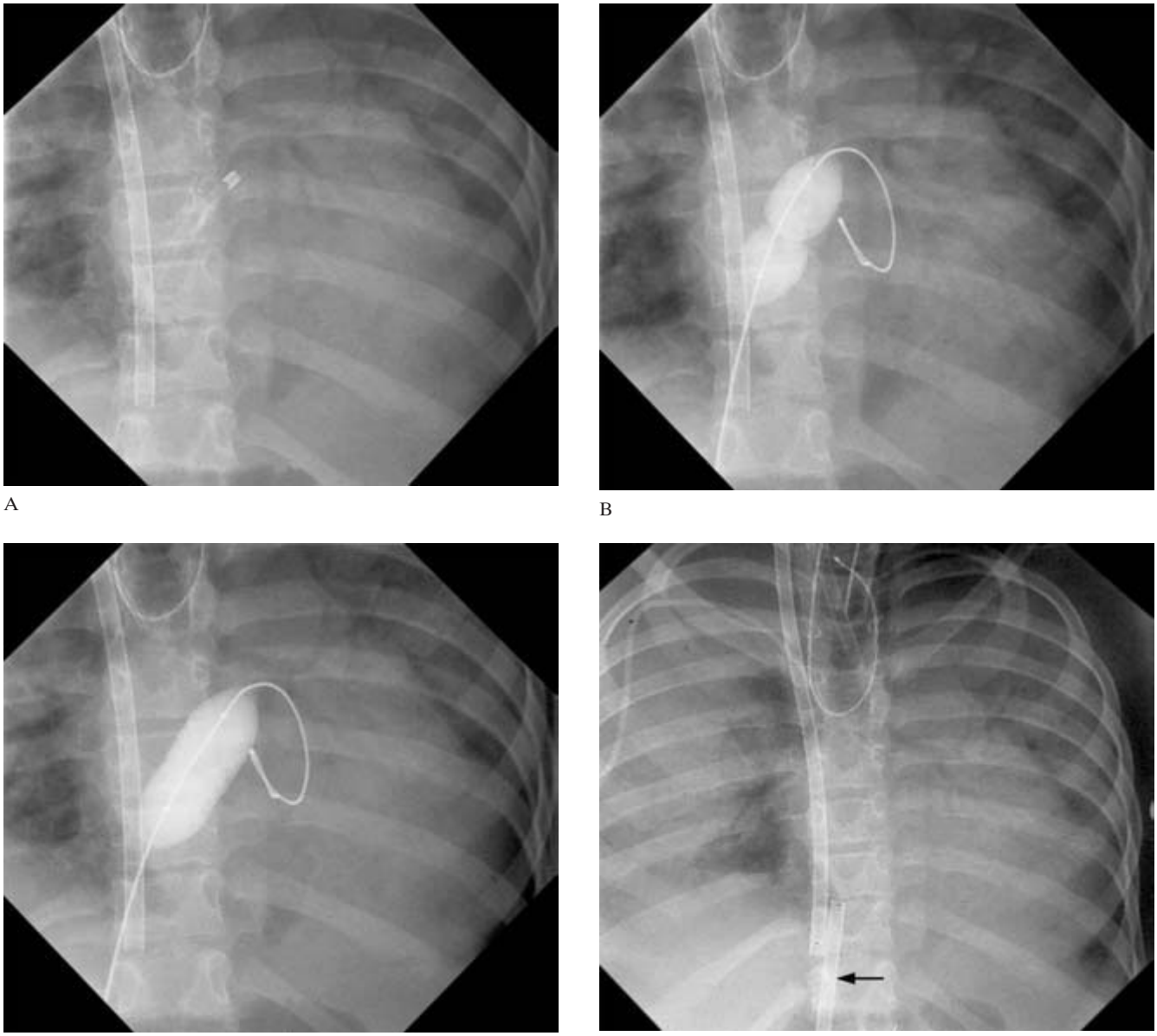


Fig. 45-1 Transcatheter percutaneous atrial septostomy. These figures demonstrate radio frequency wire perforation of the intact atrial septum (**A**), and progressive static dilation (**B**) of the perforation. Following left atrial decompression, a second venous cannula (arrow) is placed and positioned in the IVC from the femoral vein, to augment flow following urgent neck cannulation (**D**). Sternal opening is avoided.

pressure. The use of afterload reduction also reduces arterial line pressure in the circuit and enhances pump flow.

Other patient management issues

Sedation/analgesia

Patients on mechanical support require sedation and analgesia to alleviate the discomfort associated with cannulation or an open sternum. Neuromuscular blockade together with opiates and benzodiazepines are used for the first 24 h until satisfactory cannula position and circuit performance are established. After this time neuromuscular blockage should be discontinued in order to observe the patient's neurological status, in particular, the presence of any seizure activity, which could indicate neurological dysfunction.

Fluid management

Estimating fluid homeostasis on patients on mechanic support is very problematic. The estimation of fluid losses is complicated by leakage of fluid into tissues and hemorrhagic complications, frequently in the setting on ongoing renal dysfunction. The early placement of an ultrafiltration device allows for much better control of fluid balance. The control of water balance that this provides means that there can be early implementation of a nutritional support in the form of IV alimentation. The use of mechanical support does not preclude the use of the GI tract

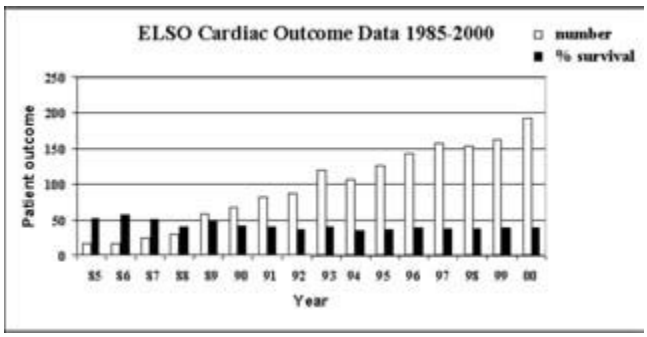


Fig. 45-2 Outcomes in ECLS reported to the ELSO Registry from 1985 to 2001.

and the use of trophic gut feeds to reduce the risk of nosocomial bacterial translation is recommended.[21,22]

Weaning from support

The decision on when to wean from support is based on assessment of ventricular function by cardiac echo. The process involves placing the patient on increasing doses of inotropes and vasodilator support and weaning back the bypass flow under echo control. This allows for an evaluation of the heart function under partial loading conditions. Once flows of 20–40 ml/kg/min have been achieved, the cannulae can be clamped and the patient tested under full loading conditions. During this period it is important to keep the patient fully heparinized, and to intermittently unclamp the cannulae to flush the lines, and prevent thrombus formation. It is also important to remember that patients on ECMO need to have their ventilation increased to full support during the weaning process. This does not apply to patients on the LVAD system who are already ventilated. The addition of inhaled nitric oxide can also be considered in patients placed on mechanical support for pulmonary hypertension and right-heart failure. When adequate cardiac function can be demonstrated to be sustained over a period of one-two hours without ECMO support, a decision can be taken regarding decannulation.

Indications

The indications for the institution of ECLS in congenital heart disease are not well defined. The most commonly described in the literature are: (a) failure to separate from cardiopulmonary bypass following repair with no residual anatomical defect; (b) failed resuscitation from cardiac arrest after surgical repair; (c) low output state in the postoperative period; (d) pulmonary hypertension post surgery; (e) acute hypoxic respiratory failure in a patient with congenital heart disease; (f) pre-operative stabilization. There can be little disputing that the first two of these represent absolute indications but a decision based on the remainder tends to be more subjective.

Outcome in extracorporeal life support

The outcomes following the initiation of ECLS in congenital heart disease depend on a number of factors which include the underlying heart defect, indications for initiation of support and complications during the support period (patient and technical). Exit from ECLS post surgical repair is either via recovery of myocardial function, death without weaning from support either due to myocardial failure or from non-cardiac complications, or via a transplant. Survival also needs to be evaluated on the basis of ICU survival, survival to hospital discharge and long-term outcome. Also, the outcome should be evaluated in relation to the number of times ECLS is used in the total institutional bypass series. The rates, which are not always reported, vary between 1% and 8.3%.[23–27] The source of these data comes from ELSO Registry, published case series and institutional experience. The overall survival to hospital discharge for cardiac support is 38% in 2937 cases reported to the ELSO Registry since 1985 (Fig. 45-2). Survival to hospital discharge in individual published case series varies between 25% and 60%[23–43] (Table 45-1).

Table 45-1 Outcome from ECLS in congenital heart disease

Author	ECMO number	LVAD number	Weaned	Survived to discharge	Per cent survival
Mehta *et al.* (2000)[41]	18	–	7	4	22
Jaggers *et al.* (2000)[26]	35	–	22	21	60
Duncan *et al.* (1999)[33]	60	20		31	39
Langley *et al.* (1998)[40]	8	1	4	2	25
Thuys *et al.* (1998)[42]	–	34	22	14	41
Kulik *et al.* (1996)[24]	64	–	31	21	32
Black *et al.* (1995)[28]	25	–		10	40
Costa *et al.* (1995)[29]	–	12	9	7	58
Walters *et al.* (1995)[27]	66	0	44	38	58
Delius *et al.* (1992)[32]	20	–	13	10	50
Ziomek *et al.* (1992)[23]	24	–	18	13	54
Raithel *et al.* (1992)[25]	65	–	44	23	35
Karl *et al.* (1991)[38]	–	12	10	6	50
Dalton *et al.* (1993)[30]	21	–	14	9	43
Weinhaus *et al.* (1989)[43]	14	–	7	5	36

Table 45-2 Outcome of ECLS by category of congenital heart disease

Diagnosis	Total number	Survived	Per cent survival
Left to right shunt (ASD/VSD/PDA/AVSD)	462	170	37
Left-sided obstructive lesion (aortic stenosis/mitral stenosis/coarctation)	266	89	33
Hypoplastic left heart syndrome	315	89	28
Right-sided obstructive lesion (pulmonary stenosis/pulmonary or triscupid atresia)	153	63	41
Cyanotic increased pulmonary blood flow (truncus/TGA)	106	32	30
Cyanotic increased pulmonary congestion (TAPVD)	322	137	43
Cyanotic decreased pulmonary blood flow (Tetralogy/DORV/Ebsteins)	305	106	35
Other	1164	482	41

(From ELSO Registry with permission.)

Outcome related to cardiac diagnosis

It would appear logical that the underlying cardiac diagnosis is an important factor in determining outcome. Generally speaking the outcomes are worse with single ventricle palliation compared to biventricular repairs and this is confirmed in the ELSO Registry (Table 45-2). This database uses a simple classification of congenital defects into obstructive (right- or left-sided) lesions associated with left to right intracardiac shunts, cyanotic lesions with decreased or increased pulmonary blood flow, single ventricle lesions and other. Data are similar to those reported in some of the other larger single institutional experiences.[24,27,33] These have shown that the survival to hospital discharge is around 40% in patients undergoing biventricular repairs whereas it is generally < 30% in single ventricle lesions. ELSO Registry data are also reported by individual lesion and according to procedure (Table 45-3). If one scrutinizes the reported case series by procedure the most impressive survival is in patients with an anomalous left coronary artery (ALCA).[44–46] This is a lesion usually associated with very poor pre-operative myocardial function which is made worse by the ischemic injury from aortic cross clamping. There is a strong case to be made for an elective decision to ECMO or VAD support for the first few days in the expectation that function will improve.[47] The other end of the spectrum is the use of ECLS following the stage one palliation for hypoplastic left heart syndrome where the outcomes have been poor.[24] Until recently the approach has been to use ECMO support with the Blalock–Taussig shunt clipped in order to prevent run off into the pulmonary circulation and inadequate systemic flow. More promising results have now been published with a change in strategy to high flow (>150 ml/kg/min) support with a VAD and the left open.[26,48] The other procedures where ECLS support has been used include arterial switch for TGA, tetralogy and AVSD repair. Survival in these groups is similar at around 30–40%. The outcome data for ECLS for individual congenital heart lesions in the cardiac programme at the Hospital for Sick Children are shown in Table 45-4. The overall survival is 25%. This represents 1% of the total open heart surgical population. The prime indication for the institution of ECMO between 1991 and 2000 was failure to wean from CPB (40/65) followed by low cardiac output (14/65).

Outcomes related to indication for support

Survival to separation from ECLS is influenced by the indication for initiating that support. The three most commonly reported indications are failure to separate from cardiopulmonary bypass, a low cardiac output state (cardiogenic shock) in the postoperative period due to myocardial injury, or postoperative cardiac arrest. There have also been reports of patients with congenital heart disease placed on mechanical support preoperatively[11,35] as well as patients who develop acute hypoxic respiratory failure in the postoperative period where ECMO is used primarily as a respiratory support mode.[32] Poor survival is reported in some series of patients who fail to separate from CPB[24,27,39,40,49] with only 10% survival reported in one recent series.[33] These data should be interpreted in the light of the fact that with increased overall experience with the use of ECLS there is an increasing

Table 45-3 Outcome of ECLS in congenital heart disease classified by procedure

Procedure	Total number	Survived	Per cent survival
TGA arterial switch	210	81	39
TAPVR repair	101	44	44
Fontan operation	100	26	26
Stage 1 HLHS (Norwood)	188	53	28
AVSD repair	64	27	42
BCPS	19	7	37
Tetralogy repair	151	64	42
VSD repair	91	28	31

(From ELSO Registry with permission.)

Procedure	Total number	Survived	Per cent survival
TGA arterial switch	9	3	33
TAPVD	10	6	60
Stage 1 HLHS (Norwood)	9	5	55
AVSD repair	8	1	13
Anomalous coronary	6	5	83
Tetralogy	7	2	29
Pulmonary atresia/stenosis	5	1	20
Aortic stenosis/IAA	6	1	17
DORV	6	1	17
VSD	3	0	0
Truncus	3	0	0
Mitral stenosis	3	0	0

Table 45-4 Outcome of ECLS in congenital heart disease classified by procedure

(From The Hospital for Sick Children Congenital Heart Programme with permission.)

tendency to initiate support in the operating room in patients with marginal function, rather than risk the development of profound low output leading to cardiac arrest in the postoperative period. This strategy has been used with success with neonates placed on LVAD after the stage I procedure for the hypoplastic left heart syndrome.[26,48] Better outcome figures are reported for ECLS initiated for low cardiac output in the postoperative period with 30% survival reported in one recent series.[33] However, a definition of what constitutes irreversible cardiogenic shock requiring ECLS support is somewhat subjective and may vary from center to center. Mixed venous oxygen saturation (SvO_2) and serial lactate measurement have been shown to be accurate predictors of death, poor outcome or the need for ECMO in several published studies.[50–53]

Several series are now reporting remarkably good survival where ECLS has been instituted following cardiac arrest, both in the post cardiotomy situation and in children with myocarditis and cardiomyopathies.[13,54] In the post cardiotomy situation, quick access to the thoracic vessels can be obtained by opening the sternum and good cerebral perfusion can be maintained by internal cardiac massage. There is an option to use either full ECMO support by placing cannulas in the right atrium and aorta or using LVAD by cannulating the left atrium. The advantage to using LVAD is that the left heart can be decompressed and if lung function is adequate, this may be a more attractive option in an emergency situation. Several centers, including our own, now have a pre-primed ECLS system available in the ICU for initiating emergency support.

When mechanical support is initiated for any of the above reasons, there should be a diligent search for anatomical defects that may have caused or contributed to the development of myocardial failure. In the first instance, this should be done with transesophageal echo followed by cardiac catheterization, if that is deemed necessary. The current ECLS support technologies include battery-operated pumps which facilitate transport either from the operating room or the intensive care unit to the cardiac catheterization laboratory. Uncorrected residual anatomical defects have been shown to have a much worse outcome with ECLS.[28,55] In the absence of this, low output or lack of function can be ascribed to myocardial failure which is potentially reversible. Recovery is frequently heralded by the return of the arterial waveform on the arterial line trace. Patients who fail to demonstrate return of function by 72 h are unlikely to separate from ECLS and the only options available are removal of life support or listing for heart transplantation. While the latter is the more attractive option, limitations of donor organ supply and the ability to preserve end organ function after more than seven days on mechanical support will influence the decision.

Investigation of residual anatomical lesions

ECMO support of the patient with critically decreased cardiac function has proved an invaluable adjunctive therapy until return of cardiac function or as a bridge to transplantation in patients with primary myocardial failure. However, the benefits of ECMO support after repair of congenital heart defects or as rescue therapy for acute postoperative collapse are less clear. Uncertainties about the benefit of prolonged expensive therapy remain. However, it is agreed generally that the presence of residual anatomic lesions requires prompt and urgent evaluation. Transesophageal echocardiography offers excellent visualization of most postoperative intracardiac anatomy as well as assessment of cardiac function during weaning of mechanical cardiac support. Indeed, the extent of cardiac dysfunction, dilation and mitral and aortic regurgitation may not be fully appreciated until TEE is performed with gradual reduction in circuit flow rates. This information is useful to determine a rational weaning strategy using inotropes, vasopressors, vasodilators and volume loading. However, TEE provides limited information about pulmonary artery stenoses particularly distal obstructions, BT shunt flow, coronary artery obstruction and occasionally aortic arch obstruction. This information is particularly pertinent to the survival of the patient with low cardiac output following the Norwood stage 1 procedure (Fig. 45-3). We have performed early cardiac catheterization in all patients who require postoperative ECMO support if the TEE does not rule out reversible hemodynamically significant lesions and spontaneous improvement in cardiac function fails to occur. Since 1990 we have taken 12 postoperative patients to the cardiac catheterization laboratory without major complications related to the procedure or transport (Fig. 45-4). In 6/12 (50%) angiography provided important additional information unsuspected or inadequately clarified by echocardiography. However, only

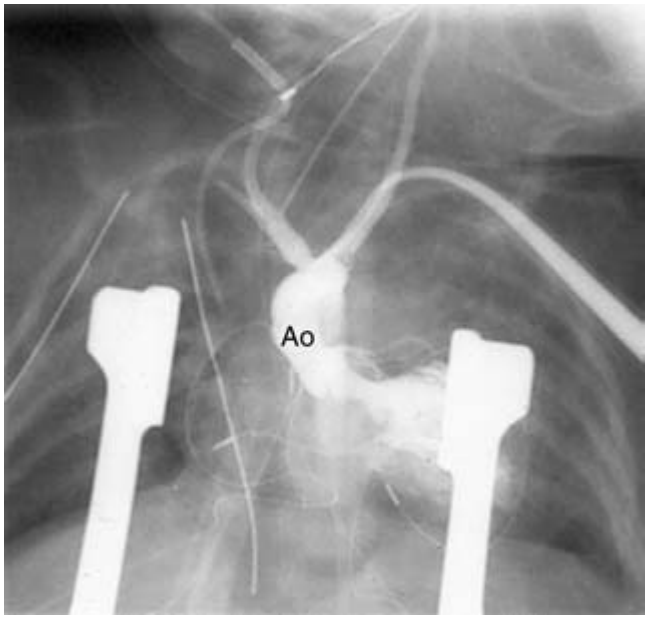


Fig. 45–3 Aortography, using the arterial cannula in a patient on ECMO with aortic incompetence. Ao, aorta.

4/12 survived weaning from ECMO support with 2/12 surviving long term (1 required cardiac transplantation following irreversible myocardial infarction after acute thrombotic obstruction to the left anterior descending artery and 1 required revision of native aortic to neo aortic anastomosis after stage 1 Norwood to relieve precoronary artery obstruction). Following revision the patient was successfully decannulated and has completed stage 3 (Fontan) with good ventricular function.[56] Cardiac catheterization and angiography can be performed safely and should be part of the evaluation algorithm of the postcardiotomy patient on ECMO.

Outcomes related to noncardiac issues

Survival following the initiation of mechanical support is dependent on more than return of cardiac function. The single most important factor that determines long-term survival and ongoing morbidity is neurological damage.[27,33] This may be caused by inadequate cerebral perfusion secondary to low output or cardiac arrest, cerebral infarction secondary to thrombus or air emboli from the circuit and cerebral hemorrhage related to anticoagulation plus or minus too high a cerebral perfusion pressure. The first indication of cerebral injury post initiation of mechanical support is frequently a development of seizure activity. In infants, the presence of a cerebral hemorrhage or infarction can be confirmed by a bedside cranial ultrasound. Neuroimaging studies in older children are more difficult to perform. Neurological injury is the most common reason for early termination of mechanical support.

The outcome in patients where ECMO is used in the postoperative period to treat acute hypoxemia depends on the reversibility of the lung disease, assuming that there are no residual cardiac problems. The overall survival in the ELSO Registry for children outside the newborn period treated with ECMO for AHRF is 40–50% survival. However, it is important to note that acute pulmonary failure outside the newborn period is not a rapidly reversible situation with a short duration of ECMO support. Average times on ECMO are usually a week to 10 days, which is considerably longer than when mechanical support is used for acute cardiac failure.

Other important factors that influence outcome following mechanical support are the development of multi-organ failure, particularly renal failure.[25,27,33,41,57] In the case series reported by Duncan[33] patients who had preserved kidney function as evidenced by ongoing urine output had a higher survival rate than those who became anuric. Survival in the postcardiotomy patients is also influenced by the amount of hemorrhage which, with the ongoing need for anticoagulation, can be very significant.[41,58] In the largest published series by Duncan[33] nonsurvivors had a nearly twofold greater blood loss than survivors.

Outcomes related to complications

Complications associated with the use of ECLS can be divided into patient related and technical complications. These are listed in Tables 45-5 and 45-6. Technical complications are lowest in programmes that have a trained ECLS team with a significant caseload volume to keep up their technical skills. The worse outcomes will be seen in small volume congenital heart programmes where ECMO is used only occasionally and the patient managed by personnel put together on an ad hoc basis rather than by a trained and experience team. Generally speaking, a minimum of 10 ECLS cases per year are required to maintain standards.

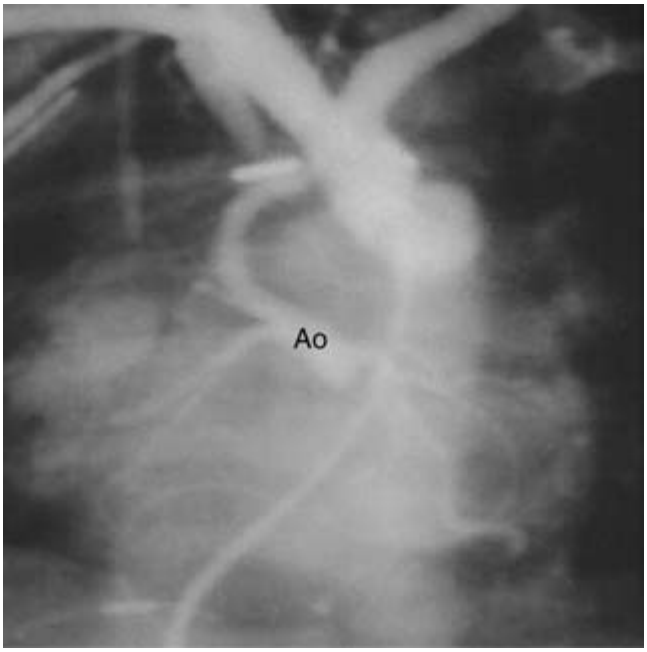


Fig. 45-4 Native aortic root (Ao) stenosis causing precoronary stenosis after the Norwood operation. The patient presented with progressive postoperative low cardiac output state with tricuspid valve regurgitation. After stabilization on ECMO and transfer to the cardiac catheterization laboratory the anastomosis was revised and the patient weaned from ECMO support. The patient has subsequently undergone Fontan operation.

Table 45-5 Principal technical complications of ECLS in congenital heart disease

Problem	Number	Percentage
Oxygenator	350	8.6
Tubing	71	1.8
Clots in circuit	646	15.5
Bleeding from surgical site	1257	30.4
Cannulae	266	6.4

(From ELSO Registry with permission.)

Table 45-6 Principal patient complications of ECLS in congenital heart disease

Problem	Number	Percentage
Brain death	244	5.9
Seizures	501	12.1
Renal replacement therapy	1595	37.8
Infections – blood culture positive	453	10.9
Hemolysis	335	8.1

(From ELSO Registry[000] with permission.)

Long-term outcomes

There are few data on long-term outcomes of ECLS in patients with congenital heart disease. Most studies only report survival to hospital discharge. The only published data on this topic come from Ibrahim *et al*.[59] who did a follow-up study on survivors of ECMO and LVAD from the Children's Hospital in Boston. The median follow-up time was 43 months for ECMO patients and 41 months for VAD patients. Cardiac outcomes, as assessed by NYHA classifications, showed that over 90% of patients were NYHA class I or class II. Based on assessments of cognitive function and the presence of gross motor or sensory abnormalities, 59% of ECMO and 20% of VAD patients had moderate to severe neurological abnormalities. This demonstrates that much work needs to be done on minimizing the neurological sequelae of ECLS which are probably multifactorial and include cannulation of neck vessels, heparinization and alterations in cerebral perfusion.

Summary

Mechanical support is the ultimate in high tech intensive care medicine, the outcomes from which can be truly gratifying. At the same time, it opens up a whole new era where the dividing line between what is death versus potentially survivable takes on a whole new meaning. The difficult part comes not in initiating mechanical support but in closing it down because of futility.[60] This is a concept that health care professionals and families sometimes have difficulty in accepting. Mechanical support can never be regarded as an open-ended therapy. It is now increasingly difficult to define what the indications and contraindications are in the setting of congenital heart disease.

All references can be found at the end of the book. See pp. 844–6 for Chapter 45.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

46

Kyong-Jin Lee and Thomas Yeh Jr

Dilated Cardiomyopathy

Definition and diagnosis

Cardiac dysfunction and dilatation span the entire spectrum of pediatric heart disease placing its burden on both the structurally "normal" and abnormal heart of the fetus, infant, child and adolescent. Primary disease of the myocardium was first described by Krehl in 1891[1] and is distinct from the cardiomyopathies that arise from valvular, coronary, hypertensive, pericardial and congenital heart diseases. This differentiation was further emphasized by the World Hearth Organization (WHO) with the development of the Task Force on the Definition and Classification of Cardiomyopathies.[2,3] Initially, cardiomyopathies were defined as "heart muscle diseases of unknown cause." This definition was in contrast to heart muscle disease of known cause; however, this oversimplification failed to recognize not only the complex interplay between the intrinsic cardiac muscle and extrinsic factors but also that new knowledge would unveil previously undetermined etiologies. The most recent 1995 report from the WHO Task Force advocates for dual classification of cardiomyopathies by (1) the dominant pathophysiology, i.e. dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy and (2) if possible, by etiological/pathogenetic factors.[3] Dual classification provides assistance in management of patients and facilitates outcome analysis by specific subsets.

Despite heterogeneous etiologies, dilated cardiomyopathy is uniformly characterized by ventricular dilatation and impaired myocardial contractility. The ventricular wall thickness is normal or reduced, although total ventricular mass is increased. In most cases, the left ventricle is equally or more severely affected. The more unusual scenario of predominantly right ventricular dilation and dysfunction has been reported.[4] The etiology of dilated cardiomyopathy in children is multifactorial (Fig. 46-1). Known causes include familial/genetic, viral and/or immune, substrate deficiencies, toxin-induced, structural congenital heart disease and the uniquely pediatric conditions of endofibroelastosis and ventricular non-compaction (see Chapter 41G).[5,6] Schwartz *et al*. provide an excellent summary of the initial investigations of the pediatric patient presenting with cardiomyopathy.[5] Their comprehensive approach differentiates between genetic and non-genetic etiologies with particular emphasis on cardiomyopathies associated with inborn errors of metabolism, malformation syndromes and neuromuscular disorders. The identification of etiology may equip the physician to prognosticate outcome and provide appropriate genetic counseling. Most frequently, the cause is idiopathic and isolated.

In the pediatric literature, outcome reporting of dilated cardiomyopathy in children is limited to case series of small numbers. This is particularly the case in the reporting of outcomes in the so-called "dilated cardiomyopathy of known causes." This chapter concentrates on outcomes of patients with "idiopathic" dilated cardiomyopathy. The reader must however understand that included in this subset are cases which have yet to be discovered etiologies.

Historically, the diagnostic criteria for dilated cardiomyopathy included: clinical symptoms of heart failure, cardiac enlargement (on chest radiography, echocardiography, radionuclide scanning, angiography), and histopathology.[7–9] More recently, parameters have been defined to satisfy an echocardiographic definition of dilated cardiomyopathy. Echocardiographic criteria include left ventricular end dimensions two standard deviations greater than normal,[7,9–11] left ventricular shortening fractions < 25–31%[7,9–12] or ejection fractions < 35–55%.[7,10,13–16]

Histological analysis of the myocardium is critical for determination of etiology of dilated cardiomyopathy. The utility of the endomyocardial biopsy resides in the ability to assess for normal myocardium and myocarditis and to perform enzyme analysis for metabolic disturbances.[17] Better survival rates and prognosis are reported in patients with acute myocarditis as the etiology of cardiac dysfunction.[13,18] Failure to exclude myocarditis confounds interpretation of much of the pediatric literature regarding dilated cardiomyopathy. The incidence of histologically proven myocarditis among patients of all ages presenting with acute heart failure or a "dilated cardiomyopathy," varies from 4–50%.[13,19–23] Despite the very low rate of serious complications in associated endomyocardial biopsies,[24–27] histological confirmation of the absence of inflammation occurs in only 13–36% of pediatric patients in series reporting outcomes of dilated cardiomyopathy.[7–9,28–32] More recent large-scale studies in the adult population mandate exclusion of myocarditis by endomyocardial biopsies.[14,33]

In contrast to myocarditis, the histopathologic features of dilated cardiomyopathy are generally non-specific regardless of etiology and age of patient. Microscopy reveals myocyte hypertrophy with large, irregularly shaped, hyperchromatic nuclei, myofibrillary loss within the myocyte and sparse lymphocytic infiltrates. Electron microscopy also demonstrates nonspecific features of both myocyte hypertrophy and degeneration including mitochondrial hyperplasia, abnormal Z bands, dilated and disorganized sarcoplasmic and transverse tubular systems, loss of myofibrils, increased lipid droplets and glycogen, myelin figures, and increased phagolysosomes.[34]

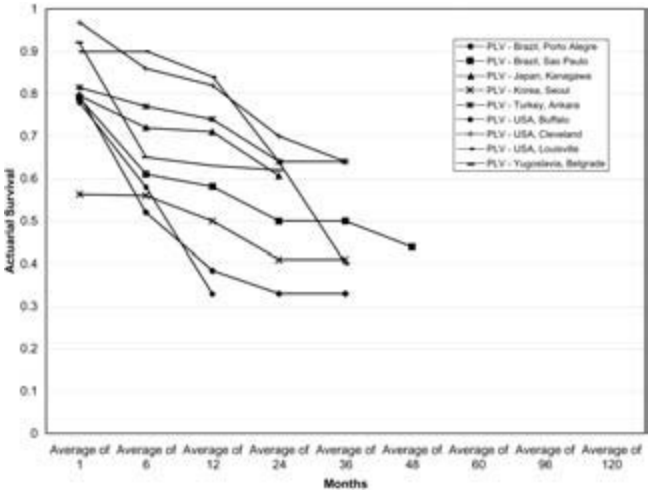


Fig. 46-1 Survival in partial left ventriculectomy series.

Incidence and prevalence

The true epidemiologic impact of dilated cardiomyopathy is unknown. It is confounded by referral patterns, ambiguities in diagnosis, and particularly by the unknown but likely substantial component of asymptomatic and undiagnosed patients.

The population-based study from Olmsted County, Minnesota, USA reports an age and sex adjusted incidence rate of 6 per 100 000 person-years.[14] Miura *et al*. report a crude incidence of 3.58 per 100 000 in the Japanese population.[35] Prevalence ranges from 14 to 43 per 100 000.[14,35–37]

Specific pediatric studies report an incidence of 0.34 per 100 000 and prevalence of 2.6 per 100 000 in the under 20-year-old Finnish population.[28] The Baltimore–Washington Infant Study reported a prevalence of 10 in 100 000 infants with cardiomyopathy.[38] Seventeen of these infants had "dilated cardiomyopathy" but included cases secondary to myocarditis, hemoglobinopathies and metabolic abnormalities.

Overall, there is a trend toward an increase in cases of dilated cardiomyopathy in the whole population likely partly attributed to improvement in case ascertainment. The Olmsted County study reported a doubling of the incidence rate between 1975–79 and 1980–84.[14]

Familial/genetic dilated cardiomyopathy

Dilated cardiomyopathy is familial in 20–35%.[11,39–42] The hypothesis that dilated cardiomyopathy is a disease of the cytoskeleton and sarcolemma ultimately leading to sarcomeric dysfunction has provided the foundation for discovery of responsible gene mutations.[43–47] Familial dilated cardiomyopathy is a heterogeneous disorder as suggested by the different patterns of inheritance: (1) the autosomal dominant pure familial dilated cardiomyopathy; (2) the autosomal dominant form in which conduction defects precede the cardiomyopathy; (3) the autosomal recessive form; (4) the X-linked form associated with mutations of genes coding for the dystrophin or tafazzin proteins; (5) mitochondrial dilated cardiomyopathy of maternal transmission; (6) right ventricular cardiomyopathy which can mimic dilated cardiomyopathy.[48]

Ten genetic loci have been mapped for the autosomal dominant pure dilated cardiomyopathy and five loci mapped for the dilated cardiomyopathy associated with cardiac conduction defects (CDDC) with identification of gene mutations of actin, desmin, δ-sarcoglycan, β-sarcoglycan, cardiac troponin T, β-myosin heavy chain and α-tropomyosin, lamin A/C proteins.[45,46] Patients with CDDC present in their twenties with mild conduction system abnormalities which may progress to complete heart block with progressive dilated cardiomyopathy.[45] Within the X-linked cardiomyopathy group, there are two well-characterized disorders. Towbin *et al.* identified the disease-causing gene, dystrophin, i.e. its severe reduction or absence in affected individuals of the X-linked cardiomyopathy (XLCM).[49,50] Affected males typically present during adolescence or young adulthood with rapidly progressive heart failure. Interestingly, despite elevations in serum creatine kinase (CK) including the muscle isoform, CK-MM, no clinical skeletal myopathy is observed.[44] Female carriers tend to develop mild to moderate dilated cardiomyopathy in their fifth decade and have slower progression. Mutations of the dystrophin gene are also responsible for Duchenne and Becker muscular dystrophies (DMD, BMD).[51] Dilated cardiomyopathy occurs in 90% of cases and is a frequent cause of mortality and skeletal myopathy is universal.[52] Barth syndrome is characterized by X-linked cardioskeletal myopathy with abnormal mitochondria, cyclic neutropenia and 3-methylglutacoic aciduria. Bione *et al.* first described the disease-causing gene G4.5 encoding the protein tafazzin.[53] Most survive infancy but dilated cardiomyopathy persists and some succumb to heart failure, sudden death or sepsis. Female carriers do not appear to develop clinical disease.[44] Dilated cardiomyopathy may be a feature of Kearns–Sayre syndrome, a mitochondrial myopathy characterized by ptosis, progressive external ophthalmoplegia, abnormal retinal pigmentation, and cardiac conduction defects.[54]

All of the genes identified for inherited dilated cardiomyopathy are also known to cause skeletal myopathy. Dystrophin mutations cause DMB and BMD, lamin A/C mutations cause Emery–Dreifuss muscular dystrophy, sarcoglycan mutations cause limb girdle muscular dystrophy and actin mutations are associated with nemaline myopathy.[43] Such associations support the hypothesis that skeletal muscle fatigue experienced by patients with dilated cardiomyopathy may be primary skeletal myopathy and not related to compromised cardiac output.

Often relatives are asymptomatic and diagnosed only by echocardiography. Except for family history, often there are no characteristics distinguishing between familial and non-familial dilated cardiomyopathy. Prospective screening revealed abnormal echocardiography in 29% asymptomatic relatives of index cases.[55] Subnormal cardiopulmonary exercise test performance in asymptomatic relatives with left ventricular enlargement but normal systolic function provides further evidence of subclinical disease.[56] Identification of affected relatives has several important implications. Monitoring may result in improved outcomes possibly through early introduction of treatment even when patients are asymptomatic. The SOLVD (Studies of Left Ventricular Dysfunction) investigators demonstrated the beneficial effects of enalapril on the reduction of heart failure symptoms and mortality in the asymptomatic patient.[57] Further, pedigree evaluation represents an essential initial step for molecular genetic studies for the identification of the disease gene.

Outcome analysis

The natural history of dilated cardiomyopathy is not completely understood. Reported outcomes vary from "full recovery" to death.[7,8,13,58] This knowledge void relates to ambiguities in epidemiologic data and heterogeneity of etiology. Asymptomatic cardiomyopathy may be present for months to years before diagnosis. Baig *et al*. report that in patients with left ventricular enlargement but normal left ventricular shortening fractions, 27% went on to develop symptomatic dilated cardiomyopathy including one sudden death and one requiring heart transplantation.[55] Mahon reported abnormal cardiopulmonary exercise tests in relatives of patients with dilated cardiomyopathy with left ventricular enlargement but normal systolic function.[56] A retrospective analysis of asymptomatic adults with idiopathic dilated cardiomyopathy demonstrated short and intermediate prognosis of 100% and 78% survival at 2 and 5 years respectively. The 7-year mortality was substantial at 53%.[16]

Adult mortality rates have demonstrated time-related improvement. One- and 5-year mortality rates of 25–31% and 50–64%, respectively, have decreased to 5–10% and 20%, respectively.[59–62] In New York Heart Association (NYHA) class IV patients, the placebo group of the CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study) trial had mortality rates of 48% and 63% at 6 months and 1 year respectively.[63]

For 1978–83, 1983–87 and 1987–92, survival rates have increased from 74% to 88% to 90%, respectively, at 2 years and 54% to 72% to 83%, respectively, at 4 years.[62] This secular trend of improved survival may be related to earlier detection of disease and better medical management.

Actuarial survival analyses in children have been based on small number series all with < 100 patients and all with lack of uniformity in diagnostic criteria. There are no series in which all patients had histopathological confirmation of idiopathic dilated cardiomyopathy. Actuarial survival ranges of 41–85% and 34–80% at 1 and 5 years, respectively, were found.[7,8,12,30,64–66] Friedman *et al*. report a cumulative survival rate of 84% in 63 patients over a mean follow-up period of 4 ± 4 years[66] and Lewis reported an actuarial survival of 52% at 11.5 years in 81 patients.[29] More dismal actuarial survival was reported by Akagi *et al*. with actuarial survival rates of 54%, 41%, and 20% at 6 months, 1 year, and 3 years, respectively.[30] As in the adult population, a secular trend towards increased survival has been demonstrated. Venugopalan reported 1-year actuarial survival increasing from 69% to 85% (1980–89 compared with 1990–97).[65] Similarly, Arola demonstrated increased 1- and 5-year survivals from 48% to 70% and 42% to 52%, respectively, in 1980–85 compared with 1986–91.[28] Complete recovery of ventricular function in the pediatric population is reported in up to 25% of patients.[7,13,58]

Dilated cardiomyopathy in the fetus

Data are scant regarding assessment and outcome of fetal cardiomyopathies.[67–69] Recently, Pedra *et al*. reported 55 (8.9%) fetuses with cardiomyopathy of 612 fetuses with abnormal cardiac anatomy, rhythm, or function.[69] Dilated cardiomyopathy occurred in 22 (40%) of cardiomyopathy cases. Etiologies included familial dilated cardiomyopathy, anti-Ro or anti-La associated endofibroelastosis, intrauterine infection and idiopathic. The overall mortality in the dilated cardiomyopathy group was dismal at 82.3%, with 8 intrauterine deaths and 6 early neonatal deaths. Diastolic dysfunction in fetal cardiomyopathy is associated with the highest risk of mortality.

Congenital heart block and dilated cardiomyopathy

The incidence of isolated congenital third-degree atrioventricular block (CAVB) is reported to be 1 in 14 000 to 20 000 live births.[70] Age at presentation appears to be an important determinant in outcome.[71–74] Jaeggi *et al*. reported 102 cases of isolated CAVB in which mortality differed depending on diagnosis as a fetus, neonate (< 28 days) or child at 43%, 6% and 0%, respectively, in the first two decades of life.[73] Recent studies report a high incidence of early pacemaker intervention. Jaeggi *et al*. report Kaplan–Meier estimates of freedom from pacemaker implantation of the fetal, neonatal and childhood subgroups as 29%, 73% and 98% at 6 months.[73] Eronen *et al*. reported that 48 (53%) of newborns received pacemaker therapy within the first 3 months.[71] A subset of patients with CAVB have associated dilated cardiomyopathy that may or may not be present at time of diagnosis.[71,75,76] Incidences range from 6% to 23%.[71,72,75] Reports consistently demonstrate a strong correlation between CAVB and dilated cardiomyopathy and poor outcome. Mortality was 62% in patients with CAVB diagnosed *in utero* or as a newborn,[71] 75% when CAVB was diagnosed after 3 months of age.[72] Mortality, heart transplantation or on the waiting list for transplantation is reported to be between 75% and 89% with this association.[75,76] Possible risk factors for poorer outcomes include maternal anti-Ro and/or anti-La autoantibodies, increased heart size at initial evaluation, absence of pace-maker-associated improvement, and presence of endocardial fibroelastosis.[73,75,76]

Arrhythmias in dilated cardiomyopathy

The myopathic process of dilated cardiomyopathy manifests with clinical signs and symptoms of decreased cardiac function. Of equal prominence, the failing heart is susceptible to cardiac arrhythmias. This is a result of pathological myocyte substrate in the milieu of neurohumoral and pharmacologic triggers. In adults, conduction abnormalities occur in 80% of dilated cardiomyopathy cases and include first degree heart block, left bundle branch block, left anterior hemiblock and non-specific interventricular conduction delay.[59] Frequent and complex ventricular arrhythmias as documented on Holter monitoring are associated with an annual mortality rate of 15% with half of the deaths being sudden presumably a fatal arrhythmia.[77] Biopsies in patients with spontaneous ventricular tachycardia or fibrillation with structurally normal hearts with a mean LVEF of 65 ± 7% demonstrated abnormalities in 89%.[78] Fifty per cent were diagnosed with idiopathic dilated cardiomyopathy, 17% myocarditis, 11% arrhythmogenic right ventricular dysplasia, 11% abnormal intramyocardial arteries and 11% normal.

Specific pediatric studies addressing arrhythmia associated with dilated cardiomyopathy are scant. Similar to the adult data, arrhythmias occur frequently with electrophysiologic conduction abnormalities consisting of supraventricular and ventricular tachycardias and atrioventricular conduction block. Friedman *et al*. reported palpitations in 14% of patients and syncope or near syncope in 8 (13%) patients.[66] Arrhythmias were present in 46% of patients of which 48% were atrial in nature.[66]

Akagi *et al*. reported 52% frequency of arrhythmias in 25 patients of which 4 required a pacemaker.[30] All patients who had a pacemaker died within a mean of 12 months. Lewis and Chabot reported dysrhythmias in 24 (30%) patients.[29] Rhythm abnormalities were more prevalent in non-survivors (53% vs. 16%).

Sudden cardiac death

Adult studies report a significant proportion of sudden death in patients with dilated cardiomyopathy accounting for up to 50% of total mortality.[59,63,79–82] In the SOLVD trial, 23% of deaths were "arrhythmic without worsening congestive heart failure."[63] The V-HeFT II (Vasodilator-Heart Failure Trial II) reports 31% of deaths to be "sudden with no warning symptoms" and 43% to be "sudden with or without warning symptoms."[83] In the CHF-STAT (Congestive Heart Failure: Survival Trial of Antiarrhythmic Therapy) trial, 52% of deaths were sudden.[77,84] The mechanism of sudden death is presumed to be predominantly arrhythmia and thus may be preventable.

Predictors for sudden death include syncope, severity of left ventricular dysfunction, baseline arrhythmias and inducibility of sustained malignant arrhythmias. The V-HeFT trials found that total mortality and both pump-failure death and sudden death were related to severity of left ventricular dysfunction as measured by ejection fraction, plasma norepinephrine or peak exercise oxygen consumption.[85] The rates of sudden cardiac death (SCD) were similar in ischemic and non-ischemic dilated cardiomyopathy. Presence of ventricular arrhythmias on Holter monitoring was associated with higher overall mortality but not an increase in the proportion of sudden vs. pump-failure deaths.[79] Other studies further support the hypothesis that left ventricular dysfunction is the strongest predictor of sudden cardiac death; however, these studies of coronary patients cannot be readily extrapolated to the pediatric population.[86–90] Syncope seems to be a powerful predictor of SCD.[80,91] Middlekauff reports that, regardless of the etiology of the syncope in advanced heart failure, the actuarial incidence of sudden death by one year is 45% in patients with syncope vs. 12% in patients without syncope.[80] Inotropic therapy has consistently been associated with increased mortality almost exclusively via sudden death.[92,93]

Reduction of sudden cardiac deaths appears to be possible. The US Carvedilol Heart Failure Study Group reported a decrease in sudden death in patients treated with carvedilol (3.8% vs. 1.7%).[94] The GESICA (Grupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina) trial reported a 27% risk reduction of sudden death in patients treated with amiodarone.[82] Comparative studies suggest superior survival with implantable cardioverter defibrillators (ICD) over drug therapy including amiodarone.[95] A primary prevention trial (Sudden Cardiac Death in Heart Failure Trial (SCD-HEFT)) comparing placebo, amiodarone and ICDs is ongoing.[79]

Patients with predominantly right ventricular dilated cardiomyopathy may represent a subset at higher risk.[4,7] Fitchett reports 5 sudden deaths in 14 patients with predominantly right ventricular dilated cardiomyopathy.[4] Of note, syncope was the initial presenting symptom in 6 patients. Arrhythmias were important in the clinical course of 12 patients.

Pediatric reports of sudden death secondary to dilated cardiomyopathy are sporadic and without exception a brief mention within case series of outcomes of dilated cardiomyopathy. Sudden death occurred in 1 of 62 patients,[7] 1 in 24 patients,[8] 1 of 25 patients,[30] 3 of 10 patients,[66] 4 of 23 patients all occurring while in hospital,[31] 7 of 63 patients,[12] 7 of 32 patients and 7 of 17 deaths.[32] Sudden cardiac death was more frequent in patients with ventricular arrhythmias on ambulatory monitoring (3 of 4 patients with ventricular arrhythmia vs. 1 of 18 patients with normal rhythm).[12]

Prognostic indicators of outcome

Ascertaining prognosis for the individual patient with dilated cardiomyopathy remains problematic. Underlying causes are important in predicting outcome yet most cases are of unknown etiology. Myocarditis and peripartum cardiomyopathy have relatively good outcomes whereas cardiomyopathy associated with infiltrative diseases, HIV infection, or doxorubicin and endofibroelastosis in children do not.[7,13,18,96,97] Grim prognosis has been reported in X-linked cardiomyopathies often with death within the first year of presentation.[98] Management of heart failure is for the most part palliative and the endpoint for many patients is heart failure related death or cardiac transplantation. A limited donor pool necessitates identifying patients whose non-transplanted mortality exceeds that associated with cardiac transplantation.

Survival during initial presentation appears to be precarious.[12,13,65] Matitiau reported that 6 of 7 deaths in children occurred < 2 months after presentation.[13] The important limitation was that this study did not histologically rule out myocarditis as an etiology. Similarly, Venugopalan reported all 12 patient deaths occurred within a year with 50% being within the first week of presentation.[65] Burch *et al*. reported 7 of 63 deaths within 3 months after presentation.[12] Further, lack of echocardiographic improvement may be associated with a higher risk of death.[12,64] Lewis reported the association of persistence (> 3 months) of left ventricular shortening fractions < 15% with poorer survival in the pediatric population.[64] One- and 5-year survival were 46% and 29%, respectively, compared with 97% and 90% respectively in the group in whom early improvement of left ventricular function was observed.

Syncope as a strong predictor of sudden death is reported in the adult population.[59] Middlekauff *et al*. reported that the actuarial incidence of sudden death by one year was significantly greater in patients with syncope (45% vs. 12%).[80] Brilakis *et al*. reported survival at 1, 2, 3, and 5 years as 81%, 74%, 69%, and 62%, respectively, in a cohort 54 patients with dilated cardiomyopathy and syncope some of whom received ICD and pacemaker therapy.[99] Fruhwald *et al*. did not demonstrate a statistically significant difference in all-cause mortality between those with or without syncope but did discover a higher rate of sudden death in the former group.[91] Pediatric studies speculate on the important role of arrhythmias in increased mortality with non-survivors having increased incidence of known rhythm abnormalities (53–71% vs. 16%).[29,32] The prognostic significance of left bundle branch block remains unclear although studies portend increased mortality (36%).[100,101]

In children, older age at presentation has been reported as a possible risk factor. Griffin identified age at presentation of > 2 years to be associated with 100% mortality during a 2-year follow-up period compared with 25% mortality in children younger than 2 years of age.[32] Similar conclusions were made by Taliercio *et al*.[8,30] To contrast, other pediatric studies have not supported this critical age of 2 years theory.[7,9,30,31,65] One must

speculate whether the higher mortality in adolescent male patients reported by Arola *et al*. reflects the undiagnosed X-linked cardiomyopathy patient subset with known grim prognosis.[7,98,102]

A number of studies show strong correlation between poor prognosis and severity of ventricular dysfunction and enlargement.[7,29,30,103–105] This has been particularly the case in the adult population post coronary infarction.[86–90] In contrast, a pediatric study of 46 patients with dilated cardiomyopathy did not identify a poorer initial shortening fraction as an indicator of adverse outcome.[106] Further, the shift of the left ventricle from an ellipsoidal to a spherical shape has been identified as a poor prognostic indicator.[13,104]

Exercise testing provides objective assessment of functional capacity in patients with heart failure and an indirect assessment of cardiovascular reserve. Its utility lies not only as a possible important prognosticator but also for objective assessment of response to therapy. Mancini *et al*. prospectively evaluated whether peak oxygen consumption during maximal exercise testing could be used to determine selection of patients in whom cardiac transplantation could be relatively safely deferred.[107] In patients in whom the maximum oxygen consumption (MVO_2) was > 14 mL/kg per min, the 1- and 2-year survival rates were 94% and 84%, respectively, vs. a 1-year survival rate of 70% in those with MVO_2 < 14 mL/kg/min. Post transplant survival at 1 and 2 years was not statistically different from those patients with MVO_2 greater than the cut-off of 14 mL/kg/min. Other studies have evaluated other MVO_2 cut-off points ranging between 10 and 18 mL/kg/min[108–110] but as Myers concludes, an optimal MVO_2 cut-off point for predicting pre-transplant survival may not exist and that peak VO_2 should be considered a continuous variable in a multivariate model to predict prognosis in severe chronic heart failure.[111] There appears to be reasonable correlation between the 6 minute walk and peak VO_2 measurements.[112,113] In recognition of the multivariate factors affecting survival, composite scores such as the prognostic score index (PSI) have been advocated.[114] This score factors the non-invasive parameters of etiology of cardiomyopathy (ischemic vs. non-ischemic), resting heart rate, left ventricular ejection fraction, mean blood pressure, peak VO_2, serum sodium and IVCD. Low risk PSI numbers had 1-year event-free survival of 93% vs. 72% and 43% in the medium and high risk groups, respectively.

Dobutamine stress echocardiography is frequently used to detect viability of myocardium in coronary artery disease. Its role in idiopathic dilated cardiomyopathy is in evolution.[101,115] Kaplan–Meier survival estimates demonstrate improved survival for patients with large inotropic responses to dobutamine (94% vs. 69%).[115] Positive response to dobutamine testing is also associated with future improvement in left ventricular function.[116] Future applications include intracoronary dobutamine infusion to assist in prognosis determination.[117]

Troponin complex on the actin filament regulates the force and velocity of muscle contraction. The subunit troponin T (TnT) anchors the troponin complex to tropomyosin. Under normal conditions, the concentration of free troponin T in the cytosol is low. Increased cytosolic concentrations reflect myocardial injury and loss of cell membrane integrity. The diagnostic and prognostic utility of TnT is extensively reported in acute coronary syndromes; however, its significance in dilated cardiomyopathy is unknown. The ongoing myocyte degeneration of dilated cardiomyopathy may be reflected in serial serum TnT measurements. Sato *et al*. reported lower survival rates in those patients with persistently elevated TnT levels suggestive of ongoing subclinical myocyte degeneration. TnT levels did not correlate with clinical presentation and appeared not to be a marker of hemodynamic decompensation but rather a manifestation of the underlying pathophysiological process.[118]

Data exist to support the negative prognosis associated with left ventricular end-diastolic pressures > 20 to 25 torr, a spherical vs. ellipsoidal left ventricular geometry, pulmonary hypertension, hyponatremia, enlarged cardiothoracic ratio on chest radiography, S3 gallop on physical examination, cardiac index < 2.5 L/min/m^2, decreased ventricular mass to volume ratio, increased levels of natriuretic factor, renin and norepinephrine.[13,29,30,59,60,109,119,120]

Treatment

Vasodilators/angiotensin converting enzyme inhibitors

Vasoconstriction in the systemic arterial and venous beds increases impedance to left ventricular ejection and shifts blood centrally from the venous capacitance vessels. The rationale for vasodilator therapy derives from efforts to decrease the preload and afterload which adversely affect left ventricular performance and contribute to the low cardiac output and venous congestion that characterize heart failure. Studies including CONSENSUS (Cooperative North Scandinavian Enalapril Survival Study), V-HeFT I, V-HeFT II, SOLVD treatment have uniequivocally demonstrated the efficacy of vasodilators including angiotensin converting enzyme (ACE) inhibitors, hydralazine and isosorbide dinitrate.[63,83,85,121]

The benefits of angiotensin converting enzyme (ACE) inhibitors in adults with dilated cardiomyopathy are undisputed through large prospective comparative trials. V-HeFT II demonstrated reduction in mortality by 28% with enalapril therapy over hydralazine and isosorbide dinitrate.[83] The SOLVD treatment trial demonstrated a 16% risk reduction in mortality and 26% risk reduction in death or hospitalization with enalapril during a average follow-up of 41 months in 2569 patients.[121] In CONSENSUS, there was a 40% reduction in crude mortality (26% vs. 44%) in NYHA class IV patients receiving enalapril.[63] The 2.5-year mortality rate in the ACE inhibitor treatment groups was *c*. 27% in SOLVD, 25% in V-HeFT II, and 36% in CHF-STAT. The Collaborative Group on ACE Inhibitor Trials reviewed the results of 7105 patients from 35 randomized, placebo-controlled trials of ACE inhibitors.[122] Overall, there were statistically significant reductions in total mortality (odds ratio [OR], 0.77) and in the combined endpoint of mortality or hospitalization for congestive heart failure (OR, 0.65). Although reductions in mortality reached statistical significance only with enalapril, similar directional benefits were observed with other ACE inhibitors (captopril, ramipril, quinapril and lisinopril). These reductions in mortality spanned across the various subgroups (age, sex, etiology, and New York Heart Association (NYHA) class). The most benefit was seen during the first 3 months of therapy and in the subgroup with the lowest ejection fraction.

Administration of ACE inhibitors has been extrapolated to children and shown similar benefits in small case series.[7,123–126] Its actions to decrease both left ventricular preload and afterload are manifested by improvement in stroke volume by *c*. 22%.[126] A retrospective comparative review of 81 patients demonstrated improved survival in the 27 children treated

with ACE inhibitors particularly during the first year after treatment.[123]

Angiotensin receptor blockers

The hemodynamic effects of angiotensin receptor antagonists (ARBs) are similar to those of ACE inhibitors but may have better tolerability particularly with the common cough side-effect (%).[127] ARBs however do not inhibit bradykinin metabolism and thus may lack this potentially beneficial vasodilatory effect. The RESOLVD (Randomized Evaluation of Strategies for Left Ventricular Dysfunction) trial demonstrated that candesartan was comparable with enalapril on exercise performance, ventricular function, NYHA functional class, and patient tolerance.[128] The combination of both drugs was more effective in prevention of left ventricular dilatation and suppression of aldosterone and B-type natriuretic peptide than either drug alone. The CHARM (Candesartan in Heart Failure – Assessment of Reduction in Mortality and morbidity) trial is ongoing comparing the addition of candesartan in patients already on ACE inhibitors with those intolerant of ACE inhibitors.[129] There are no published reports of ARBs in the pediatric population although there is anecdotal experience.

Beta-blocker therapy/carvedilol

Data support the use of β-adrenoreceptor antagonists as an adjunct to conventional therapy in an effort to slow the progression of heart failure. The negative inotropic effect of β-adrenoreceptor antagonists contraindicated its administration for many years in heart failure management. In 1975, a report from Sweden demonstrated benefits in symptoms and exercise tolerance as well as improvements in left ventricular function in patients with dilated cardiomyopathy.[130] Subsequent to this breakthrough, a number of placebo-controlled studies with various β-adrenoreceptor antagonists (metoprolol, bisoprolol, practolol, alprenolol, acebutolol, bucindolol, labetalol, carvedilol) confirmed safety of these drugs in this setting and supported further investigation.[131,132] The mechanisms of β-adrenoreceptor antagonists in heart failure are not well delineated. Unlike the selective blocking agents metoprolol and bisoprolol, carvedilol blocks both α1- and β2-adrenergic receptors. Its beneficial effects may mediate from up-regulation of cardiomyocyte β-adrenergic receptors, modulation of postreceptor inhibitory G proteins and thus ventricular remodeling, and improvement in baroreceptor function which in normal circumstances inhibits excess sympathetic outflow. Finally, its antioxidant effects may attenuate cardiomyocyte apoptosis accompanying heart failure. Large trials supporting the use of carvedilol in heart failure come primarily from the US Carvedilol Heart Failure Study Group which reported the experience of 1094 patients from 65 institutions with left ventricular ejection fraction (35% (including ischemic cardiomyopathy).[131] Follow-up ranged from 6 to 12 months. The study was terminated early on the recommendation of the Data and Safety Monitoring Board based on the finding of a significant beneficial effect on survival. The carvedilol treatment group experienced reductions in overall mortality 3.2% vs. 7.8% (risk reduction [RR], 65%), hospitalization from cardiovascular causes 20% vs. 14% (RR 27%) and combined death and hospitalization 25% vs. 16% (RR 38%). There were also improvements in the secondary end points of NYHA class and left ventricular ejection fraction. There is acknowledgement that there are some limitations in the interpretation of this study. Of cautionary note, few patients (2.9%) with NYHA class IV heart failure, were included in the study and patients hospitalized for intravenous inotropic support were excluded. Contraindications to carvedilol therapy include severe decompensated heart failure, i.e. patients likely dependent on sympathetic stimulation, marked bradycardia, sick sinus syndrome, partial or complete atrioventricular block or pre-existing liver disease. Caution is advised in patients with glucose metabolism abnormalities as signs and symptoms of hypoglycemia may be masked. The US Carvedilol Heart Failure Study Group reported a 5% carvedilol discontinuation rate from the side effects of worsening heart failure, dizziness, or bradycardia.[131]

Beta-blocker treatment for pediatric heart failure is in relative infancy with reports of small patient numbers with dilated cardiomyopathy of multiple etiologies.[106,133–137] Similar to adult management algorithms, beta-blocker therapy is initiated after patients stabilize on conventional medication regimes including angiotensin converting enzyme inhibitors.[106,134,136] Metoprolol increased shortening and ejection fractions in a multi-institutional experience of 15 children with cardiomyopathies secondary to idiopathic, anthracycline-induced, Duchenne muscular dystrophy related, postsurgical and postmyocarditis causes.[134] Four of 9 patients with idiopathic dilated cardiomyopathy increased their left ventricular ejection fraction to at least 60% after therapy (from initial ejection fractions which ranged from 21% to 46%). A multicenter report of 46 patients is the largest series of children treated with carvedilol.[106] Of the 37 patients with dilated cardiomyopathy, 24 were idiopathic. During a mean follow-up period of 13.5 months, the mean shortening fraction increased from 16% to 19% with improvements in the modified New York Heart Association class in 67%. Adverse outcomes (death, cardiac transplantation, and ventricular-assist device placement) occurred in 30% of patients. Gachara *et al*. report improvement of left ventricular ejection fraction from 25% to 39% and no mortality in 8 infants (7 with idiopathic dilated cardiomyopathy) under 24 months of age during a follow-up period of 4.5 ± 2.2 months.[135] The Toronto Hospital for Sick Children experience of 23 patients, of which 16 had idiopathic dilated cardiomyopathy, demonstrated a median improvement in left ventricular ejection fraction of 12% and median improvement in left ventricular end diastolic dimension Z-score of –1.63.[136] Kaplan–Meier analysis for freedom from death or cardiac transplantation was 91% at 2 months to 2 years. All patients were alive at a mean follow-up of 1.1 ± 0.66 years, except one patient who died post cardiac transplantation. Studies confirm the safety and efficacy of beta-blocker therapy in the pediatric population.[106,133,135,136] The discontinuation rate as a result of tolerability was between 0% and 7%.[106,134,136]

Spironolactone

Aldosterone promotes the retention of sodium, the loss of magnesium and potassium, the activation and inhibition respectively of the sympathetic and parasympathetic systems, myocardial and vascular fibrosis, baroreceptor dysfunction, direct vascular damage, and prevents the uptake of norepinephrine by the myocardium. ACE inhibition may only transiently and partially suppress the production of aldosterone.[138] RALES (Randomized Aldactone Evaluation Study) studied administration of aldactone in 1663 patients already on a baseline ACE inhibitor

therapy with left ventricular ejection fractions < 35% over a mean of 24 months.[139] It demonstrated a 30% reduction in all-cause mortality (46% vs. 35%), 35% reduction in hospitalizations and improvements in NYHA functional class in the treatment group. Most patients were in NYHA III and IV functional classes. Recommendations included consideration of aldactone for moderate to severe heart failure.

Digitalis

Drugs enhance the inotropic state of the failing heart by increases in the concentrations of intracellular sodium and cyclic AMP. Increased concentration is maintained through sodium channel agonists or through the inhibition of sodium/potassium-transporting ATPase (digitalis). Similarly, cyclic AMP synthesis is promoted through β-adrenergic agonists or by attenuating its degradation (phosphodiesterase inhibitors).

The Digitalis Investigation Group reported the effect of digoxin on 6800 patients over a 37 month follow-up period.[140] Mortality was unaffected (34.8% in placebo group, 35.1% in digoxin group). However, the digoxin group experienced 6% fewer hospitalizations particularly for worsening heart failure (26.8% vs. 34.7%, RR 0.72).

Phosphodiesterase inhibitors

Studies of cyclic AMP-enhancing agents whether the agent be a β-adrenergic agent or phosphodiesterase inhibitor all show increase in mortality.[92,93] The PROMISE (Prospective Randomized Milrinone Survival Evaluation) trial compared the impact of oral milrinone vs. placebo on 1088 patients in the NYHA functional classes III and IV over a median of 6 months.[92] The milrinone group had a 28% increase in all-cause mortality, 34% increase in cardiovascular mortality, more hospitalizations (44% vs. 39%) and more serious cardiovascular reactions including syncope. The NYHA functional class IV patients had a 53% increase in mortality. It is known that production of cyclic AMP is deficient in failing hearts[141] and that experimental animal studies demonstrate that milrinone improves the cardiac performance and survival.[142,143] The mechanism of increased mortality in humans is unknown. In rats, milrinone does not inhibit phosphodiesterase, increase cyclic AMP levels, or exert positive inotropic effects on the myocardium but appears to exert its beneficial effects primarily through vasodilation.[143] Experimental studies suggest toxic myocardial effects of cyclic AMP and enhancement of electrophysiologic mechanisms that lead to rhythm disturbances.[144–146] It is hypothesized that the decline in the production of myocardial cyclic AMP is an adaptive response to chronic heart failure and the detrimental effects of milrinone and other agents relate to their toxic effects via cyclic AMP.[146]

Thromboembolism and anticoagulation

Classic pathophysiology and biochemical studies support the clinician's suspicion of the thrombogenic milieu of the heart failure setting.[147] As such, intracardiac thrombus and embolic events, whether cerebral, systemic, pulmonary, or their combination, are well described.[7,8,30,31,41,59,65,147,148] In the adult population, prevalence estimates of thromboembolism range from 3% to 50% and incidence estimates range from 1.5 to 3.5/100 patient-years.[147] Autopsies uncovered intracardiac thrombus in 43% to 60%. Embolic events occurred in 8–16%.

Sporadic pediatric case series report intracardiac thrombus in 3 of 39 patients,[65] 3 of 13 patients,[8] 8 of 62 patients[7] and 12 (18%) of 67 patients.[149] McCrindle *et al*. reported that the left ventricular ejection fraction was not predictive of clot formation.[149] Further, thrombus formation was not significantly associated with an increase in mortality.

Vigna *et al*. reported that 8% of patients with embolism had no evidence of thrombus in the left atrium or left ventricle.[148] A left ventricular thrombus was detected in 17.5% of 80 patients. While there was 100% correlation between transthoracic (TTE) and transesophageal echocardiography (TEE) for left ventricular thrombus, TEE detected a left atrial thrombus in 18 adults who had a negative TTE, i.e. reflective of underestimation of thrombus occurrence.

There are no controlled prospective trials on the use of anticoagulation in patients with heart failure. Fuster *et al*. reported 19 embolic events during 624 patient-years in 103 patients who did not receive anticoagulation therapy (3.5 events/100 patient-years).[60] In contrast, none of 32 patients (101 patient-years) receiving warfarin therapy had an embolic event. Most larger studies failed to show a protective effect of anticoagulation with equal or higher rates of thromboembolic events in the treatment group.[83,85,150] The incidence of major hemorrhage in the adult population is between 2.3 and 6.8/100 patient-years with a suggested direct correlation with increasing age.[151] Hypothetical risk factors include severe left ventricular dysfunction, history of thromboembolism, established or paroxysmal atrial fibrillation leading to the intuitive addition of anticoagulation in heart failure management. A risk assessment including these factors might identify higher risk patients. At present, there is an absence of trial data to guide anticoagulant treatment in patients with dilated cardiomyopathy and the need for prospective trials assessing the risk–benefit ratio of antithrombotic therapy is recognized. Several trials such as Warfarin Aspirin Study in Heart Failure (WASH) and Warfarin-Antiplatelet Trial in Chronic Heart Failure (WATCH) are in progress with the hope of development of evidence-based recommendations.

Rhythm therapy in dilated cardiomyopathy

Antiarrhythmic drugs have been associated with an increase in mortality in patients with left ventricular dysfunction related to their negative inotropic and proarrhythmic effects.[152,153] Amiodarone is the only antiarrhythmic agent that is not contraindicated in heart failure associated with reduced left ventricular systolic function.[77,154–156] Amiodarone is widely believed to be effective in treating life-threatening ventricular arrhythmias; however, this conclusion is not well supported in the literature.[95,157] No randomized, placebo-controlled trials have assessed the utility of amiodarone in the prevention of recurrent sustained ventricular tachycardia or ventricular fibrillation. Amiodarone-induced suppression of ventricular premature depolarizations (VPDs) and episodes on nonsustained ventricular tachycardia (VT) is well documented.[77,158–161] In the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT), complete suppression of VPDs was achieved in 86% of the amiodarone group compared with 50% of placebo patients.[160] There are varying results regarding mortality reduction with amiodarone.[77,156] The CHF-STAT (Survival Trial

of Antiarrhythmic Therapy in Congestive Heart Failure) investigators in a randomized, double-blind, placebo-controlled trial of amiodarone in 674 patients with left ventricular ejection fractions < 40% demonstrated an increase in ejection fraction in the amiodarone group at 6, 12, and 24 months and amiodarone was significantly more effective in suppressing ventricular arrhythmias [77]. It did not reduce the incidence of sudden death. Although not statistically significant, there was a trend towards reduction in hospitalizations and cardiac death in the non-ischemic cardiomyopathy group.

The Argentinian GESICA trial demonstrated decreased mortality with amiodarone (33.5% vs. 41.4%, RR 28%).[82] There was also a 27% risk reduction of sudden cardiac death.

Resynchronization therapy

The failing dilated heart has abnormal ventricular conduction pathways as manifested by a prolonged QRS duration. Such ventricular dysynchrony may impair ejection or predispose to mitral regurgitation. Resynchronization therapy involves atrially-synchronized biventricular pacing to coordinate right and left ventricular contraction. Resynchronization therapy may be of most benefit in patients refractory to conventional medical therapy with QRS duration > 130–150 milliseconds with significant mitral regurgitation and PR prolongation.[162] The MIRACLE (Multicenter InSync Randomized Clinical Evaluation) trial was a double-blind, multi-center study of cardiac resynchronization in 228 adult patients with moderate-to-severe heart failure with QRS durations > 130 ms.[163] The primary end points of NYHA functional class, quality of life scores and 6 min walk distances were significantly better in the treatment compared with the control group. The combined risk of a major clinical event (death or hospitalization for heart failure) was 40% lower in the resynchronization group than in the control group. Of cautionary note, the follow-up period was only 6 months. Technical issues were not insignificant particularly related to the placement and maintenance of the coronary sinus pacing lead required for left ventricular pacing. Technical adverse events included coronary sinus perforation, death, or unsuccessful implantation. Other smaller series report similar successful results with resynchronization therapy.[164–167] Larger scale, longer follow-up controlled trails evaluating resynchronization therapy are in progress.[168,169]

Electrophysiologic testing

The role of programmed ventricular stimulation remains unproven. In patients with dilated cardiomyopathy without syncope, the inducibility with programmed ventricular stimulation of sustained monomorphic ventricular tachycardia ranges between 0% and 14% and of polymorphic ventricular tachycardia or ventricular fibrillation ranges between 0% and 29%.[170–177] For patients with syncope, the inducibility of ventricular tachycardia ranged from 27% to 46%.[80,99] Brilakis *et al*. demonstrated that a substantial number of patients (9 of 15) with a negative electrophysiological study eventually received an ICD.[99] Survival from the time of syncope at 1 and 3 years was 88% and 88%, respectively, for the ICD group, 86% and 76%, respectively, for the pacemaker group and 72% and 48%, respectively, for the no device group. They concluded that although electrophysiologic testing was not useful from the risk stratification perspective, it may identify other important issues such as conduction system abnormalities indicating a pacemaker.

Implantable cardiac defibrillators

Amiodarone has been adopted as the standard medical therapy for VT and VF despite scant supporting evidence. Three studies, the Canadian Implantable Defibrillator Study (CIDS),[178] Antiarrhythmics Versus Implantable Debrillators (AVID)[179] and Cardiac Arrest Study, Hamburg (CASH)[180] report improved survival with ICDs vs. anti-arrhythmic therapy including amiodarone in survivors of life-threatening ventricular arrhythmias. Meta-analysis of the three trials demonstrated a statistically significant reduction in mortality of 27% with ICDs. Amiodarone use however may continue in ICD patients to prevent ICD discharges or as primary therapy when there are economic constraints on ICD use. There is not yet a large-scale randomized study of implantable cardioverter defibrillator treatment in idiopathic dilated cardiomyopathy although studies support its use in the setting of sustained hemodynamically unstable ventricular tachycardia/fibrillation.[181] The role of ICDs in patients with LVEF ″ 35% and no record of sustained ventricular tachycardia or ventricular fibrillation is being addressed in the SCD-HEFT trial.[79]

Surgical management of dilated cardiomyopathy

Surgical therapy for dilated cardiomyopathy must be tailored to the frequently multifactorial nature of an individual patient's cardiomyopathy.[182] Until the early 1980s, "surgical therapy" was essentially limited to cardiac transplantation;[183] however, limited donor availability and the morbidity of lifelong immunosuppression have led to a search for novel treatments for dilated cardiomyopathy. Later in the 1980s, device therapy became available as bridge therapy to cardiac transplantation.[182] As experience grew treating patients with ventricular dysfunction, we learned that severe left ventricular dysfunction was not a contraindication to surgical repair. In fact, surgical therapy offered improved outcomes over medical therapy, albeit at a higher mortality. Furthermore, even though devices and transplantation were available, many patients were treated successfully without resorting to these measures.[183] Most of the published surgical work has concentrated on adults; however, pediatric data will be mentioned when available. Myocardial revascularization, device therapy, and transplantation for dilated cardiomyopathy will be covered in other chapters. Here we will concentrate on non-ischemic dilated cardiomyopathy and non-device, nonreplacement therapy.

Dynamic cardiomyoplasty

For perspective and the sake of historic completeness, dynamic cardiomyoplasty is included. In the early 1990s, a great deal of interest was generated in dynamic cardiomyoplasty. In its later development, this modality conditioned the latissimus dorsi with pacing to minimize muscle fatigue through conversion of fast twitch muscle fibers to slow twitch muscle fibers. The conditioned latissimus was then wrapped around the failing heart and paced to contract in synchrony with the heart. Recent studies have shown its effects on patient functional status in survival.[184–189]

Some investigators demonstrated improvement in functional

parameters;[189,190] however, others showed no change in ventricular function.[191] While some believed that the dynamic squeeze of the muscle wrap was important,[186,189,192–196] others came to believe that the major effect of wrapping the ventricle was prevention of further dilation and relief of cardiac wall stress.[197–199] The efficacy of this modality has been controversial in part because some studies were performed with unconditioned wraps and in others were done on normal heart, neither of which has clinical relevance. Nevertheless, this cumbersome procedure is mostly of historical interest but did form the nidus for crystallizing the newer field of passive ventricular constraining which will be discussed below.

Partial left ventriculectomy

In 1996, Randas Batista generated a new wave of interest (and publicity) with a novel surgical therapy, partial left ventriculectomy (PLV) to improve left ventricular function in end-stage heart disease.[200] The procedure was first described as excision of the lateral wall of the left ventricle between the papillary muscles. Later, Dr Batista extended the procedure to include excision of papillary muscles and mitral valve replacement (extended PLV).

Table 46-1 and Fig. 46-2 summarize the outcomes from several of the larger surgical series. This "meta-analysis" needs to be interpreted with care, because the studies were frequently designed to study different diagnostic or procedural cohorts. Some centers defined their cohort as dilated cardiomyopathy, whereas another center defined it as all patients undergoing PLV. The reader must bear in mind that even though these series are tabulated and graphed together, the outcomes from one institution are not directly comparable to another. Each study must be read in detail to understand the differences. What can be learned from the figure is the general range of survival from centers that have analyzed different cohorts of patients. In Table 46-1, care is taken to list the etiology of dilated cardiomyopathy in that table and the approach to the mitral valve, when available.

Though all the larger series are summarized, as follow-up has continued, the problem that has become apparent with PLV is that early mortality is high and that many patients have only a transient benefit, with low actuarial survival and freedom from heart failure. Sorting this out has been difficult because some studies include differing etiologies of dilated cardiomyopathy, and the surgical approach has not always been uniform, particularly with regard to mitral valve surgery. Though theories abound, the subset of patients who successfully achieve a long-lasting benefit from PLV has been difficult to identify retrospectively, and outcomes for PLV are unpredictable as a whole. Patrick McCarthy at the Cleveland Clinic has been one of the strong advocates of PLV, but at the 2002 AATS conference held in Toronto has changed his opinion based on midterm results on 62 patients with PLV in which they have come to believe that the Batista operation is not an alternative to heart transplantation because of its high risk of early failure which was largely unpredictable. The three-year actuarial survival was 53% and freedom from failure of 42%. Early and late failure precluded the use of PLV as an alternative to heart transplantation[201,202] and the procedure has been abandoned in the United States.[183]

Outcomes of PLV for dilated cardiomyopathy in children have not been reported. Anecdotal case reports of surgical success in a few children have been reported. In 1999, case reports of partial left ventriculectomy (PLV) emerged from Yugoslavia,[203] Japan,[204] and Milwaukee,[205] respectively. In Belgrade, Gradinac was the first to report a 2-year-old girl with end-stage dilated cardiomyopathy who underwent partial left ventriculectomy (PLV) and an Alfieri mitral valve repair.[203] After 1 year, her ejection fraction had improved from 19% to 34% and she was well. In Japan, an 8-month-old female with severe dilated cardiomyopathy underwent a partial left ventriculectomy and was "clinically improved" at 1 month follow-up.[204] In Wisconsin, a 3.3 kg male infant with severe dilated cardiomyopathy underwent partial left ventriculectomy and was well at 8 months of age with an ejection fraction of 50–60% and mild mitral regurgitation.[205]

Since these initial reports, four other children have been reported undergoing PLV.[206,207] Two of those required transplantation in 6 and 12 months, one of which died on postoperative day 16, and the other two were well at 18 and 35 months. In 1999, Dr del Nido[208] editorialized that dilated cardiomyopathy in children deserved special consideration, because a significant proportion of infants or children would not undergo progression and might even spontaneously recover. He argued for a coordinated multicentered effort to study patients prospectively but, to date, no such study has been forthcoming.

Mitral valve replacement

Historically, the surgical approach to mitral regurgitation was mitral valve replacement achieved by excising the mitral valve and its subvalvar apparatus. In that era, poor understanding of the relationship between ventricular function and preservation of the subvalvular mitral apparatus led to sacrifice of that apparatus and the accompanying poor outcomes.[209,210] Treating mitral regurgitation in heart failure, requires a firm understanding that the mitral subvalvular apparatus is essential to maintain ventricular function.

When looking across current series, the addition of mitral valve surgery seems to have had a positive effect on results following partial left ventriculectomy (see Table 46-2, Fig. 46-2). Independent reviews of mitral valve surgery have also shown the best survival of all. Four series of modern day mitral valve surgery in the setting of dilated cardiomyopathy have been summarized.[211–214]

Passive constraint devices

Insights learned from dynamic cardiomyoplasty stimulated the interest in passive ventricular constraint. If in fact the improvement witnessed with dynamic cardiomyoplasty was effected primarily though passive ventricular constraint then this could be much more easily achieved with a passive, non-autologous wrap. These devices have limited appeal in small children because they will, presumably, not grow (perhaps the pediatric realm is best suited to skeletal muscle wraps for this reason). Nevertheless, these modalities will be presented for the sake of completeness.

Acorn

The Acorn cardiac support device is a polyester mesh jacket which is positioned around the heart to provide diastolic support and is designed to provide flexibility and strength.[215] It is available in six sizes and is tailored to the individual heart to create a slight reduction (10% in end-diastolic dimension) in

Table 46-1 Etiologies of dilated cardiomyopathy

Idiopathic	Metabolic
FAMILIAL/GENETIC/SYNDROMIC	Nutritional
X-linked cardioskeletal myopathy (Barth syndrome)	Thiamine deficiency (Beriberi)
Noonan syndrome	Protein deficiency (Kwashiorkor)
Alstrom syndrome	Selenium deficiency
NEUROMUSCULAR DISORDERS	Beta-ketolase deficiency
Duchenne muscular dystrophy	Hypertaurinuria
Becker's muscular dystrophy	Endocrinopathies
Emery–Dreifuss muscular dystrophy	Hypothyroidism
Facioscapulohumeral muscular dystrophy	Thyrotoxicosis
Erb's limb-girdle dystrophy	Growth hormone excess
Myotonic dystrophy	Cushing's disease
Fredreich's ataxia	Pheochromocytoma
Refsum disease	Diabetes mellitus
Kugelberg myopathy	Hypoglycemia
Mini-core-multi-core Welander spinal muscular atrophy	Neuroblastoma
Nemaline myopathy	Catecholamine cardiomyopathy
Centronuclear (myotubular) myopathy	Electrolyte disturbances
Malignant hyperthermia	Hypocalcemia
Familial periodic paralysis	Hypophosphatemia
INFLAMMATORY	INBORN ERRORS OF METABOLISM
Infectious	Storage diseases
Viral	Glycogen storage disease
Rickettsial	GSD IV (Andersen disease)
Bacteria	Mucopolysaccharidoses
Myobacterial	MPS I (Hurler syndrome)
Fungal	MPS VI (Maroteaux-Lamy syndrome)
Protozoal	Sphingolipidoses
Spirochetal	Nieman-Pick disease
Non-infectious	Farber disease
Post-transplant rejection	Gaucher's disease
Collagen vascular disorders	Tay-Sach's disease
Scleroderma	Sandhoff disease (GM2)
Lupus erythematosus	GM1 gangliosidosis
Dermatomyositis	Disorders of Fatty Acid Metabolism
Myocarditis – hypersensitivity	Primary or systemic carnitine deficiency
Sarcoidosis	Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
RHYTHM-RELATED	Disorders of diminished energy production
Congenital heart block	Kearns-Sayre syndrome
Tachyarrhythmias	Complex I deficiency
Arrhythmogenic right ventricular cardiomyopathy	MERRF syndrome
CORONARY	TOXIC
Anomalous coronary arteries	Ethanol
Kawasaki disease	Chemotherapeutic agents
CONNECTIVE TISSUE DISORDERS	Phenothiazines
Osteogenesis imperfecta	Carbon monoxide
Marfan syndrome	Lead
Pseudo-xanthoma elasticum	Cocaine
OTHER	Mercury
Endocardial fibroelastosis	Radiation
Non-compacted myocardium	
Atrio-venous malformations	
Peripartum cardiomyopathy	

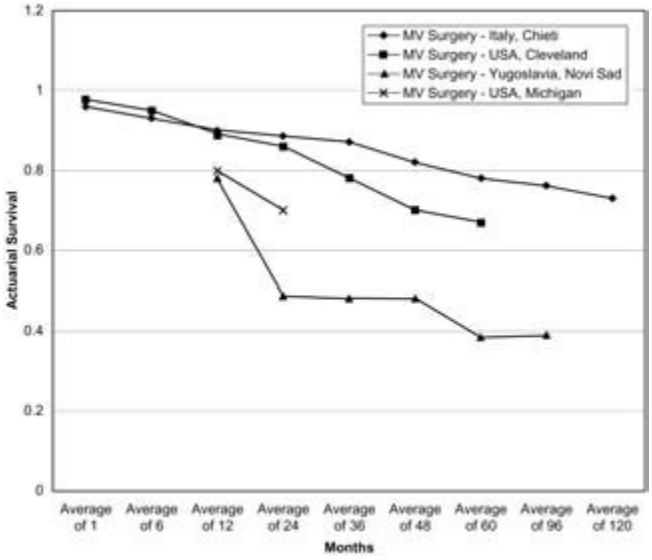


Fig. 46-2 Survival in mitral valve surgical series.

wall stress.[215] The idea of diastolic support originated from studies of dynamic cardiomyoplasty which suggested that the benefits of that procedure had more to do with the girdling effect of the latissimus dorsi than with the contractility of skeletal muscle itself.[198,199,216]

Twelve patients received the device as sole therapy, 11 with dilated cardiomyopathy. Seven were NYHA class III and 5 were NYHA class II. No intra-operative complications and no device related adverse events were reported. At 6 and 12 months there was a significant improvement in ejection fraction (from 21% to 33% to 27%) and NYHA functional class (from 2.5 to 1.6 to 1.9), and a significant decrease in both end diastolic diameter (from 74 to 64 to 64 mm), and end systolic LV diameter (from 66 to 57 to 55 mm). Mitral regurgitation diminished significantly by 3 months and quality of life improvement was present as well. No actuarial follow-up is yet available.[217]

In a second study, 5 patients with NYHA class III CHF and ischemic cardiomyopathy underwent Acorn placement in concert with coronary artery bypass grafting, +/- infarct exclusion ventricular remodeling. In this study, EF increased from 27 to 35%, LVEDD decreased from 63 to 51 mm. No early evidence of diastolic dysfunction or constriction was noted and all patients were NYHA class I at 6 months follow-up.[218]

The Acorn has had excellent outcome with no morbidity or mortality directly associated with the device. Diastolic function has not been reported and the device is currently in the second phase of PDA trials with approval at 25 US sites and an anticipated enrolment of 200 patients.

Myosplint

The Myopslint device was developed to change LV shape, decrease wall stress and improve overall LV mechanics. The device employs three ventricular splints, each attached to two epicardial pads. The splints are positioned to bisect the long axis of the LV, thereby creating two smaller ventricular cavities into a symmetric bi-lobular structure. The theory behind its design is that mural tension within each of the lobes has been decreased.[215] Chronic human studies were performed in five patients with dilated cardiomyopathy and NYHA class III. Mitral regurgitation was mild in 3 patients and moderate in 2. Four patients underwent mitral annuloplasty. In one patient, mitral regurgitation worsened necessitating Myosplint removal. In the patient who did not under go mitral annuloplasty, mitral regurgitation worsened with a decrease in LV EF from 18% to 14% and a worsened VO_2 max from 14.1 to 8.6 mL/kg/min). In the remaining 3 patients (with Myosplint and mitral annuloplasty), ejection fraction improved slightly from 23% to 25% and LV EDV decreased from 400 to 371).

The Myosplint is undergoing US FDA feasibility testing to include 20 patients from four centers as a prospective, nonrandomized, single-arm evaluation. From the early data, the role of the mitral valve and need for valvular surgery may be problematic (as it was in the early Batista experience).[215]

As is true in all of congenital heart surgery, children present unique problems with size (and the reluctance of industry to develop a range of device sizes for a small consumer base), and the need for growth (constraining the use of materials/approaches that allow for that growth). Treatment of dilated cardiomyopathy in children is still constrained by these issues. If results from adults are generalizable to children, and that is a big "if," then repairing mitral valves and perhaps the development of a passive constraint system that allows for growth are probably our best options.

Cardiac transplantation

Dilated cardiomyopathy is the most common indication for cardiac transplantation after 1 year of age.[219] Timing of listing and transplantation are of paramount concern in the setting of limited donor availability. Nield *et al*. reported a 16% waiting list mortality for 31 patients with dilated or restrictive cardiomyopathy.[220] Transplantation was achieved in 74%. The fourth official pediatric report – 2000 analyzed 4644 heart transplantations from 226 centers.[219] Actuarial survival was 80% at 1 year and nearly 70% at 5 years. The overall mortality in the first year was 50% and subsequently < 3% per year. Although > 90% of patients reported no activity limitations post transplantation, other morbidities are not uncommon including hypertension, hyperlipidemia, diabetes, malignancy, renal dysfunction and growth retardation.[219]

Novel pharmacologic treatments

As understanding of the mechanisms of cardiomyopathy and heart failure continues to grow, targeted treatment modalities are evolving. Tumor necrosis factor-(TNF-α) is a proinflammatory cytokine released from failing myocardium with high concentrations in the setting of heart failure.[221,222] Cytokine antagonists which bind irreversibly with TNF-α are currently in experimental trials (RENAISSANCE, RECOVER).[41,223,224]

A-type and B-type natriuretic peptides are released from cardiomyocytes in response to stretch and induce diuresis, vasodilation and suppression of the renin–angiotensin system. Clinical trials with exogeneous natriuretic peptides have had limited success related to tolerance. Attenuation of breakdown of endogeneous natriuretic peptides through inhibitors of neutral endopeptidases is showing more promise.[41]

Endothelins, locally acting peptides with profound vasoconstrictor effects, are found in high plasma concentrations in

Table 46-2 Summary of partial left ventriculectomy and mitral valve surgical series

Year	First author	Institution	Primary group	No. of patients	Mean age (years)	Mean follow-up (months)	Completeness of f/u	Non PLV approaches	MV surgery	MV repair	MV replacement	Idiopathic	Ischemic	Valvular	Chagas	Myocarditis	Alcohol	Familial	Dilated hypertrophic	Sarcoidosis	Arrhthmogenic RV dysplasia	Total etiologies	Perioperative mortality	1 year freedom from failure	3 year freedom from failure
2000	Bishay	USA, Cleveland	MV Surgery	44	66	40	100%	0%	100%	80%	20%	30%	30%	40%								100%	2%		
2001	Calafiore	Italy, Chieti	MV Surgery	49				0	100%	59%	41%	24%	76%									100%	4%		
2002	Radovanovic	Yugoslavia, Novi Sad	MV Surgery	76	49.9		100%	0%	100%	100%	0%	100%										100%	0%		65%
2002	Badhwar	USA, Michigan	MV Surgery	125	?	38		0	100%	100%	0%	?	?	?	?	?	?	?	?	?	?		5%		
1997	Batista	USA, Buffalo	PLV	120	53			0	43%	?	?	26%	37%	22%	9%	9%						103%	22%		
2000	Chang	Korea, Seoul	PLV	16	35			Dor 3 pts	100%	94%	6%	94%	6%									100%	44%		
2001	Etoch	USA, Louisville	PLV	20	50.1	21	100%	0%	95%	85%	10%	100%										100%	10%	49%	26%
2001	Gradinac	Yugoslavia, Belgrade	PLV	38	51	17		0	100%	74%	26%	100%										100%	8%		
2001	Cereceda	USA, Cleveland	PLV	62	54	24	100%	0%	100%	97%	3%	95%	2%	2%				2%				100%	3%	65%	33%
2000	Vural	Turkey, Ankara	PLV	27	53	27	100%	0	100%	0%	100%	100%										100%	19%		
2000	Lucchese	Brazil, Porto Alegre	PLV	44		23	?	0	75%	16%	59%	73%			11%		16%					100%	20%		
2001	Moreira	Brazil, Sao Paulo	PLV	43	45.5	28	?	0	81%	74%	7%	100%										100%	21%		
2001	Isomura	Japan, Kanagawa	PLV	74	49.5			SAVER 12 pts	89%	62%	27%	66%		14%	1%	3%			9%	5%	1%	100%	20%		

patients with heart failure. Endothelin antagonists such as bosentan show preliminary favorable hemodynamic effects.[41]

Human growth hormone, acting through locally produced insulin-like growth factor 1, stimulates myocardial hypertrophy and increased myocyte contractility. Fazio *et al*. reported preliminary experience with growth hormone therapy in 7 children with moderate to severe heart failure with significant increase in ventricular wall thickness and total mass as well as improvement in ventricular function, both at rest and during exercise.[225]

Future

Early intervention

The future direction of dilated cardiomyopathy must include earlier diagnosis and treatment in the effort to modify the cellular and subsequent functional deterioraton of the cardiomyocyte. Such benefit is demonstrated in the SOLVD prevention trial which reported significantly decreased incidence of heart failure and rate of related hospitalizations in the group treated with enalapril in patients who were in NYHA class I or II with a left ventricular ejection fraction < 35%.[57]

The Pediatric Cardiomyopathy Registry

The Pediatric Cardiomyopathy Registry (PCMR), funded by the National Heart, Lung, and Blood Institute, was established in September 1995. This registry has established the largest database of sociodemographic and clinical information on children diagnosed with cardiomyopathy at 61 centers in the United States and Canada. This registry promises to provide a wealth of knowledge regarding incidence rates as well as to study the natural and modified natural history of infants, children and young adults with cardiomyopathies.

Medical management of the pediatric patient with dilated cardiomyopathy will continue to rely on extrapolations from clinical studies of adult patients. An important distinction relates to the hypothetical potential for favorable remodeling in the cardiomyocyte of the child as compared to that of the adult. As well, it appears that the etiologies of dilated cardiomyopathies in children may be substantially different from those in adults and as such mandate separate and distinct investigation. Even now, gene therapy appears to be inevitable in the future management of some forms of inherited dilated cardiomyopathy. Finally, knowledge and improved management strategies of the dilated but structurally "normal" heart may provide tremendous insight and similar applicability to the structurally abnormal heart of the pediatric patient.

All references can be found at the end of the book. See pp. 846–51 for Chapter 46.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

47

Anne I. Dipchand

Heart Transplantation

In 1966, the first human heart transplant was performed in South Africa by Barnard.[1] By the end of the 1970s, heart transplantation was established as an effective therapy for endstage heart failure. Improvements in organ donation, organ preservation, and anti-rejection therapy have resulted in improved survival rates following heart transplantation.

Incidence

It is difficult to derive true population-based data on heart transplantation. Many factors may impact whether a patient is referred and listed for heart transplantation including a wide variability in decision making around clinical need for transplantation, availability of expertise, individual center referral patterns, and medical team and familial belief systems. Therefore, the starting point for looking at natural history and outcomes is either at the point of listing for heart transplantation or once a patient undergoes a heart transplant. There are two main sources for data on outcomes related to pediatric heart transplantation: the Registry of the International Society of Heart and Lung Transplantation (ISHLT)[2] and the Pediatric Heart Transplant Study (PHTS, a research database owned and operated by the Pediatric Heart Transplant Study Group).[3]

According to the ISHLT Registry fifth annual report (2002),[2] the annual number of pediatric heart transplant procedures has remained stable since the mid-1990s as has the age distribution (Figs 47-1, 47-2). Data from the PHTS seventh summary incorporates 1586 patients listed or transplanted from January 1, 1993 to December 31, 2000 (24 centers within North America). Table 47-1 outlines the number of transplants per year over the study period with recipient age illustrated in Table 47-2. Again the number undergoing transplantation has remained relatively stable.

The diagnoses leading to transplantation are shown in Figs 47-3 to 47-5.[2] In infants < 1 year of age, congenital heart disease has remained the most common underlying diagnosis leading to heart transplantation (Fig. 47-3). Cardiomyopathy remains the main diagnosis in the 1–10 year age group, though congenital heart disease has been increasing over the last few years (Fig. 47-4). Cardiomyopathy continues to be the majority diagnosis in adolescents (Fig. 47-5).

Survival

Overall survival

Table 47-3 illustrates data from PHTS looking at survival at any time from time of listing (including deaths both before and after transplant).[3] An era effect is evident in the data with improved survival at all times post-listing in the most recent era (1997–2000).

Waiting list mortality

Waiting list mortality is an important aspect of the overall survival for heart transplantation. It is multifactorial, primarily reflecting donor availability, but also reflecting the acuity of the waiting recipients. Donor availability is difficult to influence easily, but knowledge of waiting list mortality data can often play a role in decision making around appropriate timing for listing a patient for transplant.

Data from the PHTS demonstrate a waiting list mortality in all listed patients of 12% at 1 month, 28% at 6 months, 32% at 1 year and 39% at 4 years after listing.[3] There are marked differences based on diagnosis as illustrated in Table 47-4, with the highest waiting list mortality in patients with a diagnosis of hypoplastic left heart syndrome (HLHS). Looking only at patients listed at less that 6 months of age, those with a diagnosis of HLHS still have a higher waiting list mortality at 6 months (50%) compared with infants with other diagnoses (40%) indicating that it is not just an age-related phenomenon. Clinical stability at the time of listing also affects waiting list mortality as illustrated in Table 47-5.

Survival post-transplantation

From the ISHLT Registry data, the actuarial 10 year survival for all pediatric heart transplant recipients is 55% (Fig. 47-6).[2] There is a lower survival in the infant population most notable in the first year post-transplant, reflecting the higher early mortality. However, by 10 years, the survival rate for each age group is similar, possibly reflecting a difference in the late mortality risk between the different age groups. To explore this, Fig. 47-7 shows the conditional actuarial survival after transplantation (patients surviving to 1 year, controls for the differences in early mortality). This clearly demonstrates a significant difference in late mortality between infant and childhood recipients compared with adolescents, with a yearly mortality of < 2% per year in infants and 4% per year in adolescents. Looking at it another way, infant recipients experience 40% of their mortality within the first 30 days post-transplant while adolescents experience 25% within the first month and > 50% after 1 year (Fig. 47-8).

Data from the PHTS also show that overall survival is generally good with 73% of the 1114 transplanted patients alive at 5 years post-transplant (Table 47-6).[3] Again, there are differences based on age at time of transplant with patients trans-

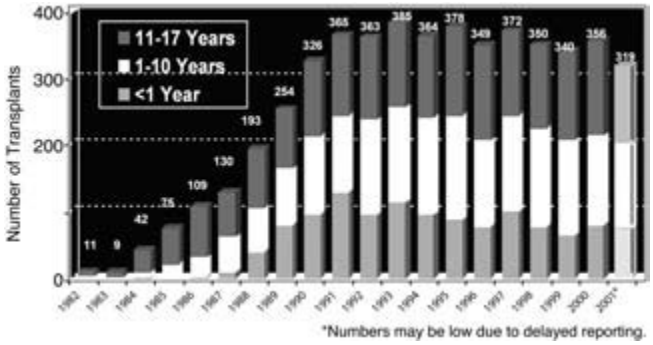


Fig. 47-1 Age distribution of pediatric heart recipients by year of transplant.

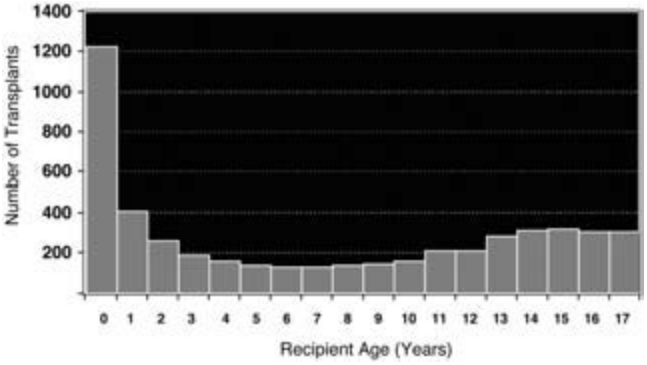


Fig. 47-2 Age distribution of pediatric heart recipients (1982–2001).

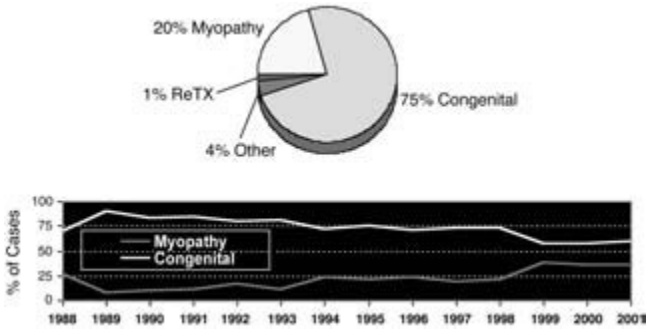


Fig. 47-3 Diagnosis in pediatric heart transplant recipients (age < 1 year).

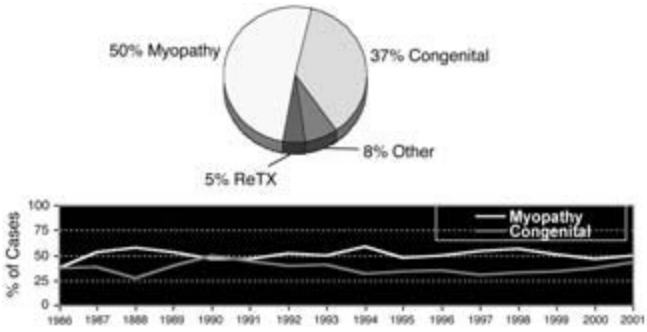


Fig. 47-4 Diagnosis in pediatric heart transplant recipients (age 1–10 years).

Table 47-1 Number of listings and transplants per year (Pediatric Heart Transplant Study)*

Year	No. listed	No. transplanted
1993	201	131
1994	171	125
1995	204	120
1996	165	128
1997	212	147
1998	233	167
1999	205	146
2000	195	150

*(From Boucek *et al.*[2] with permission.)

Table 47-2 Age distribution of patients undergoing transplant (n = 1114) (Pediatric Heart Transplant Study)*

Age	No. of patients
0 to 1 month	91
1 to < 6 months	294
6 months to < 1 year	88
1 year to < 6 years	214
6 years to < 12 years	164
12 years to < 18 years	252
18 years to < 30 years	7
Not specified	4

*(From Boucek *et al.*[2] with permission.)

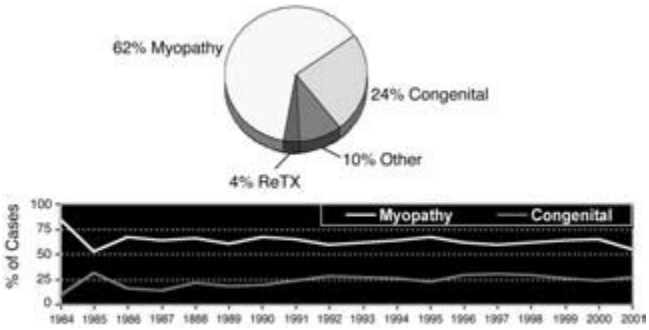


Fig. 47-5 Diagnosis in pediatric heart transplant recipients (age 11–17 years). Pediatric heart transplantation actuarial survival (1982–2001).

Table 47-3 Survival at any time post-listing (n = 1583) (Pediatric Heart Transplant Study)*

Time after listing	Survival (%)
1 month	88
6 months	75
1 year	72
2 years	69
3 years	66
4 years	64
5 years	62
6 years	62
7 years	59

*(From Boucek *et al.*[2] with permission.)

Table 47-4 Waiting list mortality by diagnostic group (Pediatric Heart Transplant Study).* Patients censored at the time of transplant

	Mortality (%)	
Diagnosis	6 months	1 year
HLHS†	48	58
Congenital	26	34
Non-congenital‡	20	20

*(From Boucek *et al.*[2] with permission.)
†HLHS, hypoplastic left heart syndrome.
‡Cardiomyopathy, myocarditis, retransplantation, tumors, arrhythmias, etc.

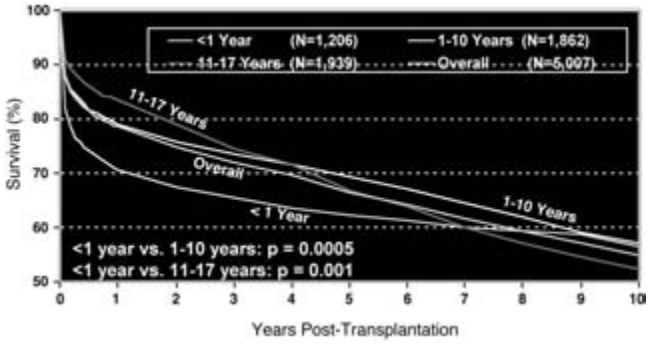


Fig. 47-6 Pediatric heart transplantation actuarial survival (1982–2001).

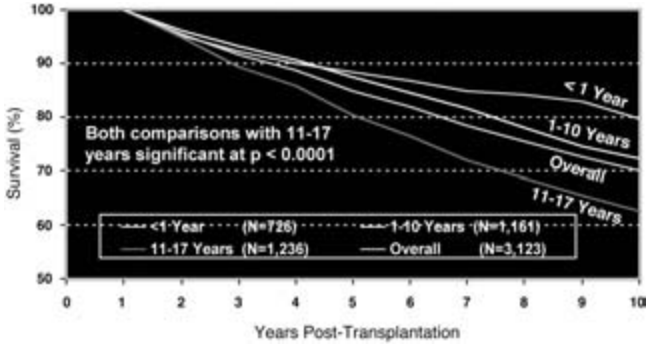


Fig. 47-7 Pediatric heart transplantation conditional actuarial survival (1982–2001).

planted at < 1 year having a lower survival rate than older patients – likely due to the higher early mortality.

When survival data are analyzed by era, significant improvements in the results of pediatric heart transplantation are evident, with the 4 year actuarial survival for 1982–87 being 20% less than that for 1998–2001 (Fig. 47-9). The majority of improvement seems to be a decrease in the mortality within the first few months post-transplant. Looking at conditional survival again for the different age groups within the most recent era, the difference between the infants and adolescents is further accentuated with infants having a > 95% conditional 3-year survival while that of adolescents is approximately 80% (Fig. 47-10).

Pretransplant diagnosis also has an impact on post-transplant survival.[2] For patients with congenital heart disease, there is a significantly higher early mortality for infants compared with adolescents (Fig. 47-11). However, by 10 years post-transplant, the survival curves are the same. This difference does not exist for the different age groups when the diagnosis is cardiomyopathy (Fig. 47-12). Further data from the PHTS demonstrate that patients with a diagnosis of HLHS have a lower overall survival compared with other congenital etiologies, and non-congenital etiologies have the best overall survival. [3]

Table 47-5 Waiting list mortality by clinical status (Pediatric Heart Transplant Study).* Patients censored at the time of transplant

	Mortality (%)		
Status	6 months	1 year	2 years
1†, < 6 months	44	50	52
1, > 6 months	29	30	32
2	8	11	

*(From Boucek *et al.*[2] with permission.)
†United Network for Organ Sharing (UNOS) Status 1 (sicker patients).

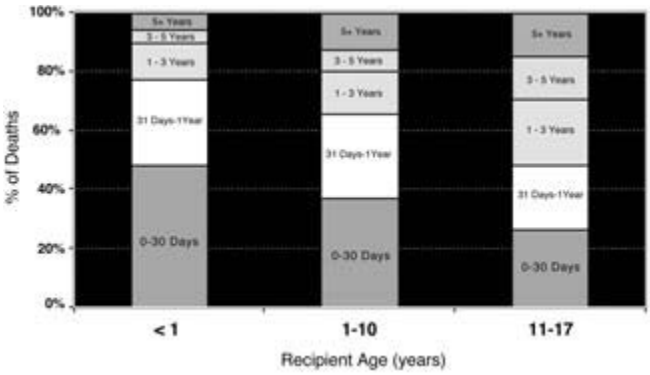


Fig. 47-8 Pediatric heart recipients: Time of death (1988–2001).

Table 47-6 Survival post-transplantation (n = 1114) (Pediatric Heart Transplant Study)*

Time post-transplant	Survival (%)
1 month	92
6 months	86
1 year	84
2 years	81
3 years	78
4 years	76
5 years	73
6 years	72
7 years	68

*(From Boucek *et al.*[2] with permission.)

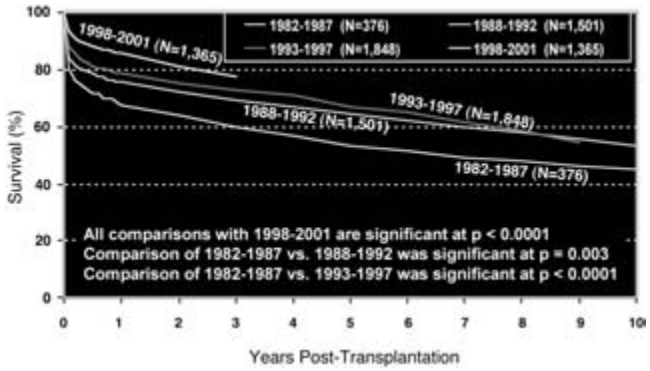


Fig. 47-9 Pediatric heart transplantation actuarial survival by era (1982–2001).

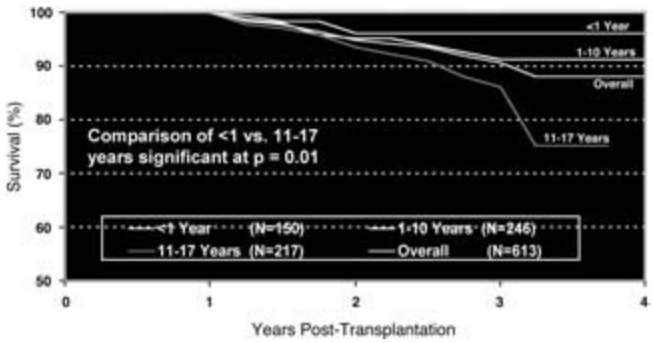


Fig. 47-10 Pediatric heart transplantation conditional actuarial survival for recent era (1998–2001).

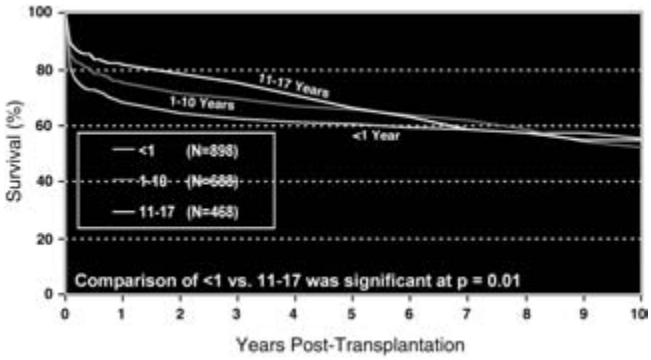


Fig. 47-11 Pediatric heart transplantation actuarial survival by age group for patients with congenital heart disease (1988–2001).

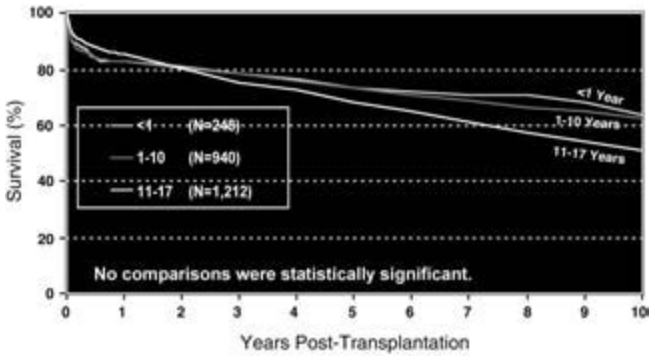


Fig. 47-12 Pediatric heart transplantation actuarial survival by age group for patients with cardiomyopathy (1988–2001).

Risk factors for mortality

Risk factors for 1-year mortality following pediatric heart transplantation are outlined in Table 47-7.[2] The leading risk factor is a diagnosis of congenital heart disease followed by need for mechanical ventilation, diagnosis other than congenital/cardiomyopathy/retransplantation, mechanical assist devices, and donor cause of death. Table 47-8 confirms the observation that younger age is an additional risk factor. Table 47-9 lists the factors that were not significant for 1-year mortality.[2]

Clinical status at the time of transplant also affects overall survival with lower survival for sicker patients, especially for those < 6 months of age.[3] Differences in survival have also been noted when data are stratified for donor heart cold ischemic time with lower per cent survival for times of 181–300 minutes or > 300 minutes compared with < 180 minutes.[3]

Risk factors for 5-year mortality include life support at the time of transplant (odds ratio 1.93, $P < 0.0001$) and a diagnosis of congenital heart disease (odds ratios 1.64, $P = 0.001$).[2] The primary risk factors for 5-year mortality conditional on survival to 1 year is a previous transplant (odds ratio 3.39, $P = 0.02$) or inotropic support at the time of transplant (odds ratio 3.30, $P < 0.0001$).[2]

Causes of death

There were 248 deaths (22%) amongst the 1114 transplanted patients followed by the PHTS.[3] Infection, rejection, graft failure, sudden cardiac death, and coronary artery vasculopathy (CAV) are the major causes of death in children (Table 47-10).[3–5] Acute rejection also accounts for the majority of graft failure including death and retransplantation due to graft

Table 47-7 Pediatric heart transplants (1996–2001). Risk factors for 1 year mortality in descending order of magnitude ($n = 1554$)

Variable	Odds ratio	*P*-value	95% Confidence interval
Diagnosis: congenital heart disease	2.01	< 0.0001	1.44–2.80
Ventilator	1.92	0.001	1.30–2.83
Diagnosis: other (not congenital, cardiomyopathy or retransplant)	1.92	0.009	1.17–3.13
VAD	1.85	0.04	1.03–3.32
Donor COD: other (not head trauma, CVA, CNS tumor, or anoxia)	1.56	0.04	1.03–2.38

Table 47-8 Pediatric heart transplants (1996–2001). Risk factors for 1 year mortality continuous factors (n = 1554)

Variable		Odds ratio	P-value
Recipient age: linear			0.007
Recipient age: quadratic			0.001
	0 years	2.05	
	3 years	1.33	
	6 years	1.03	
	9 years	0.97	
	12 years	1.09	
	15 years	1.48	

Table 47-9 Pediatric heart transplants (1996–2001). Factors not significant for 1 year mortality

Previous transplant	In ICU or hospital
Donor history of hypertension	Donor clinical infection
Height (recipient/donor)	ICD
Weight (recipient/donor)	Ischemia time
Gender (recipient/donor)	Center volume
Age (donor)	PRA
Year of transplant	Total bilirubin

Table 47-10 Causes of death post-heart transplant (n = 248) (Pediatric Heart Transplant Study)*

Cause of death	No. of patients (%
Infection	43 (17)
Rejection	
Acute	40 (16)
Hyperacute	1 (0.4)
Early graft failure	39 (16)
Sudden cardiac death	28 (11)
Coronary artery disease	15 (6)
Non-specific graft failure	11 (4)
Respiratory failure	10 (4)
Neurologic	10 (4)
Multisystem organ failure	9 (4)
Pulmonary hypertension/RV failure	7 (3)
Lymphoma	6 (2)
Arrhythmic	5 (2)
Pulmonary hemorrhage	4 (2)
Hemorrhage	3 (1)
Congestive heart failure	2 (1)
Renal failure	2 (1)
Other (defined)†	6 (2)
Other (not defined)	7 (3)

*(From Boucek *et al.*[2] with permission.)
†Aspiration pneumonia, necrotizing enterocolitis, obliterative bronchiolitis, technical (intra/perioperative), thrombus, unknown (n = 1 each).

failure.[5] Most sudden deaths are likely attributable to rejection or CAV.

Data from the ISHLT Registry also confirm the increasing mortality due to CAV to which 40% of deaths after 3 years are attributed (Fig. 47-13). Before that, acute rejection is the main cause of death – especially in the first year post-transplant (Fig. 47-14).[2]

Indications and contraindications

Indications

Indications for pediatric heart transplantation can be divided broadly into two groups: life-saving or life-enhancing. Life-saving indications include the following:

- endstage myocardial failure in the context of:
- cardiomyopathies or myocarditis
- congenital heart disease
- post-cardiotomy heart failure
- malignant arrhythmias refractory to medical or device management
- complex congenital heart disease with no options for surgical palliation at an acceptable risk
- unresectable cardiac tumours causing obstruction or ventricular dysfunction (systolic or diastolic)
- unresectable ventricular diverticula.

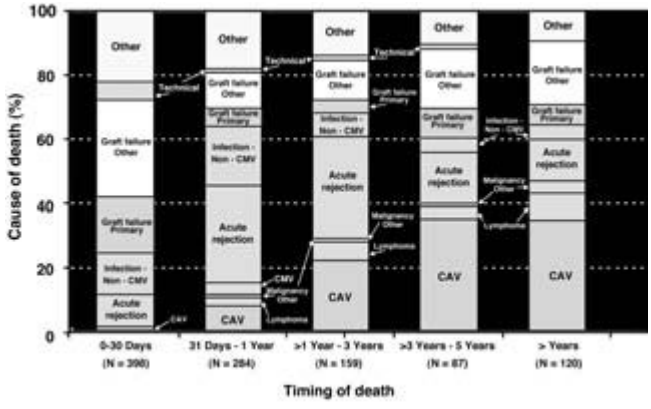


Fig. 47-13 Pediatric heart transplant recipients: Cause of death (1982–2001).

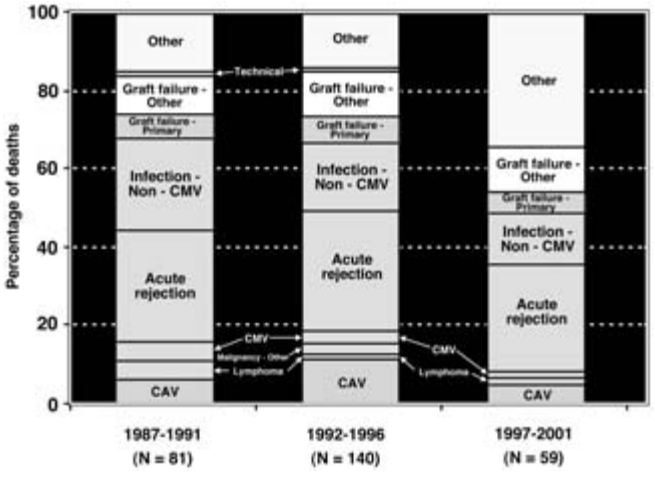


Fig. 47-14 Pediatric heart transplant recipients: Cause of death by era: deaths in 31 days to 1 year.

Life-enhancing indications include treatment of excessive disability, unacceptably poor quality of life, or long-term morbidity in the setting of failing myocardial function, complex congenital heart disease, or after failed surgical palliation of congenital heart disease.

Guidelines for listing adult patients for heart transplantation, based on a comparatively uniform population with a predictable natural history, have been published by both the American Society of Transplantation[6] and the Canadian Cardiovascular Society.[1] No such guidelines exist for the pediatric population or for adults with complex congenital heart disease. As in the adult population, criteria need to be designed to identify patients who are at the greatest risk of dying and who will derive the greatest benefit from cardiac transplantation.

If patients are old and cooperative enough for exercise testing, there are some objective data in the literature as to when heart transplantation is indicated. Although some controversy exists over the degree of impairment in exercise required to justify transplantation, in general, patients with peak oxygen consumption (VO_2) < 10 mL/kg/min should be listed for transplant.[6–11] Patients with a VO_2 > 18 mL/kg/min will experience 1-year survival rates above 95% and should be followed expectantly.[6] Management of patients with a VO_2 between 10 and 18 mL/kg/min remains controversial. A blunted systolic blood pressure (BP) response to exercise (systolic BP at peak exercise < 120 mmHg), and/or chronotropic incompetence, when associated with a VO_2 < 15 mL/kg/min or a peak VO_2 < 50% predicted help redefine the prognostic value of intermediate VO_2 values.[6,10]

Contraindications

Part of the purpose of a pretransplant assessment should be to identify factors that are potential contraindications, and to decide whether they are compelling enough to preclude candidacy for organ transplantation.

Cardiopulmonary contraindications to heart transplantation in the pediatric population included fixed pulmonary hypertension, pulmonary vein atresia or progressive stenosis, and severe hypoplasia of the branch pulmonary arteries or the thoracic aorta. Other contraindications, which can be relative, include irreversible multisystem organ failure, progressive systemic disease with early mortality, active infection, malignancy, morbid obesity, diabetes mellitus with end-organ damage, hypercoagulable states, and severe chromosomal, neurologic, or syndromic abnormalities.

Elevated pulmonary vascular resistance (PVR) is an independent risk factor for mortality both early and late after heart transplantation.[11–13] The actual degree of pulmonary hypertension precluding heart transplantation has varied as there is a continuum of increasing risk as PVR rises. Gajarski *et al.*, reported intermediate outcomes in 8 pediatric patients with PVR > 6 units m^2.[13] He concluded that it is the reactivity of the vascular bed as opposed to the absolute measure of PVR that correlated with outcome.

Complicating factors that are no longer considered contraindications to heart transplantation include complex congenital heart disease (abnormalities of situs, systemic venous abnormalities, anomalous pulmonary venous drainage without stenosis, some pulmonary artery anomalies), previous sternotomy/thoracotomy, non-fixed pulmonary hypertension, noncardiac congenital abnormalities, kyphoscoliosis with restrictive pulmonary disease, nonprogressive or slowly progressive systemic diseases with life expectancies into the third or fourth decade (genetic or metabolic cardiomyopathies), and diabetes mellitus without end-organ damage.

Risk stratification

Given the discrepancy between waiting lists and availability of donor organs, some means of assessing pretransplant risk in relation to post-transplant outcome is desirable in order to facilitate decision making concerning to whom valuable resources are allocated. We retrospectively looked at all 115 heart transplant recipients at the Hospital for Sick Children (unpublished data) and assigned them to one of three risk categories (standard, moderate, high) based on objective criteria (Table 47-11). Preliminary results demonstrated survival to 30 days post-transplant was 89%, 75%, and 42% for standard, moderate, and high risk patients, respectively. Rejection episodes were not significantly different between the high risk and the standard or moderate risk patients. Though there was a significant difference in survival for the high risk group, the reasonable percentage surviving still likely justifies continuing to transplant this population of patients.

The use of extracorporeal membrane oxygenation itself as a bridge to transplantation remains controversial given the high morbidity and mortality. Recent published experience supports reasonable and acceptable outcomes.[14,15] Looking specifically at institutional results for patients supported by extracorporeal membrane oxygenation (ECMO), there were 18 patients who underwent heart transplantation from ECMO. Median age was 6.8 years (10 days to 17 years). Mean duration of ECMO was 5.7 + 3.8 days. Median follow-up was 2.2 years (1 month to 7.2 years). Fourteen patients survived to hospital discharge. Univariate analyses of risk factors ($P < 0.05$) for poor outcome were higher creatinine before and during ECMO, significant fungal infection, and high exposure to blood products. The following did not play a role in survival to hospital discharge: original diagnosis, duration of ECMO support, wait time from listing to transplant, lactate level, cardiac arrest, indication for ECMO, site of vascular cannulation, use of ultrafiltration or bacterial infection. Patients on ECMO support may have successful outcomes despite circumstances that may previously have been considered relative contraindications (cardiac arrest, length of support, bacterial infections).

Table 47-11 Definition of pretransplant risk categories (see text)

Category	Definition
Standard	All patients not fitting criteria below
Moderate	Intubated, pulmonary hypertension, multiple or recent open heart surgery, multiple inotropes, protein losing enteropathy
High	ECMO*, sepsis, intact atrial septum in HLHS, pulmonary vein anomalies, positive PRA,† acute retransplant

*Extracorporeal membrane oxygenation.

†Panel reactive antibodies.

Neonatal advantage

There is accumulating evidence that there may be an advantage to transplanting patients in early infancy. [2,16] As outlined above, there is consistent evidence from survival curves that infants < 6 months of age have an improved long-term survival (out as far as 10 years) compared with older age groups (Figs 47-7, 47-8, 47-10). Data from Loma Linda University Medical Center have demonstrated that amongst a population of infants with HLHS, those transplanted at 1–6 months of age had a lower survival rate and higher graft loss than those transplanted at less than one month of age (Fig. 47-15). [16]

Surgical/perioperative issues

Donor issues

Donor resuscitation and support have a significant bearing on the suitability of an organ for transplantation. There is an accumulating body of knowledge on the effect of brain death on heart function and the best methods to support the circulation to preserve cardiac function for organ donation. Seemingly marginal donor organs can be made acceptable for transplantation with appropriate interventions and support with guidance from an experienced intensivist. [17–19]

The technique of donor cardiectomy is beyond the scope of this discussion but is reviewed in the surgical transplant literature. [20] Much emphasis has been placed on the method of donor organ preservation, especially cardioplegia and preservation solution, and optimal temperature for transport. Ischemic times of over 4 hours utilizing current organ preservation techniques have been shown in multi-institutional studies to be a risk factor for reduced short- and long-term survival in adult heart transplant recipients. [21] In the pediatric population, ischemic times of over 8 hours have been reported without adversely affecting short- or long-term outcomes, especially in infant donors. [22,23]

In some complex forms of congenital heart disease, there may be a need to harvest portions of branch pulmonary arteries, aorta, inferior vena cava (IVC), or the innominate vein to facilitate the anastamoses within the recipient (i.e. hypoplastic or absent central pulmonary arteries, dextrocardia with left superior vena cava, isomerism with interrupted IVC and others).

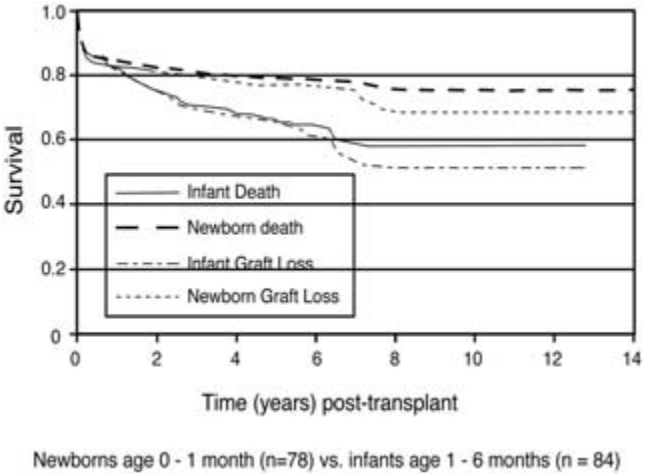


Fig. 47-15 Neonatal advantage.

Surgical techniques

There are different surgical approaches for the surgical procedure in the recipient. [24] Several retrospective studies have looked for differences in outcomes related to the type of approach. The bicaval approach, which is currently the standard in the adult population, has been described to be associated with fewer tachyarrhythmias, slightly better hemodynamics, less tricuspid regurgitation, fewer pacemakers and better exercise tolerance.[25–27] Other studies have shown no differences,[28] or only differences in the incidence of atrial tachyarrhythmias.[29] The only randomized trial demonstrated that the bicaval technique had better hemodynamics and survival.[30] The biatrial technique has been associated with conduction disturbances requiring pacemaker placement in 4–15%,[31] a higher thromboembolism risk, poor atrial synchrony, and more atrioventricular valvar regurgitation due to distortion of atrial anatomy.[32]

In summary, the preponderance of retrospective data supports a potential benefit related to the bicaval approach in adult heart transplant recipients. The most consistent finding is improved atrial function. There is fairly consistent finding that tricuspid regurgitation is decreased. There are conflicting data about the requirement for pacemaker therapy and atrial arrthymias, both short- and long-term after transplantation. However, in the pediatric population, patient size, heart location, situs, systemic venous, and pulmonary venous anatomy must all be taken into consideration when determining the surgical approach.

Recipient management

The same skills and techniques are necessary coming off cardiopulmonary bypass as in more routine cardiac operations, but there are concerns unique to the post-operative heart transplant recipient. The acutely denervated heart is frequently in a slow sinus or junctional rhythm and atrial pacing and/or isoproterenol is frequently needed. Elevated pulmonary vascular resistance with some element of right heart dysfunction is not uncommon. In addition, some degree of ventricular dysfunction as a result of ischemia-reperfusion injury (compounded by donor brain-death) can lead to acute decompensation of the transplanted heart – compounding the right ventricular dysfunction specifically. This is the life-threatening problem in the early management of these patients. There is center-to-center variability in the management of acute right heart failure. In general, maneuvers should include atrial pacing and/or isoproterenol, inotropic support, low filling pressures, avoidance of hypercapnea and acidemia, and pulmonary vasodilation with sodium nitroprusside, milrinone, phenoxybenzamine, and/or nitric oxide.

Immunologic issues

Panel reactive antibodies

Screening panel reactive antibody (PRA) testing is performed on patients before transplantation in an effort to minimize the risk of allograft rejection post-transplantation. PRA tests for the presence of preformed HLA antibodies to a random panel of donor lymphocytes. High PRA titres (> 10%) are associated with an increased incidence of rejection and reduced survival post-cardiac transplantation.[33,34] Previous open heart surgeries,

especially those necessitating the placement of homograft material, can lead to an increased incidence of elevated PRAs. There are various strategies to try to lower PRAs in sensitized patients including plasmapheresis, IVIG, cyclophosphamide, and antimetabolite treatment before transplantation.[35,36] In some high-risk cases, prospective donor/recipient crossmatching may be necessary to identify donor/recipient pairs that may be at risk of hyperacute or early vascular rejection.

ABO incompatible (ABO-I) transplantation

Heart transplantation between donors and recipients with incompatible blood groups is usually contraindicated because of the high risk of hyperacute rejection. Newborn infants do not produce isohemagglutinins and the complement system is not fully developed. West *et al*., have clearly demonstrated that heart transplantation across major blood groups is possible in the infant population and postulates that this may reflect the immaturity of the infant immune system or even represent the first human example of tolerance. [37] The obvious advantage of ABO-I transplantation is a reduction in waiting time and waiting list mortality. Whether immunologic advantages will be proven (i.e. tolerance or graft accommodation) remains to be determined.

Post-transplant issues

Post-transplant issues in the pediatric population are somewhat different than in adults. Care of children post-heart transplantation must take into consideration physical growth and multisystem development, stage of immunologic development, intellectual, emotional and social maturation, educational activities, and other pediatric quality of life parameters. Each one of these aspects and how they are considered within the management plan can affect the morbidities and mortalities post-heart transplantation. The hallmark of post-transplant care is meticulous long-term attention to details with ongoing surveillance and a high index of suspicion for transplant-related problems.

Immunosuppression

A discussion of post-transplant immunosuppressive therapy is beyond the scope of this text. However, the goal of immunosuppressive (IS) therapy is to prevent the occurrence of allograft rejection while minimizing toxicity, infectious, and malignant complications. There is ongoing controversy over what is the optimal IS regime. Overall, aim for low-intensity IS therapy that is individualized and flexible for each patient. Choice of IS therapy has significant impact on short- and long-term morbidity and mortality post-heart transplantation. There are a myriad of agents, dosages, protocols, and combinations that have been used as both induction and maintenance IS, making definitive comparisons and recommendations difficult.[2] Therapy tends to be center-specific and dependent on clinical experience and preferences of individual transplant programs.

Rejection

Rejection is the process of destruction of genetically foreign material by the host's immune system. The severity and timing depend on the degree of genetic dissimilarity between donor and recipient. Although acute graft rejection remains an important potential cause of mortality and morbidity post-transplant, its incidence and impact on graft survival have decreased over the years due to improved IS regimes. It is difficult to identify risk factors for rejection pretransplant other than sensitized patients (positive PRA).

The presence of pre-formed antibodies of the recipient to the donor graft leads to hyperacute rejection (immediate graft failure upon revascularization). Histology reveals antibody and complement deposition and polymorphonuclear lymphocyte infiltration. It can be pre-empted by antibody crossmatch and blood group matching, but cannot easily be reversed. Less than 1% of all heart grafts are lost due to hyperacute rejection.

By 6 months post-transplant, 61% of patients have had at least one episode of acute cellular rejection.[3] The majority of transplant recipients will have at least one episode of rejection in the first year post-transplant, but are usually asymptomatic and identified on routine surveillance EMB, are easily treated, and do not result in significant morbidity and mortality. Of patients alive at 1 year, 27% will experience an episode of late rejection within 3 years.[3] Mortality among patients with late rejection is significantly higher than those without late rejection.[38] Late rejection episodes are also more often associated with hemodynamic compromise requiring inotropic support. Rejection with hemodynamic compromise is associated with a higher incidence of graft failure and mortality, with only 50% of patients alive at 1 year after an episode.[39] Rejection often recurs with only 33% of patients with one episode remaining free of subsequent episodes at 5 years following the event.[40] Risk factors for rejection, late rejection, rejection with hemodynamic compromise, and recurrent rejection include older recipient age, black or Hispanic race, more frequent early rejection, greater than one episode in the first year post-transplant, and shorter time since a previous rejection episode.[38–40]

Acute graft dysfunction may occur in the absence of typical histologic features of acute cellular rejection. This is referred to as humoral or vascular rejection and is a microvascular immune-mediated injury in the absence of cellular infiltrate and necrosis. It also is a rare form of rejection and can be difficult to diagnose.[3]

Infections

Infections are an important cause of morbidity and mortality post-transplant (Table 47-10). Data from PHTS demonstrate that 40% of patients have an infection within 1 year post-transplant.[3] This number is again higher (50%) in patients who are sicker at the time of listing, especially those < 6 months of age.

A number of infections are predictable based on experience and can be managed with standard prophylactic, pre-emptive or full treatment protocols. In order to facilitate this, both donors and recipients undergo extensive screening, both serologic and otherwise, to predict potential donor organ-acquired infections that may require prophylactic or pre-emptive treatment in the highest risk time period (immediately post-transplant). Examples of this include the Epstein–Barr virus (EBV), cytomegalovirus (CMV), and toxoplasma.

Certain infections within a recipient themselves may become reactivated following introduction of immunosuppression. Again, pretransplant serologic testing would identify the possibility to heighten awareness, and routine post-transplant surveillance can sometimes allow for prophylactic or

pre-emptive treatment (EBV, CMV, hepatitis B, hepatitis C). Reactivation disease may also require treatment due to concurrent immunosuppression (i.e. varicella, shingles).

Of special mention within the pediatric population is the impact of EBV exposure given the high probability of negative exposure in the recipient. Prophylaxis is recommended for 3–4 months and surveillance should include regular testing for virus replication by polymerase chain reaction (PCR) techniques. Conversion from a negative to a positive EBV PCR requires consideration of antiviral therapy, especially in the first 6 months post-transplant. Primary infection can be severe and multisystemic, especially if within the first 3–6 months post-transplant, but the risk always exists and should be treated with antiviral therapy. Patients with a chronic viral load (persistently positive EBV PCR) should be considered for chronic antiviral therapy and regular screening for the development of post-transplant lymphoproliferative disorder (PTLD).

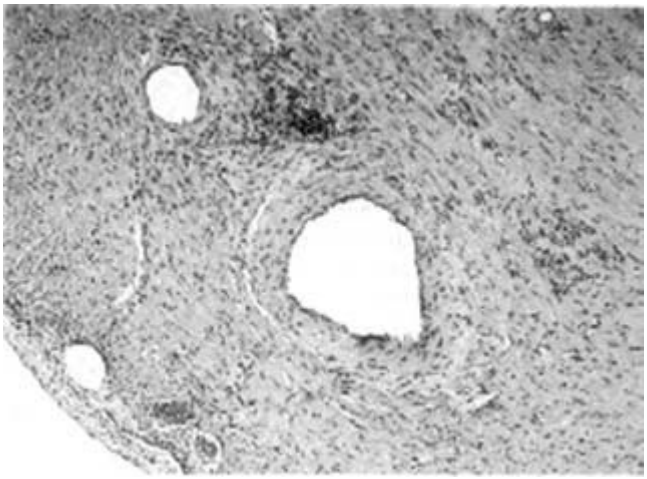
Most pediatric transplant recipients have not finished their routine schedule of immunizations. Titres should be checked pretransplant. Efforts should be made pretransplant to immunize with as many vaccinations as is feasibly possible and developmentally appropriate, most importantly live viral vaccines. Post-transplant, vaccination schedules should not be resumed for 6 months. Appropriate titres should be checked post-vaccination to determine response given the suppression of the immune system. Patients should never receive live viral vaccines post-transplant.

Transplant coronary artery vasculopathy

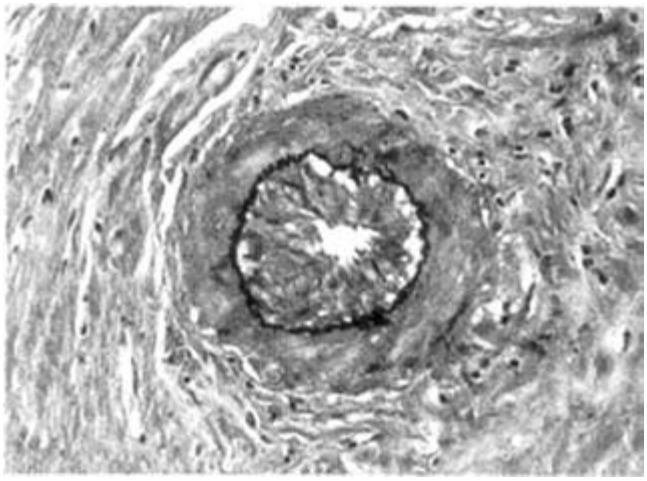
Transplant coronary artery vasculopathy (CAV) is a diffuse, chronic vascular injury to the graft. Graft ischemia results from circumferential thickening of the vascular intima (Fig. 47-16). Early clinical signs of CAV are almost non-existent in heart transplant recipients. Since the transplanted heart is denervated (i.e. not "connected") to the nervous system, the patients may not experience characteristic chest pain (angina), even in the face of significant myocardial ischemia. The diagnosis of CAV can be difficult with first clinical manifestations being symptoms of advanced disease including congestive heart failure, ventricular arrhythmias and death.

The pathogenesis of CAV is multifactorial and includes both immune- and nonimmune-related factors. It is associated with donor-specific cell-mediated alloreactivity to vascular endothelium.[41] It is promoted by a number of cytokines and growth factors.[42] There is probably some relationship between number of acute cellular rejection episodes and the risk for CAV.[43–49] Nonimmune-related associations include CMV,[50–52] possibly chlamydia,[53,54] hypercholesterolemia,[55–58] smoking,[44,47] hypertension,[44] elevated homocysteine,[59,60] elevated troponin T levels,[61] and cumulative prednisone dose.[48]

After the first year post-transplant, CAV is the commonest cause of morbidity and mortality.[2] Figure 47-17 illustrates freedom from CAV for the first 5 years post-transplant. This is highly dependent on the aggressiveness of screening and diagnosing CAV. Angiography for the diagnosis of CAV is now being questioned as the "gold standard" as it tends to underestimate CAV compared with pathology or intravascular ultrasound (Figs 47-18, 47-19).[3,62,63] In addition, angiography provides minimal information on the impact of CAV on graft function. Finally, once transplant coronary artery disease is evident angiographically, short-term mortality is high.[62,63] Supportive evi-



A



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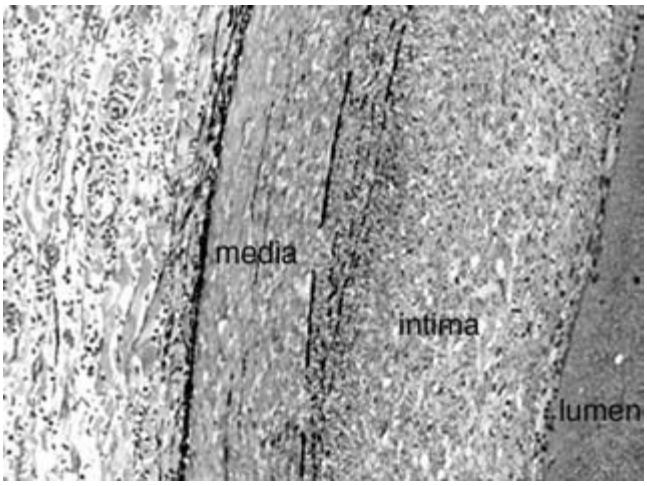

C

Fig. 47-16 Microscopic views of the resected coronary arteries. No coronary artery vasculopathy in **A** and coronary artery vasculopathy with diffuse intimal thickening in **B** and **C**.

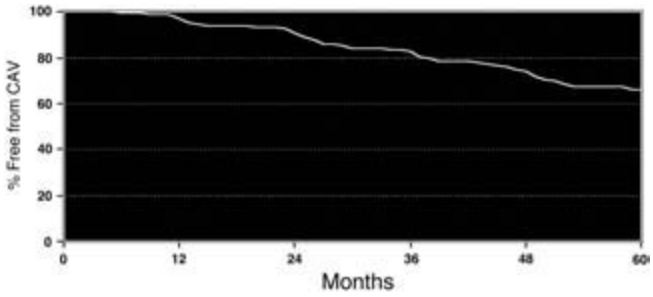

Fig. 47-17 Freedom from coronary artery vasculopathy for pediatric heart recipients (April 1994–December 2000).

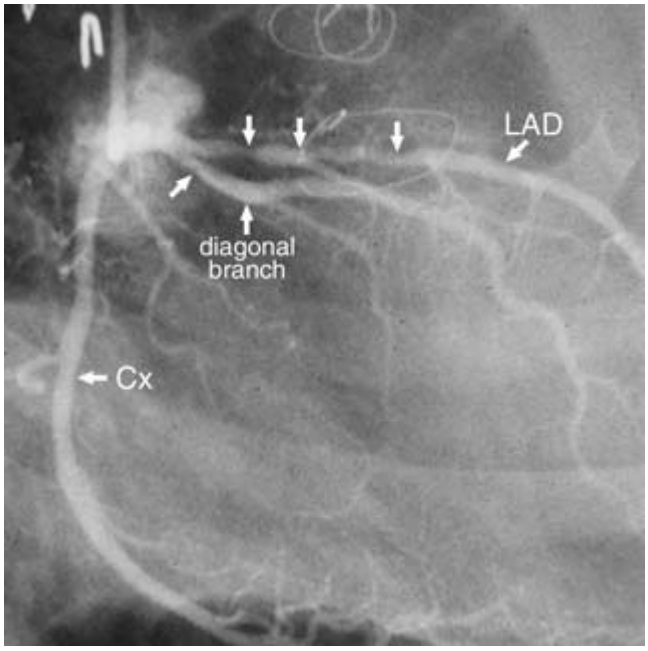

Fig. 47-18 Left coronary angiogram demonstrating multiple areas of irregularity (arrows) of the left anterior descending coronary artery (LAD) and diagonal branches in a transplant recipient. Cx, circumflex coronary artery.

dence for the presence of ischemia may be obtained by exercise testing and nuclear medicine scintigraphy,[61] but the application of these testing modalities is limited to older, cooperative patients and abnormalities are manifested, if at all, at relatively advanced stages of the disease. In the youngest and smallest of patients, there may be no modality for diagnosing CAV as repetitive angiography may be technically challenging and exercise testing/nuclear medicine scans not feasible.

The use of dobutamine stress echocardiography (DSE) has been advocated in adult heart transplant recipients for routine surveillance for CAV;[64] in some centers even replacing routine angiography. Several studies carried out in adult patients now predict a relationship between an abnormal DSE and CAV-related events.[62–64] Preliminary studies in children, including one from this institution, have supported the feasibility and safety of DSE in the pediatric population, in addition to providing preliminary evidence for a role in identifying children with CAV.[65–67]

Because of the limitations of angiography, intravascular ultrasound (IVUS), has become more attractive for the identification and study of progression of CAV (Fig. 47-19). Thus far it has been used predominantly as an adjunct to angiography in the adult population.[68–70] The application of IVUS in the pediatric population is presently limited to older children due to the size of the available IVUS catheters.

Lipid-lowering therapy, specifically HMG-CoA reductase inhibitors, has been shown to play a role in the prevention of CAV. Kobashigawa *et al*. randomly assigned adult patients early post-transplant to pravastatin (n = 47) or no pravastatin (n = 50).[71] At 1 year follow-up, the use of pravastatin reduced the incidence of acute rejections associated with hemodynamic compromise, improved one year survival, and reduced the development of CAV. This was independent of cholesterol level. Therefore, the benefit of HMG-CoA reductase inhibitors goes beyond cholesterol reduction. Similar findings have been shown for a combination of low-cholesterol diet and simvastatin post-transplant.[72]

There are data in the adult literature indicating that the use of the calcium channel blocker, diltiazem, may also have a benefit in the prevention of CAV, but no long-term data are yet available.[73,74] There are very preliminary data for a role of angiotensin converting enzyme inhibitors (ACEI) in reducing vascular intimal hyperplasia.[74]

Treatment of CAV is very difficult, especially in the pediatric population. In the adult population, percutaneous transluminal angioplasty (PTCA) and/or stenting for discrete lesions has been successfully performed.[1] However, the majority of patients are not amenable to these techniques due to the diffuse nature of the disease. Similarly, coronary artery bypass grafting (CABG) has also been successfully performed in a limited number of patients, but has a very limited role.[1] An added factor for the pediatric population is that patient size often precludes

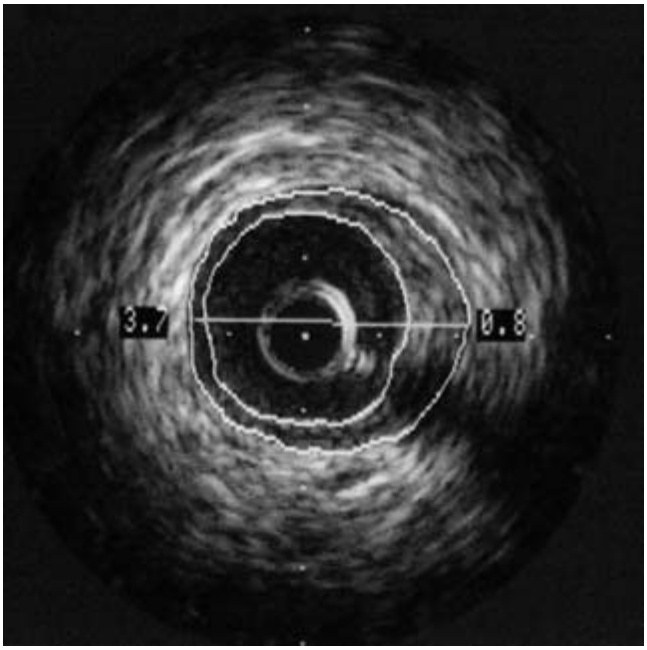

Fig. 47-19 Intravascular ultrasound of the left anterior coronary artery demonstrating intimal thickening due to transplant coronary artery vasculopathy.

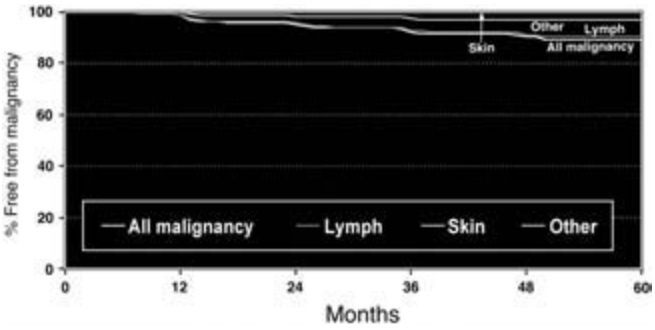

Fig. 47-20 Freedom from malignancy for pediatric heart recipients (April 1994 to December 2000).

any of these interventions. Therefore, patients with CAV may be candidates for retransplantation.

Malignancies

Malignancies are another important cause of morbidity and mortality post-transplantation. They can be *de novo*, reactivation of previous cancer, or due to chronic viral infections. The latter is the most significant in the pediatric population. Figure 47-20 illustrates freedom from malignancy for the first 5 years post-transplant, which is > 95%.[2] From the PHTS database, there were 49 malignancies in 1114 patients (0.04%), with 39 (80%) being due to post-transplant lymphoproliferative disorder (PTLD). Survival with PTLD was 95% at 1 month, 67% at 1 year, and 63% at 5 years. Again, as with any registries, these numbers are dependent on reporting, and underestimate estimates from other sources.

Post-transplant lymphoproliferative disorder (PTLD) refers to all clinical syndromes associated with lymphoproliferation post-transplant ranging from a mononucleosis-like illness to malignancies with clonal chromosomal abnormalities. EBV plays a major role in the development of PTLD with the highest risk for development being a primary EBV infection. As noted above, given the naivity of the pediatric population to EBV, primary infection and, consequently, PTLD is more common in pediatric patients. There are no controlled clinical trials comparing interventions or therapies for PTLD. The most important initial treatment is to reduce immunosuppression (or even discontinue). Antiviral medication in combination with immunoglobulin therapy is the mainstay of treatment with both acyclovir and ganciclovir having beneficial effects.[75,76] There are newer monoclonal antibodies that are showing promise.[77,78] Adjunctive therapy has included conventional chemotherapy, tumor debulking and local radiation.

Post-surgical complications

The main post-surgical complications are related to the sites of the various vascular anastamoses. Stenoses can develop at the sites of the systemic venous anastamoses (SVC/IVC), pulmonary artery anastamoses (MPA or branch PAs), or the aortic anastamosis/reconstructed aorta. These may all be amenable to intervention in the cardiac catheterization laboratory. Less commonly, the size of the left atrial anastamosis may be a problem. If it is hemodyamically significant and not recognized in the operating room at the time of the post-operative transesophageal echocardiogram, it will likely cause hemodynamic instability in the immediate post-transplant period and require a revisit to the operating room to revise. Rarely, progressive pulmonary vein stenosis can be a problem, especially if there were pulmonary venous concerns before transplant.

Other complications

Common complications that contribute to the morbidity post-transplant include hypertension, renal dysfunction, hyperlipidemia and diabetes amongst others (Table 47-12). These generally relate to the type and amount of immunosuppressive medications prescribed to the patient.

Renal dysfunction can be a significant source of morbidity in the post-transplant period. There may be antecedant compromise due to low cardiac output, chronic diuretic therapy, or mechanical support. Post-transplant, there are further insults perioperatively, and multiple nephrotoxic agents. Patients should undergo annual renal function testing including a glomerular filtration rate and screening for renal tubular acidosis. If there is renal dysfunction or it develops, kidney-sparing IS should be considered.

Osteopenia can be medically significant if it leads to osteoporosis and subsequent pathologic fractures. Many of the older patients with congenital heart disease have preexisting osteope-

Table 47-12 Post-heart transplant morbidity for pediatrics. Cumulative incidence for survivors (April 1994–December 2001)

Outcome	By 1 year		By 5 years	
Hypertension	44.2%	(n = 1507)	60.0%	(n = 365)
Renal function	(n = 1516)	(n = 389)		
Normal	94.9%	92.5%		
Renal dysfunction	3.2%	5.9%		
Creatinine > 2.5 mg/dL	3.2%	0.8%		
Chronic dialysis	1.4%	0.8%		
Renal transplant	0.0%	0.0%		
Hyperlipidemia	8.6%	(n = 1578)	17.1%	(n = 398)
Diabetes	3.2%	(n = 1509)	4.9%	(n = 366)
CAV	2.5%	(n = 1363)	11.4%	(n = 228)

nia due to lack of mobility or exercise. Screening should be done with an annual bone mineral density and prophylaxis or treatment as appropriate.

Other less medically problematic complications include hypomagnesemia and cosmetic side effects (hirsutism, gingival hyperplasia, acne, hair loss).

Growth

Growth retardation is a well-recognized morbidity in pediatric heart transplant recipients. Amongst the population followed by PHTS, growth velocity fell between the time of listing and the time of transplant. Catch-up linear growth occurred during the first year, but patients remained shorter than their age-matched peers at 6 years post-transplant. Patients transplanted for reasons other then congenital heart disease maintained steady linear growth post-transplant, but also did not achieve population means. Patients with a diagnosis of HLHS or those at a younger age at transplant showed less catch up growth.[79]

Growth data have also been analyzed in relation to steroid use post-transplant.[2] Though there were some minor differences with regards to height (linear growth) off prednisone, there did not appear to be any differences in weight gain across the age groups.

Functional status

The majority of pediatric heart transplant recipients experience excellent functional status post-transplant with > 95% reported to have no limitations at 5 years' follow-up.[2]

Strategies to improve outcomes

Donor availability

Despite improved survival, the overall number of reported pediatric heart transplant recipients remains stable, underlining an ongoing problem with donor organ availability.[2,3] There remains a worldwide gap between the supply and demand for transplantable organs which is growing. Of the patients currently on a heart transplant list in Canada, approximately 50% will never receive a transplant. In Canada in 1999, there was a 21% increase in the number of patients listed for heart transplant but only a 6% increase in the number of donors, resulting in an annual 25% mortality waiting.[1] This problem exists despite expanding acceptance criteria for donor hearts and using "marginal donors." Ongoing efforts must be made at every level of society to improve donor organ availability.

Donor

As discussed above, there is ongoing improvement and protocol development for the management of organ donors to preserve organ function following brain death. Aggressive resuscitation and stabilization using these techniques will help to facilitate more suitable potential donors and allow for improvement in the clinical status of marginal donors.

Given the data on differences in survival based on cold ischemic time, further optimization of organ preservation techniques to allow for longer cold ischemic times is warranted. This would allow for procurement of organs over greater distances, helping to increase the donor pool for any given patient.

Fetal listing

With recent advances in fetal echocardiography, more fetuses are being diagnosed with congenital heart disease at earlier stages of gestation. This has opened the door for early parental decision making regarding the possibility of heart transplantation, and has made fetal listing an option, should they wish to pursue it. Potential advantages of fetal listing include an extended time to wait for a donor organ, a favorable stage of immunologic maturation (see sections on Neonatal advantage and ABO-incompatible transplantation), avoidance of prostaglandin, inotropic or mechanical support, and limited need for risky interventions. Potential disadvantages include high pulmonary resistance with potential right heart failure in the transplanted heart, uncertainty of additional extracardiac lesions and/or undiagnosed chromosomal abnormalities, and a potential risk to the mother of an expedient delivery.

At the Hospital for Sick Children, diagnoses considered for antenatal listing include HLHS, single ventricle anatomy with risk factors for surgical palliation (severe atrioventricular valve regurgitation, decreased function), unresectable cardiac tumors, right atrial isomerism syndromes, and intractable arrhythmias. Assessment includes a detailed fetal echocardiogram for diagnosis, a detailed anatomic antenatal ultrasound for other anomalies, amniocentesis for chromosomes, and maternal blood for viral exposure and other infectious surveillance. Listing is once the fetus reaches an age of pulmonary maturity, usually at > 35 weeks gestation, and an estimated fetal weight of > 2.5 kg.

Listing criteria

As discussed under Indications, the existing stratification for listing for heart transplantation is based on a relatively predictable course of deterioration in a relatively homogeneous population with well-studied predictors of outcome. Clinical predictors of outcome are not well established for the pediatric population, especially younger patients and those with congenital heart disease. Criteria need to be designed to identify patients who are at the greatest risk of dying and who will derive the greatest benefit from cardiac transplantation. By optimizing time of listing, one would postulate that there would be some impact on early and late mortality in addition to the morbidities post-transplant.

Post-transplant care

Clearly more effective IS is needed to prevent death and graft loss following cardiac transplantation given the incidence of rejection and transplant coronary artery disease and that the major causes of death are rejection and graft failure.

All references can be found at the end of the book. See pp. 851–4 for Chapter 47.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Hamilton, Earl D. Silverman, Gil J. Gross, and Joel A. Kirsh

Congenital Heart Block

History

Congenital heart block is a rare disorder of the fetus and newborn. It is characterized by an interruption in conduction of the cardiac rhythm from the atria to the ventricles. The natural history is well known. Congenital heart block was first reported by Morquio[1] in 1901, first confirmed electrocardiographically by Van den Heuvel in 1908,[2] defined by Yater in 1929[3] and was diagnosed antepartum in 1945 by Plant and Steven.[4]

Congenital heart block can appear in isolated or familial form, displaying a variable incidence between 1/2500 and 1/20 000 live newborns, depending on the methodology of the published studies.[5] Its diagnosis is sometimes accompanied by coexisting structural cardiopathy. In cases of normal cardiac anatomy, it is usually associated with clinical or subclinical autoimmune disease.

Evidence of association with anti-Ro/La

In 1977, McCue and colleagues described a series of 22 children with congenital complete heart block, 14 (63.6%) of which were born to 11 mothers with clinical or laboratory evidence of connective tissue disease (primarily lupus erythematosus). Seven mothers had both clinical and laboratory evidence of disease while four had only positive laboratory studies including fluorescent antinuclear antibody, rheumatoid factor, and depressed complement levels. The authors recognized that antinuclear antibodies of the IgG class cross the placental barrier and hypothesized that placental transmission of such antibodies may affect the fetal cardiac conduction system.[6] In the same year, Chameides and colleagues described six infants with congenital heart block born to mothers with systemic lupus erythematosus, and also postulated a causative relation.[7]

Neonatal lupus syndromes including congenital heart block are considered to result from a common pathogenic mechanism, the passive transfer of maternal autoantibodies. Autoantibodies such as those directed against SSA/Ro and SSB/La (proteins of the Ro ribonucleoprotein particle) gain access to the fetal circulation via the normal active transport system of the placenta before 20 weeks' gestation. An autoimmune myocarditis has been described which may be the result of these autoantibody effects on the fetal heart.[8]

In many cases, the appearance of maternal autoimmune disease may be delayed for some time.[9] In addition to systemic lupus erythematosus (SLE), Sjøgren's syndrome is also associated with congenital complete heart block. [10] The manifestation of AV block with SLE or Sjøgren's syndrome is almost uniquely a fetal disease, as adults with this disease rarely demonstrate atrioventricular block,[11] although lesser degrees of conduction system disease may occur. In 67 adults with systemic lupus, of whom 36 were anti-Ro positive, a significantly higher prevalence of myocarditis and conduction defects was found in the anti-Ro positive group.[12] However, a genetic predisposition for developing conduction system disease occurs in adults and is associated with HLA B27 with or without clinical or radiological signs of associated rheumatic disease such as ankylosing spondylitis. These include supra-Hisian second or third degree atrioventricular block, sinus node dysfunction and fascicular or bundle branch block.[13]

Serology

Antibodies to SS-A/Ro have been proposed to be a serologic marker for the neonatal lupus syndrome, which is characterized by congenital heart block, cutaneous lupus or both. The antibodies occur in the mother and are transiently found in the child's serum.[14] The relation between congenital heart block and maternal connective-tissue disease was studied by antibody screening of serum samples obtained in connection with 45 cases of isolated congenital complete heart block.[15] Serum was available from 41 mothers (17 who had connective-tissue disease and 24 who were healthy) and 21 children. Thirty-four mothers had antibody to the soluble tissue ribonucleoprotein antigen called Ro(SS-A), as identified by immunodiffusion. Anti-Ro(SS-A) was found in seven of eight serum samples collected from affected children when they were less than three months old but in none of 13 samples obtained when these children were older. It appears that maternal anti-Ro(SS-A) antibody crosses the placenta and is a marker for risk of congenital complete heart block; its absence from maternal serum suggests that a child is unlikely to be affected. Thus, anti-Ro(SS-A) or a related antibody is probably involved in the pathogenesis of congenital complete heart block.

Ro(SS-A) autoantibodies are found in the majority of the cases of "idiopathic" CHB, are of maternal origin, and constitute a marker for the syndrome. When pregnancies with echocardiographically confirmed, isolated congenital heart block were assessed, all mothers had evidence of circulating anti-Ro antibody.[16] In the study of Taylor and colleagues, 35/35 mothers of babies with congenital heart block had either Ro (SS-A) or La (SS-B) antibodies, compared to 0/5 mothers of babies with other types of heart block, 10/29 women with connective tissue disease without babies with heart block, 4/445 normal pregnant women and 2/109 healthy nonpregnant women. Of 15 babies

with congenital heart block, 10 of 10 who were < 3 months old possessed antibody. Antibody titres in affected but not in normal infants were lower compared with their mothers' titres, suggesting deposition of antibodies in the baby's tissues.[17] A reduction in anti-Ro (SS-A) binding in the affected newborn of a twin pregnancy suggests that anti-Ro antibodies are consumed and thus intrinsically involved in the pathogenesis of the disease.[18] However, not all infants of SS-A antibody positive mothers are affected.[19]

In a study by Buyon *et al.*, antibodies specific for one or more components of the Ro/ribonucleoprotein particle were found in sera from all 20 mothers of permanently affected infants. However, no antibody specific for a single peptide of this particle was common to all sera. The predominant antibody response in the NLE group was to the newly recognized 52-kDa SSA/Ro peptide component (in contrast to 60-kDa SSA/Ro). Antibodies directed against the 48-kDa SSB/La antigen were demonstrated in 90% of NLE mothers, often accompanying antibodies against the 52-kDa SSA/Ro component. The combination of antibodies to 48- and 52-kDa structures was significantly increased in the NLE group, with an odds ratio of 35:1.[20] In another study, the odds of giving birth to a child with CHB were increased by a factor of 22 for women with antibodies to Ro(SS-A) and/or La(SS-B) compared with women who did not have these antibodies.[21] However, anti-52 kDa Ro antibody levels in mothers of children with congenital heart block did not differ from anti-Ro/SS-A positive mothers of healthy children[22] Specific antibody profiles do not distinguish among the manifestations of the neonatal lupus syndromes.[23] Although there is no unique antibody profile specific for CHB, mothers with a high or low risk of having a child with CHB can be identified.[24] Reichlin and colleagues assessed eluates from the heart of a child who had succumbed to CHB and suggested that anti-native 60-kDa Ro/SS-A may have a major role in the immunopathogenesis of CCHB.[25] Silverman and colleagues assessed antibody titres against recombinant 52 kD Ro protein and peptide fragments (fine specificity) of the La protein and suggested that the autoantibody response to the Ro/La particle can differentiate sera from mothers of children with NLE and sera from mothers of unaffected children.[26] Autoantibody levels and fine specificities appeared to fluctuate with time, a finding that has been contradicted by others.[27] Anti-calreticulin antibodies have also been identified as markers for CCHB. Calreticulin is involved in calcium storage and therefore anti-calreticulin antibodies might influence the development of CCHB.[28] However, there is still no definitive test to determine prospectively which babies will be affected. Treatment during gestation is still controversial and, if attempted, should be reserved for fetuses with potentially life-threatening disease.[29]

The cellular target of autoantibodies in CCHB has also been the subject of much work. Antibodies raised against maternal anti-La antibodies react strongly with the surface immunoglobulin on the myocardial fibres from a CCHB heart but not those of a control fetal heart. Both La and Ro antigens can be identified on the surface of affected heart muscle cells, in addition to complement. This suggests that induction of Ro and La antigens on the surface of myocardial fibres during fetal development may be critical in the localization of the specific autoantibodies and subsequent evolution of congenital complete heart block.[30]

Mothers who have one child affected are at risk for having a second child affected, but are often asymptomatic. Autoantibodies reactive with fetal heart tissue are present in a higher proportion of mothers of infants with CCHB, but these antibodies may not react selectively with the conduction tissue. It has been suggested that a second factor is necessary to induce the condition.[31] HLA associations in this syndrome are HLA-DR3, HLA-B8, HLA-MB2, and HLA-MT2, and these occur in mothers but not infants.[32–35] Maternal DR3 and Ro antibody seem to be independent factors associated with CCHB.[36] CCHB does not appear to be related to a specific HLA pattern in affected children,[37] although some family studies suggest otherwise.[38]

CCHB in twin pregnancies

Neonatal lupus erythematosus may occur in only one fraternal twin. The presence of circulating antibodies in the unaffected twin suggests that the anti-Ro antibody is a necessary but not sufficient factor for the occurrence of tissue injury in children with neonatal lupus erythematosus. HLA determinants were suggested to be involved in the expression of disease in neonates who have been exposed to the anti-Ro antibody,[39] but the presence of discordant outcomes in identical twins would not be in keeping with this.[40] Placental transfer of anti-Ro(SSA) or anti-La(SSB) alone to the fetus is not sufficient for the expression of congenital complete heart block. There must be a second event determining which infant develops complete heart block, but this is unknown at present.[41] An alternative explanation is that anti-La antibodies cross-react with laminin in the placenta, possibly preventing the majority of potentially pathogenic antibodies from reaching the fetal circulation.[42]

Pathology

The pathology of the conduction system in congenital complete heart block has been described by a number of investigators including Lev, Bharati, Anderson, Ho, James and others.[43] The A-V node is often isolated by collagen at all its margins except at the junction with the His bundle.[44] The anticipated area of the atrioventricular node may be occupied by fibrous and adipose tissue, and the sinus node may also show hypoplasia.[45] Hearts of patients with CCHB have absence of the approaches to atrioventricular node, as well as having partial or complete absence of the AVN.[46] In the evaluation of a fetal death, subacute myocarditis has been associated with microcalcifications of the conductive tissue.[47] IgG deposition has been reported in the conduction system of hearts of babies who died from heart block.[48,49] Small infiltrates of mononuclear cells and limited, patchy deposition of complement were also observed.[48] Alternately, immune-triggered apoptosis (programmed cell death) is another possible explanation for the pathogenesis of CCHB.[50]

Pathophysiology (Fig. 48–1)

The pathophysiology of CCHB remains unclear. National registries have been established in the US and Canada.[51] Assays for anti-Ro (SSA) and anti-La (SSB) antibodies should be performed on sera of pregnant women with SLE and newborns with CCHB.[52] Data from the NIH registry substantiate that autoantibody-associated CHB carries a substantial mortality in the neonatal period and frequently requires pacing. The recurrence rate of CHB is at least two- to threefold higher than the

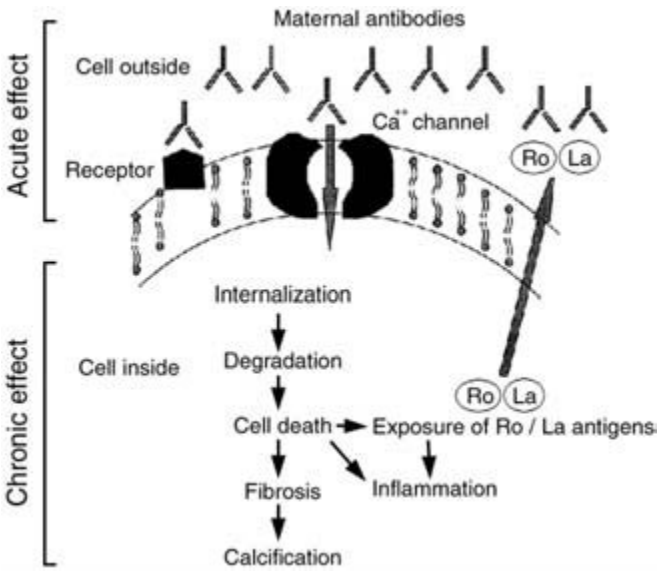

Fig. 48-1 Hypothesis of the pathophysiology of congenital complete heart block. Maternal autoantibodies may cross-react and target the neonatal calcium channel or an associated receptor. The associated alterations in Ca^{++} flux may trigger cellular events which increase the surface expression of autoantigens. Surface expression of autoantigens directs additional immune-mediated injury. (From Boutjdir *et al*.[50A] with permission.)

rate for a mother with anti-SSA/Ro-SSB/La antibodies who never had an affected child, supporting close echocardiographic monitoring in all subsequent pregnancies, with heightened surveillance between 18 and 24 weeks of gestation.[53]

Clinical presentations

Frohn-Mulder suggested that two types of heart block can be recognized. Typical congenital heart block is associated with maternal anti-Ro/SS-A antibodies and numerous obstetric and neonatal complications, but heart block that is identified later in life is rarely associated with maternal autoimmunity and has a lower risk for recurrence.[54] Patients occasionally present with lesser degrees of AV block.[55–57]

The radiologic manifestations of complete AV block, although not specific, have been described in detail and include simulated shunt vascularity, pulmonary venous hypertension, redistribution of blood flow to the upper lungs, cardiomegaly and variation in cardiac size on serial examinations.[58] Heart size is reduced significantly after pacemaker implantation.[59]

Levy and colleagues monitored 20 patients with congenital complete heart block (CHB) with ECG tape recordings while awake and asleep. Episodes of marked ventricular slowing during sleep (pauses > 3 s) were noted in 35%.[60]

Cecconi and colleagues followed 38 patients with detailed evaluation and follow-up. Twenty-two patients were asymptomatic, and 16 had symptoms such as syncope or presyncope, marked exercise intolerance, presyncope and marked exercise intolerance, heart failure or mild dyspnea on exertion. Electrocardiograms showed a narrow QRS in all patients. Holter monitoring showed a marked bradycardia (awake heart rate ″ 55 beats/min in infants, ″ 40 beats/min in children and adults) in 15 patients and junctional pauses of > 3 s in 9 of them. The exercise test showed a markedly reduced exercise tolerance in 2 patients and exercise-induced complex ventricular arrhythmias in 3 patients. Echocardiography showed a structurally normal heart and a normal left ventricular function in all patients. The electrophysiologic study always showed a supra-Hisian site of block.[61]

Fetal diagnosis

Antenatal diagnosis has been reported for many years.[62–64] Fetal electrocardiography has been used to confirm the diagnosis,[65,66] but M-mode and real-time two-dimensional echocardiographic studies have become the standard for diagnosis.[67,68] Echocardiographic assessment of the heart can give an accurate prognosis in fetal bradycardia and provide a basis for appropriate obstetric management. Isolated complete heart block often has a good prognosis if the pregnancy is carefully managed.[69] Hydrops fetalis may complicate the neonatal presentation,[70,71] but is much more common in patients with heart block and structurally abnormal hearts,[72–74] as is neonatal death.[75] The detection of congenital complete heart block (CCHB) in a fetus should alert the obstetrician that the welfare of both the mother and the newborn infant may be in jeopardy. An awareness of this uncommon cause of fetal bradycardia and judicious intrapartum monitoring can avert hasty and unnecessary cesarean section for suspected fetal asphyxia.[76] However, when this inadvertently occurs, a staged approach to pacing can be initiated.[77] On the other hand, close evaluation may identify the fetus at risk where delivery may be beneficial.[78] Habitual fetal loss is also an occasional complication of maternal SLE in pregnancy, and it is as yet unclear to what extent fetal heart block or other mechanisms contribute to this loss.[79,80] In one series of children with CCHB, the mothers did not have an increased risk for spontaneous abortions.[81] However, in other studies, combined fetal and newborn loss related to congenital heart block is reported to be as high as 50%.[82,83] An individual heart rate does not necessarily predict the outcome *in utero* or the need for postnatal pacing.[84]

Heart block and the QT interval

An association of QT interval prolongation with congenital heart block has been recognized,[85] with approximately 25% of patients demonstrating some QT prolongation.[86] This association is separate from the entity of 2:1 AV block which occurs due to ventricular refractoriness in congenital long QT patients with marked prolongation of the QT interval.

Clinical outcomes

Adults with CCHB may have associated findings of mitral valve prolapse.[87] Endocardial fibroelastosis is a recognized association with congenital complete heart block,[88] and can occur in a concordant fashion in twins with congenital complete heart block.[89] It can also occur in anti-Ro antibody-exposed pregnancies in the absence of complete heart block.[90]

The prognosis of congenital complete atrioventricular block (CCHB) is usually considered favorable in adults. This belief is based on studies comprising a limited number of patients and with rather short observation times. The natural history of the disease has been investigated by a prospective follow-up

through several decades of adult life of patients with a large group having well-defined CCHB without structural heart disease. Prophylactic PM treatment was recommended even for symptom-free adults with CCHB because of the high incidence of unpredictable Stokes–Adams attacks with considerable mortality from first attacks, a gradually decreasing VR, significant morbidity, and a high incidence of "acquired" mitral insufficiency.[91]

We reviewed our institution's experience with isolated congenital heart block (CAVB) to identify pre- and postnatal predictors of mortality and the requirement for pacemakers in infancy and childhood. The medical records of all cases encountered at our institution from 1965 to 1998 were analyzed. Of 102 cases identified, 29 were diagnosed *in utero* at an average of 26 weeks' gestation, 33 as neonates and 40 as children at an average age of 5.7 years. (Fig. 48-2) Maternal anti-Ro and/or anti-La antibodies were present in 95% of fetal and 90% of neonatal cases, but only in only 5% of mothers of older children. Mortality in the three groups was 43%, 6%, and 0%, respectively (Fig. 48-3) Increased mortality risk was associated with a fetal diagnosis of complete heart block (13/15 deaths), fetal hydrops (6/6 cases), endocardial fibroelastosis (5/5 cases) and delivery at < 32 weeks (4/6 cases). Timing of pacemaker implantation differed significantly among fetal vs. neonatal and neonatal vs. childhood cases. At 20 years of age only 11% and 12% of CAVB patients with neonatal and childhood diagnosis, respectively, were not paced (Fig 48-4).[92]

Maternal outcomes

The development of rheumatic disease in asymptomatic mothers identified by the birth of a child with congenital heart block is common but not universal.[93] The long-term outcome for the mothers of children with CCHB is more reassuring than generally assumed.[94] In the experience of Press and colleagues, 25% of the mothers with an undifferentiated auto-immune syndrome and only 2% of the initially healthy mothers developed SLE.[95]

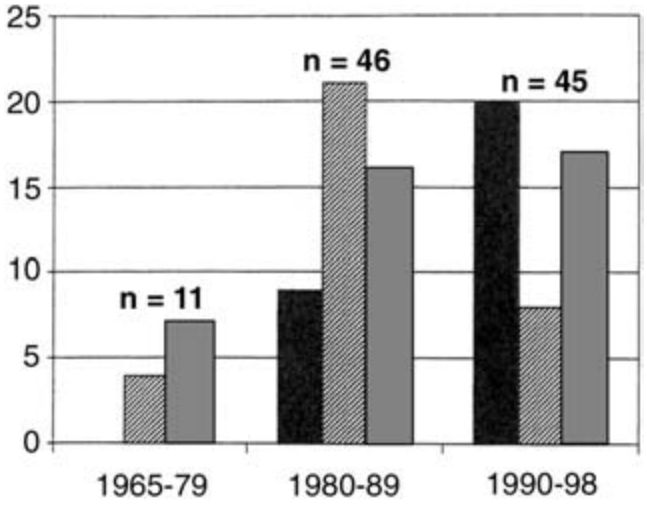

Fig. 48-2 Fetal, neonatal or childhood presentation of congenital heart block vs. era fetal presentation (solid bars) increased significantly during our experience compared to neonatal (hatched bars) and childhood presentations (grey bars). (Reprinted rom Jaeggi *et al*.,[92] Copyright (2002), with permission from The American College of Cardiology Foundation.)

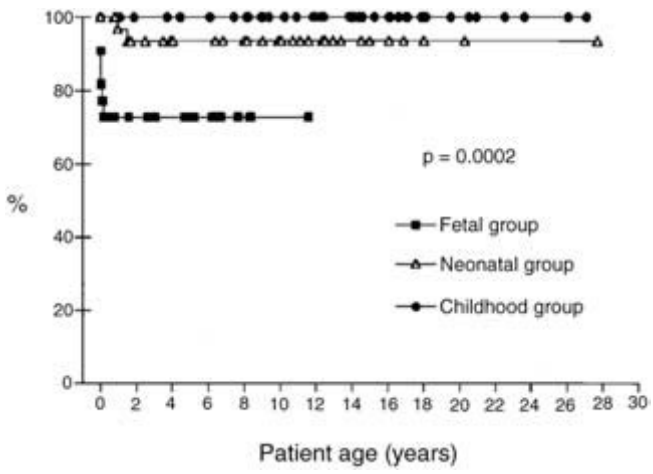

Fig. 48-3 Fetal, neonatal or childhood survival from time of diagnosis. (Reprinted from Jaeggi *et al*.,[92] Copyright (2002), with permission from The American College of Cardiology Foundation.)

Natural history

"Unaffected" infants may have somewhat longer PR intervals, but still within normal range.[96] Occasionally, patients will present with lesser degrees of AV block.[97]

Although return of A-V conduction has been described in rare patients after long periods of high-grade or complete congenital heart block,[98,99] it remains unclear whether this disorder is truly reversible.

Newborns with CCHB have had a neonatal mortality rate of up to 20% without treatment.[100] and as high as 15–16% even with treatment.[101,102] Congenital complete heart block may be associated with fatal Stokes–Adams attacks later in life as well.[103,104] The mortality is highest in the neonatal period, much lower during childhood and adolescence and increases slowly later in life.[105] Most patients who survive beyond infancy are able to lead relatively normal lives.[106]

In Cecconi's study, 20 patients (53%) underwent cardiac pacing at a median age of 14 ± 10 years and were followed up for 110 ± 59 months (range 18–253) after pacing; prophylactic pacing was performed in 10 patients.[61] Indications for cardiac pacing were: syncope or presyncope (7 patients), presyncope and marked exercise intolerance (1 patient), neonatal heart failure (1 patient), marked exercise intolerance (1 patient), neonatal marked bradycardia (2 patients), marked bradycardia with junctional pauses of > 3 s and/or complex ventricular arrhythmias (7 patients) or complex ventricular arrhythmias (1 patient). No death occurred during the follow-up. In 9 of 20 patients who had cardiac pacing, indication for this procedure appeared during the follow-up (development of symptoms, marked bradycardia and/or complex ventricular arrhythmias). Complications of pacing were infrequent (9 complications in 7 patients). All patients who had pacing showed an improvement of exercise tolerance; 11 of them underwent exercise test after pacing which showed a significant increase in exercise duration. In the 3 patients with complex ventricular

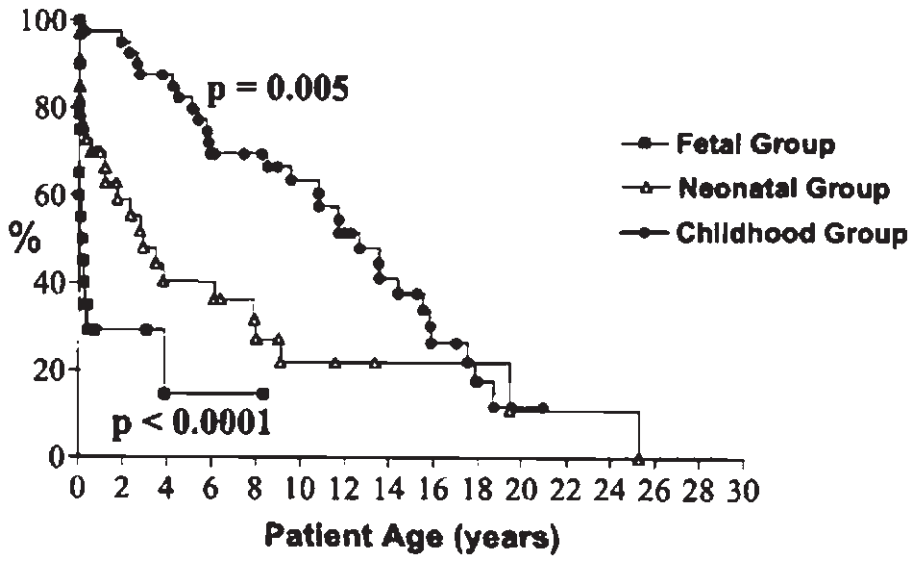

Fig 48-4 Kaplan–Meier freedom of pacemaker implantation comparing fetal, neonatal and childhood diagnosis of CAVB. Global differences between the groups (log-rank; 2 = 28.4, $P < 0.001$) were further analyzed using log-rank tests and Bonferroni corrections. Time of implantation differed significantly between the childhood group and the neonatal group (2 = 7.8, $P = 0.02$) and between the childhood group and the fetal group (2 = 33.9, $P < 0.001$) but not between the neonatal and fetal groups (2 = 4.4, $P = 0.09$) after adjustment for multiple comparison. (From Jaeggi *et al.*[92] with permission.)

arrhythmias, they observed suppression after atrioventricular sequential pacing.

Prediction of syncope (Stokes–Adams attacks)

Stokes–Adams attack is a historical description for sudden cardiovascular syncope associated with bradycardia.[107] Congenital heart block can be associated with fatal Stokes–Adams attacks.[108] More typically, Stokes–Adams attacks occur without major sequelae and initiate the placement of a permanent pacing system.[109] Stoermer and Schramm recognized that patients with congenital heart block usually had faster, narrow-complex escape rhythms and a good prognosis compared to other patients with AV block, but that most would eventually require pacemaker implant.

Karpawich and colleagues provided the first detailed assessment of risk factors for (potentially fatal) Adams–Stokes attacks in the patient with congenital heart block. Twenty-four children with congenital complete AV block were followed up for 1–19 years. One or more Adams–Stokes episodes were experienced by 8 children, 1 of whom died. Only a persistent heart rate at rest of 50 beats/min or less demonstrated a significant correlation with the incidence of syncope. Intracardiac electrophysiologic study was of little benefit because site of block did not correlate with syncope. Ventricular pacemakers were implanted in 10 children. Each child was asymptomatic over a 1- to 10-year follow-up period.[110]

Dewey and colleagues followed 27 patients prospectively with Holter monitors for a mean of 8 years. Eight of 13 patients with a mean daytime heart rate below 50 beats/min (group A) had cardiac complications such as sudden death, syncope, presyncope, or excessive fatigue. Six of the 8 also had junctional instability. None of the 14 patients with a mean daytime heart rate of 50 beats/min or more (group B) had an adverse clinical outcome.[111]

The reports of Dewey and Karpawich did not study patients with isolated CHB exclusively, but included patients with congenital heart block in the face of structural heart disease. Nagashima and colleagues studied a small group of patients with isolated CHB, and considered junctional exit block as a possible risk factor.[112] A prolonged RR interval > 3 s is now accepted as a risk factor.[112] Other identified risk factors for syncope include ventricular ectopy and poor chronotropic response to exercise,[111] More recently, Michaelsson and colleagues demonstrated that such risk factors do not always predict Stokes–Adams attacks (even fatal ones) in adults,[91] and suggested that all patients over age 15 years with congenital heart block receive permanent pacemakers.[113]

In 5 subjects with congenital complete A-V block, the site of block as determined by invasive electrophysiologic study could not be predicted from the surface ECG.[114] Certainly, the block is supra-Hisian in the majority of patients.[115]

Subsidiary ventricular pacemaker function was evaluated in 20 children with congenital or surgically induced complete heart block, and long-term ECG tape recordings were performed in eight of these children. His bundle recordings showed that the site of block did not allow separation of patients with symptoms from those without symptoms. Prolonged recovery times were present in patients with block above the His bundle recording site who had symptoms of syncope or dizziness, as well as in patients who had a wide QRS. However, some asymptomatic patients with heart block above the His bundle recording site also had long recovery times.[116]

A fixed or decreasing low ventricular rate neonatally and a prolonged QT time seem to be bad prognostic signs.[105] QT prolongation in congenital complete heart block may be associated with episodes of torsade de pointes[117] which may occur even late in life.[118,119] Symptoms in early infancy were a more serious risk factor in the experience of Reid and colleagues.[104] Patients who developed ventricular ectopics with exercise had lesser increments in their junctional rates with exercise and were more likely to subsequently experience syncope and require pacemaker insertion.[120]

Sholler and Walsh found that heart rate on electrocardiogram or Holter monitor did not clearly distinguish a subgroup at risk. The presence of alternate "risk factors," such as atrial enlargement seen on electrocardiogram, cardiomegaly seen on X-ray film, a prolonged QT interval or ventricular ectopy on Holter monitoring were independent predictors of symptoms and poor outcome.[121]

Normand and colleagues assessed for the presence of syncope, cardiac failure, low heart rate, increased QRS duration, prolonged QTc, infrahisian AVB, long pauses or arrhythmias on Holter monitoring as indications for pacemaker therapy. The only significant prognostic factors in this series were a previous history of syncope, increased QRS duration and a QTc of > 0.45 s.[122]

Michaelsson and colleagues provided an update of their studies on the natural history of congenital complete AV block. A risk for heart failure, syncope, and sudden death is present at any age including fetal life. Unfavorable prognostic signs *in utero* are low and include decreasing ventricular rate, hydrops, AV valve regurgitation, and low aortic flow velocity. Indications for pacing in infancy are congestive heart failure, ventricular rate < 55 beats/min in isolated block and < 65 beats/min with associated disease, prolonged QTc, syncope attacks, frequent ventricular ectopic beats, and alternating ventricular pacemakers. Indications for immediate pacing in childhood and adult life are syncope, presyncope, low ventricular rates, periods of junctional exit block, prolongation of QTc and mitral regurgitation. Pacing is recommended to all patients older than 15 years.[113]

Exercise tolerance

Patients with congenital complete heart block can adapt to exercise through an increase in ventricular rate (from a mean resting rate of 50 beats/min to a mean exercise rate of 112 beats/min), an increase in stroke volume, or (to a lesser degree) an increase in venous oxygen extraction.[123] In most patients with CCAVB, the LV was enlarged with normal geometry and enhanced systolic function during the first two decades of life.[124] Resting cardiac output is maintained at a normal level by an increase in end-diastolic volume, but no appreciable change in the end-diastolic volume occurs during exercise.[125] However, 68% (17/25) of heart block patients have significant ventricular ectopy (frequent unifocal ectopy or worse) on exercise. There is a significant trend toward more frequent and more severe ectopy with increasing age and also in patients with QRS prolongation.[126]

In patients with congenital complete atrioventricular (AV) block, treadmill exercise testing demonstrated a significantly lower ventilatory threshold than normal. There was an inadequate hemodynamic adjustment to the relative exercise bradycardia and a higher than normal anaerobic/aerobic energy supply. The resting heart rate did not predict either exercise bradycardia or the degree of exercise intolerance.[127]

Therapy

Fetal therapy

Early corticosteroid treatment of the mother's disease had no beneficial effect on AVB in the fetuses reported by Herreman and colleagues.[10] A combination of dexamethasone and plasmapheresis also did not reverse congenital complete heart block, although the fetal status appeared to improve.[128] Similar improvement was seen in other cases treated with corticosteroids.[129–131] The concentration of total maternal IgG and antibodies to SSA(Ro) and SSB(La) can be decreased by > 60% by this therapy.[132,133] The use of intravenous gammaglobulin has also been attempted.[134]

Maternal administration of ritodrine may increase the fetal ventricular rate and can be considered in life-threatening fetal bradycardia induced by complete heart block.[135] Such sympathomimetic drugs are effective but are poorly tolerated by the mothers.[136,137]

Pacing therapy

Ten patients ranging in age from 8 months to 15 years were treated with an implanted *P*-wave, synchronous epicardial pacemaker.[138] Furman also describes successful pacing in children,[139] and Vanetti and colleagues describe an early, large French series of 241 children with atrioventricular block 40.7% of which were congenital.[140] Early pacing systems demonstrated significant lead failures, short battery life (mean of 17 months) and possible complications of asynchronous pacing.[141] The development of epicardial steroid-eluting leads has improved the application of pacing systems.[142,143]

A single pass lead has been suggested to provide a simple means of reliable atrial synchronous ventricular pacing in growing children with complete heart block.[144–147] However, coexisting sinus node disease should first be ruled out.[148]

In 18 of the 24 children with disabling complete A-V block, pacemaker therapy provided relief of symptoms and prolonged life,[149] a finding confirmed by others.[150] Transvenous pacing can be accomplished in relatively young children.[151] The use of actively anchorable endocardial leads is recommended to allow for the placement of long electrode loops in the cavity of the right atrium without increasing the risk of dislodgement.[152]

Complications

Pacemaker therapy in sixteen children over a period of 56 patient years resulted in nineteen complications necessitating surgical treatment.[153] Lead complications may eventually occur in up to 50% of patients.[39] Pacing complications or failure were the cause of death in 2/16 patients with CCHB reported by Villain and colleagues.[154]

Medicolegal issues

CCHB is considered a contraindication to professional pilot status.[155]

Differential diagnosis

Anatomic heart disease was present in 25/65 (39%) infants with congenital heart block, with ventricular inversion/L-transposition of great arteries complex occurring most frequently (20/25 infants).[156] AV block in the face of structural heart disease may be present in the first trimester,[157] in contrast to patients with structurally normal hearts who usually present beyond 16 weeks of gestation.

In a series of 23 patients with congenital heart block, 7 cases were combined with a corrected transposition of the major vessels.[158] Fox described 26 patients with atrioventricular discordance and a variety of ventriculoarterial connections who have had appropriate intracardiac repairs. Seven of 26 patients (26.9%) died early postoperatively, but only 2 (11.1%) of 18 patients operated upon since May 1972 died. Ten patients (40%) developed permanent complete heart block.[159] In 40 patients with ventricular inversion and l-transposition of the great arteries reported by Gillette, there were 11 subjects with complete

AV block.[160] In the detailed series of Huhta and colleagues, atrioventricular block was present in 4/107 patients at birth. The risk of natural onset AV block continued at a rate of *c*. 2% per year after diagnosis. The presence of an intact ventricular septum made AV block more likely.[161]

Complete block below the His recording site was associated with syncope in one patient and sudden death in another.[160] Patients may have two AV nodes, connected by a Mönckeburg sling, but with neither node connecting to their respective bundles.[162] Corrected transposition with AV block may rarely complicate disorders of laterality such as Kartagener's syndrome.[163] Patients with corrected transposition may also have manifest accessory pathways. It should be recognized before ablation of such a pathway that this might be the only route of atrioventricular conduction.[164]

Inherited abnormalities characterized by conduction defects is association with atrial septal defects may occur without associated forearm defects.[165] Alternately, forearm defects may be associated through one or more inherited syndromes.[166,167]

Complete AV block is also frequently present in patients with left isomerism, a not unexpected finding since the AV node is a right atrial structure.[168,169] The incidence rate of complete A-V block in left isomerism is nearly 20% of the cases described.[170] The histological pattern of congenital complete heart block in cases with left isomerism is discontinuity between the AV node and the conduction axis, in contrast to the pattern of atrial-axis discontinuity produced in the structurally normal heart with CCHB related to maternal anti-Ro antibodies.[171]

Complete AV block may also occur in the presence of right atrial isomerism. The histology of the conduction system may demonstrate separate anterior and posterior AV nodes, neither connected with the atrial myocardium.[172]

Though diphtheritic infections are known to affect the cardiac conduction system, authenticated cases of post-diphtheritic block persisting after the infection are rare.[173] Fetal viral myocarditis has also been suggested as a cause for congenital heart block.[174]

Mesothelioma of the atrioventricular node may result in complete heart block, which may be present for many years before death.[175–178]

A syndrome of multiple lentigines associated with retardation of growth, hypertelorism, abnormal genitalia and complete atrioventricular block (LEOPARD syndrome) has been described.[163]

All references can be found at the end of the book. See pp. 854–7 for Chapter 48.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Rejane F. Dillenburg, Joel A. Kirsh, Gil J. Gross, and Robert M. Hamilton

Long QT Syndrome

The long QT syndrome is a familial disorder of myocardial repolarization, which affects young people with structurally normal hearts. Defective genes that encode for ion channels expressed in the heart cause the repolarization abnormality that leads to torsade de pointes and, in some cases, to sudden death. The prolonged QT interval was considered for many years to be the hallmark of the disease, but it has been demonstrated that individuals with normal QT intervals may be gene carriers and may still be at risk of ventricular arrhythmias and sudden death.

Factors to consider in the diagnosis of LQTS include clinical symptoms, family history and prolongation of the QT interval on the surface ECG. Symptoms may include syncope, seizures or aborted sudden death, particularly in the setting of specific initiating events (see below). A family history of sudden death should be sought for. Keating[1] described criteria for considering a patient as affected, unaffected or uncertain, depending on the presence of symptoms and the QTc interval. Patients with symptoms and a QTc > 450 ms as well as those asymptomatic patients with a QTc > 470 ms were classified as affected. Asymptomatic patients with a QTc < 410 ms were classified as unaffected. The uncertain diagnosis group thus included both patients with symptoms and a QTc < 440 ms and patients without symptoms and QTc between 410 and 460 ms.

The Schwartz criteria (Table 49-1) are probably the most popular method for categorizing patients with suspected long QT syndrome.[2,3] The first proposed criteria were published in 1985 and included major and minor findings. Less than a decade later, prompted by new developments in knowledge about the disease, reassessment and diagnostic refining took place and the criteria were revised and republished in 1993. This update was based on observed gender-related differences in the length of the QT interval, the large spectrum of newly recognized clinical manifestations and the contribution of molecular biology to the understanding of LQTS.

Although these criteria, and indeed the majority of published data on LQTS, refer to older patients, a number of studies have specifically addressed the manifestations of LQTS in children. LQTS is a hereditary disease with different clinical characteristics and prognosis in children as compared to adults; children who present at younger ages most probably have the most severe form of the disease with a higher risk of sudden death. Children are more likely to present with sudden cardiac death as the first event than adults. Clinical studies performed in adults may be skewed in favour of those who survived.[4,5]

Incidence and prevalence

The incidence of LQTS in the general population is not known, but has been estimated by some authors to be *c*. 1 in 10 000–15 000 live births.[6,7] There are more data regarding the prevalence of LQTS amongst deaf individuals. Fraser identified 9 cases of Jervell–Lange–Nielson (JLN) syndrome amongst 1765 deaf children, and then extrapolated the prevalence of the JLN subtype of LQTS in children between 4 and 15 years of age living in England, Ireland and Wales as being between 1.6 and 6 per million.[8,9] In a meta-analysis of published series, Schwartz *et al*.[10] estimated the prevalence of LQTS amongst deaf individuals as 0.28%.

Two other studies have also reported on prevalence of LQTS in children with congenital hearing loss.[11,12] One of these studies investigated 350 school children between 6 and 19 years old with congenital deafness.[12] Eight children were identified as having a prolonged QTc above 440 ms. These children and their families were assessed for symptoms and QT prolongation on the ECG, 24 h ambulatory ECG, exercise test and echocardiographic results. The prevalence of LQTS among deaf-mute children in this study was 0.57%.[12] A case-control study from Turkey identified 5 patients with prolonged repolarization among 132 deaf children, with a prevalence of 3.78% in this population. The mean QT, QTc, JT and JTc intervals and the dispersion values were significantly longer than those of control subjects.[13,14]

Studies in the pediatric population (Table 49-2) have indicated that the proportion of JLN amongst identified LQTS populations is between 4.5%[4] and 9%[11] suggesting that the Romano-Ward variant of LQTS is at least ten times more common than JLN. However, difficulties in ascertaining the true incidence of LQTS in the non-deaf population give support to Schwartz's contention that LQTS is likely to be more "underrecognized than rare."

Data from the International Registry[15,16] demonstrated the proportion of the JLN variant in the general LQTS population to be between 6% and 10%. Subsequent data published in 1998[5] demonstrated the results of genetic testing in 38 large families. A total of 728 families were enrolled in the study at that point. There were 246 (45%) gene carriers among 541 genotyped family members. Currently, there is incomplete characterization of the entire genetic profile of the LQTS, which makes it difficult to establish incidence/prevalence figures, even when utilizing genetic information.

Table 49-1 Diagnostic criteria for the LQTS

Criteria	Points††
ECG findings*	
A QTc †	
≥ 480 ms^{-}	3
460–470 ms$^{1/2}$	2
450 ms$^{1/2}$ (in males)	1
B Torsade de pointes‡	2
C T-wave alternans	1
D Notched T wave in three leads	1
E Low heart rate for age§	0.5
Clinical history	
A. Syncope‡	
With stress	2
Without stress	1
B Congenital deafness	0.5
Family history¶	
A Family members with definite LQTS**	1
B Unexplained sudden cardiac death below age 30 among immediate family members	0.5

*In the absence of medications or disorders known to affect these electrocardiographic features.
†QTc calculated by Bazett's formula, where QTc = QT/$\sqrt{RR}$.
‡ Mutually exclusive.
§Resting heart rate below the second percentile for age.
¶The same family member cannot be counted in A and B.
**Definite LQTS is defined by a LQTS score ≥ 4.
††Scoring: ≤ 1 point, low probability of LQTS; 2 to 3 points, intermediate probability of LQTS; ≥4 points, high probability of LQTS. (Reprinted from Schwartz,[3] Copyright (1993), with permission from Lippincott Williams & Wilkins.)

Molecular diagnosis and genotype–phenotype correlations

Over the past decade, basic scientists in conjunction with clinical cardiologists have published an impressive amount of research on the long QT syndrome (Table 49-3).[17–26] Since the publication by Keating[1] in 1991, five loci associated with the Romano–Ward (RW) and Jervell-Lange-Nielsen (JLN) syndromes have been described to date. Specific locations on each chromosome have been determined and the genes encoding for ion channel proteins have been sequenced, with the exception of LQT4. There are still genes to be discovered, given that the genetic mutations described to date are responsible for only about 50% of the genotyped patients. [17]

Neyroud described three JLN children from two different families, in which LQT was inherited in an autosomal dominant pattern and deafness was inherited in an autosomal recessive pattern. Splawski described a similar scenario. These findings are suggestive that one form of JLN is caused by homozygous mutation in KVLQT1.[26,37] Heterozygous mutations in KVLQT1 cause RW syndrome (prolonged QT and no deafness), while homozygous mutations in KVLQT1 cause JLN (prolonged QT and deafness). Wang[7] suggests that in RW syndrome with heterozygous KVLQT1 mutation, there are still some functional potassium channels in the inner ear, and congenital deafness thus does not occur in these patients. In JLN patients with homozygous mutations in KVLQT1 there is no functional potassium channels formed in the heart and in the inner ear, the latter leading to deafness.

Genotype–phenotype correlation

The understanding of patients with LQTS has been refined since genetic characterization of each subtype allowed correlation with clinical aspects. Originally, two forms of LQTS were described based on the pattern of transmission, as autosomal dominant (Romano-Ward) and autosomal recessive (JLN).[9,10,27] There is a broad diversity in phenotypic expression of each LQTS subtype attributed to variable penetrance of genetic activity or variable function of the ion channels encoded by the responsible genes. Multiple publications[5,28–37] have described the phenotypic characteristics of each LQTS genotype, including differences between genotypes of baseline observations, triggers for cardiac events, and mortality (Table 49-4).

Evolution of diagnostic and management algorithms

- 1856–1937: isolated case reports.
- 1957: first complete description of the disease by Jervell and Lange-Nielsen – sudden death, ventricular arrhythmias and deafness.[39]
- 1963–1964: independent contribution from Romano and Ward, describing the same clinical features of JLN disease, but without deafness.
- 1966: Yanowitz demonstrated the effect of right stellectomy or left stellate ganglion stimulation on the ECG and QT prolongation.[40]
- 1971: two reports with opposite conclusions in the same year. Moss and McDonald: first left cervicothoracic sympathetic ganglionectomy with successful outcome.

Ratshin: demonstrated failure to shorten QT interval by left stellate ganglion blockade – question about the rationale for surgery, and left stellectomy was abandoned.

Table 49-2 Studies of prevalence of LQTS in deaf individuals

Reference	Type of study (design)	Years of study	No. of cases	Denominator	Incidence (%)
Fraser *et al.* 1964[9]	Cross sectional	–	9	1765	0.005
Schwartz *et al.* 1975[10]	Retrospective meta-analysis	5	14	5077	0.28
Ocal *et al.* 1997[12]	Prospective	Prevalence	2	350	0.57
Ilhan *et al.* 1999[13]	Prospective	Prevalence	5	132	3.78

Table 49-3 Molecular biology of LQTS

Reference	Year	Subtype	Chromosome/locus	Gene	Current	Inheritance
Keating *et al.*[1]	1991	LQT1	11p15.5	KvLQT1	Decr I Ks	AD
Wang *et al.*[18]						
Jiang *et al.*[19]	1994	LQT2	7q35–36	HERG	Decr I Kr	AD
Curran *et al.*[20]	1995					
Jiang *et al.*[19]	1994	LQT3	3p21–24	SCN5A	Incr I Na	AD
Curran *et al.*[20]	1995					
Schott *et al.*[22]	1995	LQT4	4p25–27	Unknown	Unknown	
Takumi *et al.*[23]	1988	LQT5	21q22.1–22.2	MinK (KCNE1)	Decr I Ks	AD
Chevillard *et al.*[24]	1993					
Abbott *et al.*[25]	1999	LQT6	21q22.1–22.2	MiRP1 (KCNE2)	Decr I Kr	AD
Neyroud *et al.*[26]	1997	JLN1	11p15.5	KvLQT1(KCNQ1)	Decr I Ks	AR
Takumi *et al.*[23]	1988	JLN2	21q22.1–22.2	MinK (KCNE1)	Decr I Ks	AR
Chevillard *et al.*[24]	1993					

(From Chiang and Roden[26A] with permission.)

- 1975: Schwartz demonstrated T-wave alternans induced by left stellate ganglion stimulation.[41]
- 1975: Schwartz published the sympathetic imbalance hypothesis, suggesting left stellectomy and beta-blockade as therapies.
- 1976: Schwartz demonstrated that the protective effect of left stellectomy was in fact the increase in VF threshold, independent of the QT interval shortening.
- 1979: International Registry started.
- 1980: Schwartz suggested that the spectrum of LQTS might be larger that previously thought and that it may include patients with normal QT intervals.
- 1985: Schwartz suggested that there might be a possibility that the basic defect in LQTS could be an as yet unknown intracardiac abnormality that might decrease electrical stability with an attendant increase in myocardial vulnerability to the effect of sympathetic discharges.
- 1986: Moss and Schwartz proposed that the unknown intracardiac abnormality may be an alteration in one of the K^+ repolarizing currents.
- 1987: Eldar reports on beneficial effects of permanent pacing combined with beta blockers on the outcomes of the LQTS.[42,43]
- 1991: Keating identified linkage of the LQTS to Harvey ras-1 gene locus on the short arm of chromosome 11 in one large family.
- 1991: Towbin confirmed linkage to the Harvey ras-1 gene in 65% of 23 families, providing evidence for the genetic heterogeneity of LQTS.
- 1992: On longer follow-up, combined therapy proved to be less effective than previously thought.[44,45]
- 1995–1996: three LQTS genes were identified in 9 months' time.
- 1995: Schwartz provided evidence for gene specific differential responses to various interventions.
- 1997: Neyroud demonstrated that the JLN recessive syndrome is caused by homozygous or by compound heterozygous mutations.
- 1998: Priori provided first evidence that even the RW variant can be transmitted as a recessive trait.

Table 49-4 Clinical characteristics in common forms of LQTS

	LQT1	LQT2	LQT3
Gene mutated	KCNQ1(KvLQT1)	HERG	SCN5A
Current affected	I Ks	I Kr	I Na
Estimated prevalence (%)	45	40	10
Mean QTc	490 ± 43	495 ± 43	510 ± 48
% of events occurring with exercise or emotional stress	97	51	39
Exercise related trigger	+++	+	+
Other triggers	Swimming	Loud noise	
% with events to age 10	40	16	2
% with events to age 40	63	46	18
Median age at first event	9	12	16
QT shortening with exercise	< Normal	Normal	> Normal
Efficacy of beta blockade to prevent events	+++	++	+(?)
Efficacy of mexiletine to shorten QT	–	+	+++

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Table 49-5 Risk factors for mortality

Reference	Study type and year	No. of patients	Mortality at specific time points	Risk factors for mortality
Schwartz *et al.*[10]	Retrospective, 1975	203	5%/year	Deafness
Moss *et al.*[15]	Retrospective analysis of prospectively collected data, 1985	196	1.3%/year	Congenital deafness, syncope, female, previous TdP/VF
Moss *et al.*[16]	Prospective, 1991	3,343	0.9%/year	QTc, HR

Mortality

Left untreated, the long QT syndrome carries with it a significant risk of sudden death, particularly in selected patients with specific risk factors (see below). Multivariate analysis has demonstrated four variables as significant risk factors for cardiac events (syncope and sudden death): congenital deafness, history of syncope, female gender and prior occurrence of torsades de pointes and/or ventricular fibrillation (Table 49-5). The most potent risk factor was congenital deafness, present in only 6% of the population.[3]

The change in mortality rate from the reports of Schwartz[10] to Moss[15,46] from 5% per year to 1.3% per year may be explained as follows. In the first study, deafness (itself a predictor of the more severe JLN variant) was more prevalent, at 30% compared to 6% in the second study. Schwartz's patient population were less likely to be asymptomatic (3% vs. 43%), as well as less likely to be on beta blockers (25% vs. 96). These data suggest that there was a significant improvement in survival after adequate therapies were instituted for these patients.[3]

The 1991 report of the LQTS Registry[16] demonstrated important data with respect to mortality events. A total of 147 patients (4.4%) from the total population died before age 50. The mean age at death was 21 years. Mortality occurred predominantly in young patients (57% by age 20), in those with previous syncopal episodes, with marked QT prolongation and without antiadrenergic therapy. The cumulative probability of events using birth as time of origin has shown that by age 12, 50% of LQTS patients and 8% of the affected family members have had a cardiac event. Using date of enrollment as time of origin, the probability of events at 10 years of follow-up was 37% for probands and 5% for affected family members.[16]

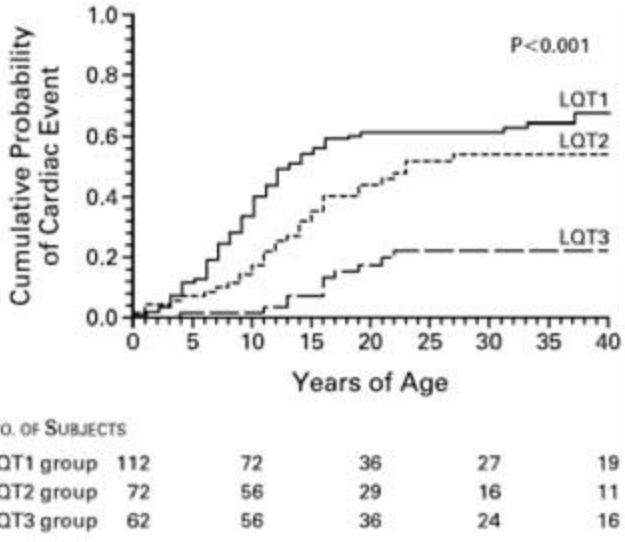

Fig. 49-1 Kaplan–Meier estimate of the cumulative probability of a cardiac event in genotyped LQT1, LQT2, and LQT3 patients. *P* value computed using log-rank test. Numbers of subjects at risk are given for each decade of age. (Reprinted from Zareba *et al.*,[5] Copyright (1993), with permission from Lippincott Williams & Wilkins.)

The third publication from the International Registry[5] evaluated the clinical course of LQTS based on genotype of the patients (see Fig. 49-1). Genetic testing was performed in 541 members of 38 large families with linkage analysis. The primary endpoints were syncope, aborted cardiac arrest requiring defibrillation and sudden cardiac death. Only events occurring from birth to age 40 were included to avoid possible confounding effects of ischemic heart disease or other diseases. Of the 541 genotyped, 246 patients were gene carriers: 114 had LQT1, 72 had LQT2 and 62 had LQT3 subtype. By age 15, there was a significantly higher proportion of LQT1/LQT2 patients (53% and 29%, respectively) who had had their first cardiac event when compared to LQT3 (6%). The frequency of cardiac events was significantly higher in LQT1/LQT2 patients (63% and 46% respectively) than among LQT3 patients (18%). However, LQT3 patients had a higher chance of death during a cardiac event (20%) than the other LTQS subtypes (4% each for LQT1 and LQT2).

Evidence-based strategies to improve outcomes

The international registry report published by Moss[15,46] in 1985 demonstrated that two interventions had significant beneficial effects reducing the occurrence of cardiac events during follow-up: left stellate ganglionectomy and beta-blocker therapy. This study was a retrospective analysis of prospectively accumulated data. While statistical techniques were used to adjust for risk differences between treated and non-treated patients to assess the independent effect of treatment on outcome, each physician individually decided the management of individual patients. As a result, the effects of therapy may have been over- or underestimated depending on selection bias of lower- or higher-risk patients, respectively. The recommendations were that patients with LQTS and high risk factors (congenital deafness, history of syncope, female gender and documented malignant arrhythmia) should be treated prophylactically with beta blockers in the maximal tolerated dose. Left stellate ganglionectomy was felt to

be indicated in patients with recurrent life-threatening arrhythmic episodes refractory to beta blockade. The recommendation for patients without risk factors but with positive family history of sudden death was to start beta blockers.

There is now general agreement that beta-blocker therapy is beneficial, and several studies have documented its efficacy in the prevention of syncope in 75–80% of LQTS patients.[3–5,15,16,46,47] However, beta blockers are not completely effective in preventing cardiac events, with a 20–25% risk of recurrent syncope and an ongoing risk of sudden cardiac death.[3] A study that included patients from the International Registry demonstrated that there is a significant reduction in the rate of cardiac events, although the patients who have the most benefit are those who were asymptomatic before starting therapy.[49] Another important issue to consider regarding effect of beta blockers in the majority of published retrospectively analyzed data is that therapy was usually used for those patients perceived to be at higher risk of cardiac events.

There is experimental evidence that the different subtypes of LQTS may have different responses to beta-adrenergic blockade. A study in canine myocardium where transmembrane action potentials were measured from epicardial cells, M cells and endocardial cells with a simultaneous recorded transmural electrocardiogram during infusion of beta-adrenergic agonists and antagonists demonstrated that beta blockers are protective in LQT1 and LQT2, but may actually facilitate TdP in LQT3.[50] These findings are in concordance with the observation that in the LQTS subtypes where the delayed rectifier potassium channels are defective and are usually dependent on an adrenergic trigger to the precipitation of ventricular tachycardia, beta blockers are effective. In sodium channel gene mutations, the role of beta blockers is not as well defined.[51]

Left cardiac sympathetic denervation

The sympathetic nervous system was initially thought to play a significant role in the pathogenesis of the LQTS. Surgical techniques to accomplish left cervicothoracic ganglionectomy improved the results in survival, but were not completely effective.[52]

The efficacy of LCSD in LQTS patients was demonstrated in a report on 85 individuals in whom a similar follow-up time was available before and after the procedure. The authors demonstrate a highly significant ($P < 0.0001$) decrease in the number of patients with cardiac events (from 99% to 45%), in the number of events per patient (22 ± 32 to 1 ± 3) and in the number of patients with five or more cardiac events from 71% to 10%. The authors conclude that the findings demonstrate that for LQTS patients who continue with syncope or cardiac arrest despite the use of beta blockers, LCSD is a very effective therapy.[52]

Bhandari described 10 patients with LQTS and recurrent syncope or cardiac arrest caused by ventricular arrhythmias that underwent left cardiac sympathetic denervation after failure of high-dose beta-blocker therapy. All patients had a prolonged QT interval at rest (548 ± 51 ms, mean ± SD) and corrected QT interval (QTc) (556 ± 43 ms). The QT interval shortened significantly after surgery, but the QTc interval still remained abnormally prolonged in 9 of 10 patients. On follow-up of 38 months, 8 of 10 patients had recurrent symptoms (cardiac arrest in 3; 1 death), syncope in 4 and presyncope in 6. Symptoms were not controlled with the addition of beta blockers, and resolved with more extensive sympathectomy (3 patients), pacemaker implantation (3 patients) and a cardioverter-defibrillator (1 patient). Only 1 patient remained asymptomatic without drug therapy or pacemaker-defibrillator.[53]

Cardiac pacing

While there are favorable data regarding the efficacy of cardiac pacing in preventing cardiac events in LQTS patients, pacemaker implantation in these patients is usually accompanied by beta-blocker therapy.[48] Thus the therapeutic effects of the two interventions are difficult to separate. A recently published study[54] with prospectively collected data and a retrospective analysis report data on isolated pacemaker therapy in a single family with 60 members affected by mutations in SCN5A (LQT3, Brugada). The authors considered the use of beta blockers a relative contraindication in this family with a strong history of sudden death at night in the presence of sinus bradycardia and bradycardia-dependent QT prolongation. Thirty affected individuals had a pacemaker implanted, with a prophylactic indication in 28 patients, while 2 of the 30 had symptoms (syncope). On follow-up of 4.5 years, none of the patients who had a pacemaker implanted had sudden death, while sudden death occurred in 5 patients among the remaining 30 without a pacemaker. This study, while small and non-randomized, demonstrates a benefit of isolated pacing therapy.

The rationale for the combined therapy approach with beta blockers and pacing was the prevention of pauses and the prevention of polymorphous ventricular tachycardia that might be triggered by increased adrenergic tone. Eldar *et al*.[42] suggested that the best mode of pacing for patients with the LQTS is DDD. The single atrial chamber pacing mode proved to be inadequate, with 5 patients having episodes of AV block. Two patients had syncope due to persistent episodes of 2:1 AV block.

Two pacemaker-programming strategies may be used to prevent post extrasystolic pauses and pause-dependent early afterdepolarizations and torsade de pointes. One method of preventing these pauses is to increase the pacing rate, but there are case reports of tachycardiomyopathy with the need for cardiac transplant on long-term pacing at higher rates.[55] Viskin proposed an alternative method for prevention of torsade de pointes by rate smoothing involving a pause-prevention pacing algorithm.[56]

Clearly there is a need for longer follow-up studies in these small populations with LQTS in order to assess more accurately the relative risk of malignant outcomes such as sudden death or aborted sudden death in patients with defibrillators. Dorostkar *et al*. showed a relatively high failure rate of combined pacing and beta-blocker therapy even in compliant patients (17%).[45]

Implantable cardioverter-defibrillators

In the largest cohort to date, with 37 patients treated with combined therapy with beta blockers and pacing, 28 (76%) compliant patients remained asymptomatic during a 6 year follow-up period. The rate of cardiac events (sudden death, aborted sudden death, appropriate ICD discharge and syncope) was 24% in all patients and 17% in compliant patients. Among the four deaths, there was one patient who died despite combined therapy and good compliance with beta blocker. Two adolescent patients died after discontinuing beta-blocker therapy, while on

combined therapy. The authors recommend "back-up" defibrillator therapy in high-risk noncompliant patients, in whom the risk of death and aborted sudden death was 57%.[45]

Resuscitated sudden death is an indication for ICD implantation in the LQTS patient, and the initial approach for such patients has switched from more conservative therapies in the past few years. The incidence of appropriate ICD discharges in higher risk populations of LQTS patients has been demonstrated to be 60%, at a follow-up of 31 months.[57]

Gene-specific therapy

The current therapeutic strategies for LQTS do not guarantee complete protection from cardiac events. Beta-adrenergic blockade, left cardiac sympathetic denervation, pacing and implantable cardioverter-defibrillators, isolated or in combination, have been shown to significantly decrease mortality when compared to no therapy, but better treatment options will hopefully be available in the near future. Molecular identification of various LQT genes and detailed description of their mutations should lead to the development of gene-specific therapy.[7] There is already important experimental and clinical evidence of the use of drugs and electrolyte infusions to manipulate ion channel activity and thus affect the abnormal repolarization characteristic of LQTS.[50,58–63]

Mexiletine, a Na^+ channel-blocking agent, shortened the QTc in patients with LQT3 related to abnormal Na^+ channels. It had only a modest effect on shortening of the QT interval in patients with other types of LQTS.[60] Elevated potassium concentration stimulates outward HERG potassium current.[64] Based on this finding, Compton *et al*. studied patients with LQT2 syndrome and demonstrated that increasing serum potassium concentration determined significant shortening of the QT interval from 629 to 425 ms.[59] Specific K^+ channel opening agents have also demonstrated promise.[61,62]

While gene-specific therapies for LQTS are effective in shortening the QT interval on the ECG, there are (as yet) no data concerning the clinical outcomes in terms of elimination of ventricular arrhythmias and the associated clinical manifestations of syncope, seizures and sudden death.[7]

All references can be found at the end of the book. See pp. 857–9 for Chapter 49.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Robert M. Hamilton, Joel A. Kirsh, and Gil J. Gross

Supraventricular Arrhythmias

Assessing the evidence

In identifying optimal practice in the management of pediatric arrhythmias, evidence from the literature should be assessed critically. However, many frameworks for the grading of evidence ignore all studies except large, randomized trials. This approach is impractical when assessing best practice for rare conditions such as pediatric rhythm disorders. However, the American Heart Association Committee on Emergency Cardiovascular Care have recently devised a set of evidence-based assessments (Table 50-1) which have been systematically applied to the formation of guidelines for cardiopulmonary resuscitation and emergency cardiac care.[1,2] The advantage of applying this system to recommendations in our limited population of children and young adults is that it allows for "evidence" from animal studies, mechanical studies, extrapolations of data, rational conjecture and historical acceptance of standard practice, with appropriate relative weighting.

Introduction

Supraventricular arrhythmias are defined as abnormal rhythms which require structures above the bifurcation of the bundle of His. They are classically subdivided into reentrant mechanisms, automatic mechanisms, triggered arrhythmias and other or undefined mechanisms. Reentry may be confined to normal structures, or utilize accessory conduction pathways.

Supraventricular arrhythmias in structurally normal hearts

Supraventricular tachycardias (SVT) of any mechanism may occur in grossly structurally normal hearts. Three mechanisms (accessory pathways tachycardias of Wolff, Parkinson and White (WPW) or concealed WPW, atrioventricular node reentrant tachycardia (AVNRT) and atrial ectopic tachycardia (AET)) make up the large majority of SVT in children, with the proportion of each mechanism changing during development (Fig. 50-1).[3] A relatively complete list of mechanisms, their presentations and electrocardiographic findings are presented in Table 50-2.

Reentrant tachycardias usually share a number of common features. They are usually paroxysmal in presentation, unless the tachycardia circuit is so long or the conduction velocity so slow that spontaneous termination (caused by an advancing depolarizing wavefront reaching a retreating line of refractoriness) becomes exceedingly unlikely. Reentrant tachycardias are often initiated by a single premature event, and may be similarly terminated by 1–2 premature events. Reentrant tachycardias should respond to appropriately delivered cardioversion by termination and a return to sinus rhythm, although such terminations can be exceedingly brief, or followed by immediate reinitiation.

Sinus node reentry

Sinus node reentry is a tachycardia of reentrant mechanism occurring in the high right atrium just beneath the superior vena cava with a normal P wave and activation of the high right atrium before the high left atrium.[4] An invasive study of the mechanism of supraventricular tachycardias in 103 children identified sinus node reentry in 10.[5] The sinus node consists of pacemaker cells surrounded by alternate cell types in either a gradient or mosaic model of tissue architecture.[6] These cells are able to drive the surrounding atrial tissue without being suppressed electrotonically, and reentry of excitation is typically prevented by entrance block. Injury to the sinus node area might be expected to result in an increased incidence of sinus node reentry, such as following the Mustard atrial baffle repair of transposition of the great vessels. Sinus node reentry has also been identified in a neonate, and could be terminated by adenosine.[7] Electrophysiological assessment demonstrated a prolonged sinus node recovery time.

Atrial muscle reentry

Atrial muscle reentry can be subdivided into macroreentry and microreentry, based on the ability of gross anatomical mapping techniques to identify a circuit. When a macroreentrant circuit occurs in adults, utilizes the IVC-tricuspid valve isthmus as a critical pathway, and is characterized by typical "P-wave" morphology and cycle length, it is termed atrial flutter. Atrial macroreentrant arrhythmias which occur following surgery for congenital heart disease are now termed intra-atrial reentrant tachycardia (IART) or incisional reentrant atrial tachycardia (IRAT), with the former term being the most accepted (see IART below). Atrial muscle reentry can be acutely converted with appropriately delivered cardioversion, and often with programmed or burst atrial pacing as well. Although most forms of macroreentrant AT are insensitive to adenosine, rarely macroreentrant AT with zones of decremental slow conduction can demonstrate adenosine sensitivity. Adenosine-sensitive AT is usually focal in origin and arises either from the region of the crista terminalis (inclusive of the sinus node).[8]

Table 50-1 Evidence-based assessments of supraventricular arrhythmias

Level 1	Statistically significant RCTs
1A	Meta-analysis of multiple positive RCTs, statistically significant results
1B	One of more positive RCTs, statistically significant results
1C	Meta-analysis with inconsistent but significant results
Level 2	Statistically insignificant RCTs
2A	Meta-analysis of positive RCTs, but not statistically significant
2B	One of more positive RCTs, not statistically significant
2C	Meta-analysis of inconsistent RCTs; not statistically significant
Level 3	Prospective, controlled but not randomized cohort studies
Level 4	Historic, nonrandomized cohort or case–control studies
Level 5	Human case series
Level 6	Animal or mechanical model studies
6A	Animal studies
6B	Mechanical model studies
Level 7	Reasonable extrapolations from existing data; quasi-experimental designs
Level 8	Rational conjecture (common sense); historical acceptance as standard practice

Congenital atrial flutter

The most common presentation of atrial muscle reentry in children with structurally normal hearts is "congenital atrial flutter." In a series of 3383 apparently healthy newborn infants studied in one region of England, one infant had atrial flutter.[9] In a series of 32 newborns or infants with tachycardia, six had atrial flutter.[10] This disorder has been recognized for many decades, and is usually not associated with any obvious cardiac malformation or maternal disease.[11,12] Possible exceptions include an association with maternal lithium use in case reports,[13] an association with persistent primary congenital hypothyroidism in 1/243 cases,[14] and an association with atrial septal aneurism.[15,16] However, a small case–control study did not demonstrate any difference in the incidence of atrial septal aneurisn between patients with or without atrial tachycardia.[17] In addition, an association with apparent concealed accessory pathways was reported in 3 of 9 fetuses/infants presenting with atrial flutter.[18] The atrial cycle length during flutter ranged from 135 to 180 ms (mean 149 ms; mean atrial rate 403 beats/min), and there is usually a 2:1 ventricular response to atrial flutter.[19] Although some infants may respond to medication such as digoxin therapy (7/21 in our experience),[20] conversion of the rhythm should be accomplished more quickly in severely ill infants, by cardioversion if necessary.[21] Heart failure or hydrops fetalis were present in 14/25 of our series.[20] Quinidine and verapamil should be avoided.[12,22] Adenosine is usually ineffective in achieving conversion,[23] but may be helpful for diagnosis.[24] Conversion can be achieved with atrial overdrive pacing,[10] which can now be successfully delivered through esophageal pacing[19] resulting in successful conversion in approximately 71% of cases.[25] Most studies now suggest that chronic therapy is unnecessary and that recurrences are rare.[19,20,26–28] Lisowski and colleagues demonstrated that of the 43 live-born infants diagnosed *in utero*, 12 were still in atrial flutter at birth. Electrical cardioversion was successful in eight of nine patients, and no recurrences occurred beyond the neonatal period. Four patients with fetal flutter and hydrops showed significant neurological pathology immediately after birth (Fig. 50-2).[29]

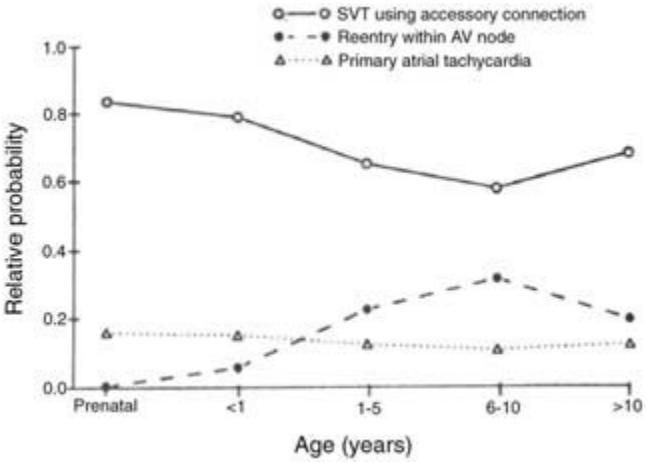

Fig. 50-1 (Reprinted from Ko *et al.*,[3] Copyright (1992), with permission from Excerpta Medica, Inc.)

Fetal atrial flutter

Fetal atrial flutter can be diagnosed by fetal electrocardiography[11] or fetal echocardiography.[30,31] Important advances in ultrasound technology, such as color coded M-mode Doppler[32] and tissue color Doppler ultrasound have greatly added to the accuracy of rhythm classification in fetal arrhythmias (Fig. 50-3). If cordocentesis is considered warranted, adenosine administration may be helpful in confirming the diagnosis.[33] One case report associates the presence of prenatal stenosis of the ductus arteriosus with fetal atrial flutter.[34] Another identifies idiopathic dilatation of the right atrium as an association.[35]

Jaeggi *et al.* published their own case series and a review of the literature in 1998,[37] the results of which are summarized in their table. Atrial flutter accounted for one-third of fetal tachycardias in their series, as in others.[38] The most consistent finding in their detailed review was the absence of recurrence of atrial flutter in follow-up, as confirmed by others (Fig. 50-4).[29]

Fetal atrial flutter is frequently associated with fetal heart failure (hydrops fetalis), death[39,40] or adverse neurological outcome,[29] although in one study the incidence of hydrops fetalis was no higher with atrial flutter than with other mechanisms of fetal tachycardia.[41] Fetal atrial flutter has been successfully treated by maternal administration of digoxin,[42,43] although this is less successful in achieving conversion than for other fetal supraventricular tachycardias.[40] Both digoxin and flecainide appear to have some success in the therapy of atrial flutter, with small case series suggesting combined efficacy in the face of hydrops fetalis,[44] and no adverse effects in most series.[45] Failure of digoxin may be related to differential digoxin levels attained between mother and fetus,[46] particularly in the face of placental effects of hydrops fetalis.[47] Sotalol has been effective at achieving conversion to sinus rhythm in eight of ten fetuses with atrial flutter.[48] As an alternative, intraperitoneal administration of antiarrhythmic drugs to the fetus in fetal tachyarrhythmias with severe hydrops fetalis has been achieved, with

Table 50-2 Supraventricular arrhythmias in structurally normal hearts: mechanisms, their presentations and electrocardiographic findings

Mechanism	Diagnosis	Presentation	Resting ECG	AV relation	PR or RP interval	P wave axis
Reentry	Sinus node reentry	Paroxysmal	Normal	1:1 or AV block	Normal PR	Normal
Reentry	Atrial muscle reentry	Paroxysmal	Normal	Variable or 2:1 AV block	Often 1° AVB if 2:1	Variable, Often – ve in 2,3,AVF
Reentry	AV node reentry	Paroxysmal	Normal	Usually 1:1	P under QRS	-ve in 2,3,AVF if visible
Reentry	His bundle reentry	Paroxysmal	Normal	1:1 or VA block	Short RP if 1:1	-ve in 2,3,AVF
Reentry with accessory pathway	WPW	Paroxysmal	Short PR and delta	1:1	Short RP (> 80 ms)	Variable
Reentry with accessory pathway	Concealed WPW	Paroxysmal		1:1	Short RP (> 80 ms)	Variable
Reentry with accessory pathway	Mahaim	Paroxysmal	Normal PR and delta	1:1	Short RP (> 80 ms)	-ve in 2,3,AVF
Reentry with accessory pathway	PJRT	Incessant	Normal	1:1	Long RP	-ve in 2,3,AVF
Automatic	AET	Incessant	Normal	1:1 or AV block	Often 1° AVB	Normal with P" in V2 or LAR
Automatic	JET	Incessant	Normal	1:1 or VA block	Short RP if 1:1	-ve in 2,3,AVF if 1:1
Triggered	NPJT	Incessant	Normal	VA block	VA dissociated	Normal
Other or unknown	CAT (MAT)	Incessant	Normal or 1°AVB	Variable AV block	N/A	Multiple (≥ 3) P morphologies
Other or unknown	AF	Incessant or paroxysmal	Normal	Variable AV block	N/A	No isoelectric baseline

PJRT, permanent form of junctional reciprocating tachycardia; AET, atrial ectopic tachycardia; JET, junctional ectopic tachycardia; NPJT, nonparoxysmal junctional tachycardia; CAT, chaotic atrial tachycardia; MAT, multifocal atrial tachycardia; AF, atrial fibrillation.

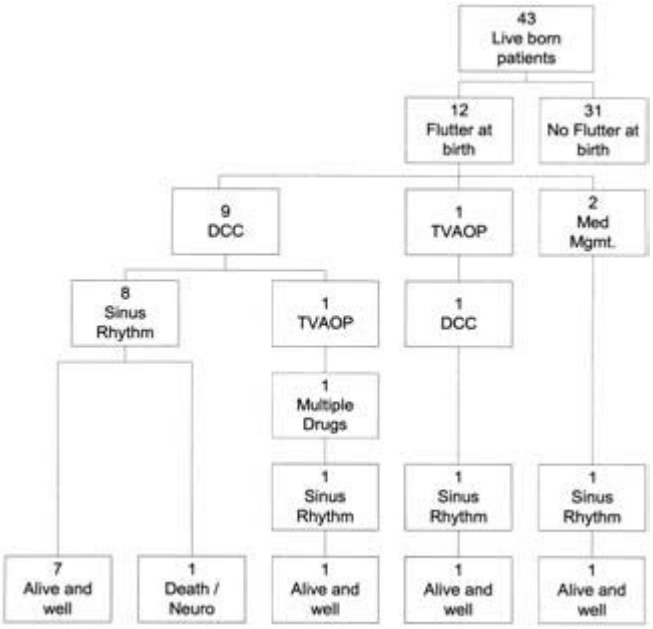

Fig. 50-2 (Reprinted from Lisowski *et al.*,[29] Copyright (2000), with permission from The American College of Cardiology Foundation.)

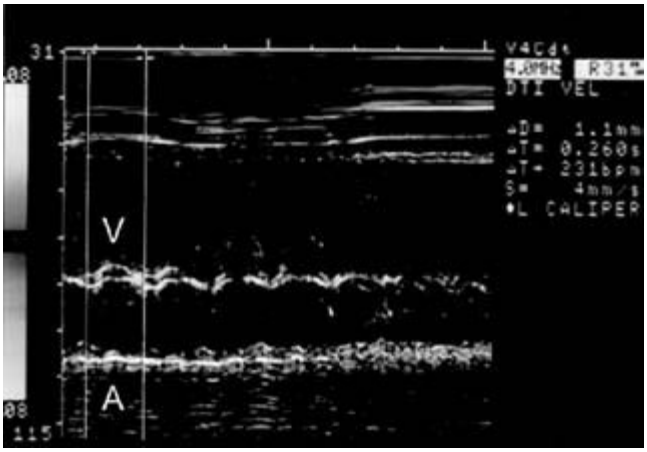

Fig. 50-3 Tissue color Doppler imaging. (Reprinted from Cotton,[36] Copyright (1997), with permission from Lippincott Williams & Wilkins.)

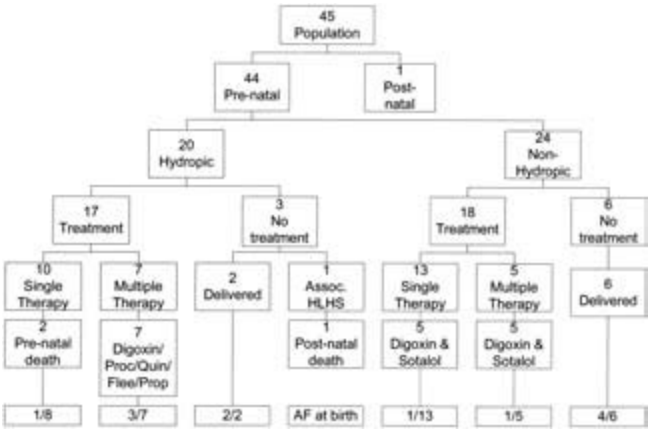

Fig. 50-4 (Reprinted from Lisowski *et al.,*[29] Copyright (2000), with permission from The American College of Cardiology Foundation.)

effective block of AV conduction.[49] In severe cases, drugs such as amiodarone can be administered by a combination of routes (intravenous, intraperitoneal and transplacental) to achieve conversion.[50] Protocols for the treatment of fetal tachycardias in general and fetal atrial flutter in particular continue to evolve.[51]

Atrioventricular node reentry

Paroxysmal reciprocating tachycardias of the AV node are characterized by prolongation of the P-R interval in the beat immediately preceding the tachycardia, and are generally accepted as being related to longitudinal dissociation of the A-V node.[52] The exact site of the reentrant circuit in AV nodal reentry remains controversial. While recent ablative techniques suggest that the atrium is required, other explanations for these interpretations are available. The AV node is a highly anisotropic structure and extends through Koch's Triangle. Data suggesting the atria are not necessary include the presence of AV dissociation during supraventricular tachycardia (SVT).[53]

Basic investigations in atrioventricular (AV) node reentry identify a dual AV conduction system, and atrial echo beats occurred when the refractory period of the slow conduction pathway is shorter than the fast pathway. Slow–fast AV node reentry (anterograde conduction over the slow pathway and retrograde conduction over the fast pathway) occurs most frequently. The fast–slow and intermediate varieties are much less common. AV nodal reentrant tachycardia can be cured surgically using direct AV nodal dissection (or perinodal cryoablation),[54] although surgery has largely been supplanted by catheter-delivered AV nodal modification. A high (> 95%) cure rate occurs with radiofrequency ablation with experienced electrophysiologists. Most electrophysiologists prefer the posterior approach, which results in absent or very poor conduction over the slow AV node pathway: the PR interval is minimally changed. This approach is highly successful for all three forms of AV node reentry and associated with a less than 1–2% incidence of heart block in most experienced laboratories.[55]

Atrioventricular node reentrant tachycardia is a moderately frequent cause on SVT in children, occurring in 8/33 children studied invasively by Gillette,[56] and in 25/103 children in a subsequent study.[5] However, dual A-V nodal pathways alone are common and may be a benign finding in arrhythmia-free children with heart disease.[57] Esophageal or intracardiac electrophysiologic studies can usually differentiate AV node reentry from other forms of SVT. The V-A interval was < 70 ms in 11/12 patients with AV node reentry versus more than 70 ms in all 16 patients with accessory pathway tachycardias.[58] Wolff and colleagues described atypical AV node reentry in two children in 1978. This unusual form of atrioventricular (A-V) nodal utilized a fast pathway for anterograde conduction and a slow pathway for retrograde conduction, the reverse of the usual form of A-V nodal reentrant tachycardia. In both cases the retrograde effective refractory period of the fast pathway was longer than that of the slow pathway, resulting in the establishment of this unusual reentry circuit. The patients had a superior P axis with a P-R interval shorter than the R-P interval during tachycardia.[59]

Multiple series of arrhythmia surgeries in children occurred in the era before radiofrequency catheter ablation, and most of these included children with AV node reentry tachycardia. The total efficacy of surgical treatment for all tachycardias was 97%[60] and 2/2 (100%).[61]

The pediatric RF ablation registry has been tracking procedures across multiple participating institutions for nearly a decade. Initial success rates for ablation of atrioventricular-node reentry (63 of 76 procedures) was 83%[62] In a single institution, Van Hare *et al*. demonstrated success in 15/17 children (88%).[63] By 1997, the pediatric RF ablation registry reported an immediate success rate of 96% for AVNRT, with a 71% freedom from recurrence at 3 years (Fig. 50-5).[64]

Bundle branch reentry

Based on our definition of SVT, bundle branch reentry may be defined as supraventricular if its circuit crosses the bifurcation of the bundle of His, or ventricular if it is entirely confined to one fascicle.[65] In either case, the features typically show a bundle branch block pattern of broad QRS, and a specialized conduction system potential preceding surface activation on intracardiac electrophysiologic study. Bundle branch reentries typically occur in several distinct patterns: They may be associated with dilated or ischemic cardiomyopathy. We have studied two such patients with dilated cardiomyopathy. One was treated with ablation of the bundle branch, but it recurred or the patient developed an alternate ventricular tachycardia several months later. The other was successfully treated with ventricular overdrive pacing through a permanent implantable defibrillator for

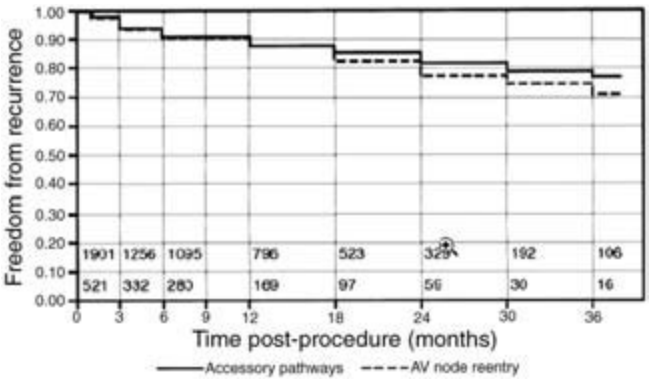

Fig. 50-5 Recurrence data for PSVT (Reprinted from Kugler *et al.*,[64] Copyright (1997), with permission from Excerpta Medica, Inc.)

many months before going on to receive a heart transplantation for worsening heart failure. In addition to bundle branch reentry in dilated cardiomyopathy which usually involves both bundle branches, tachycardia within the right bundle branch has only rarely been described.[65] Alternately, tachycardia may occur in a right bundle branch block, left axis deviation pattern (left posterior fascicular tachycardia) which is typically verapamil sensitive. This tachycardia has been described in multiple reports since 1981 and is often referred to as Belhassen's tachycardia.[66–69] This tachycardia may cause myocardial dysfunction in children if incessant, but usually responds to verapamil therapy.[70–73] In a small series of 8 patients, 5 patients eventually resolved their tachycardia spontaneously. Radiofrequency ablation was successful in 2 of the 3 patients with persisting tachycardia.[74] Ablation is usually successful, particularly when mapping is guided by the presence of a presystolic Purkinje potential.[75]

Wolff–Parkinson–White syndrome

In 1930, Wolff, Parkinson, and White described a series of young patients who had a bundle branch block pattern on electrocardiogram (ECG), a short PR interval, and paroxysms of tachycardia. Case reports began appearing in the literature in the late1930s and early 1940s, and the term Wolff–Parkinson–White (WPW) syndrome was coined in 1940. In 1943, the existence of an accessory connection between atria and ventricles was confirmed, which is about 50 years after Kent's description of myocardial fibers that were believed to conduct from atria to ventricle.

The term preexcitation was first published by Ohnell in 1944 (the same year that the term delta wave was coined); "preexcitation indicates an additional excitatory spread in the ventricles of the heart, coupled to auricular excitation." WPW syndrome is not the only form of preexcitation, but it is the most common. Initially, through the surgical treatment of WPW syndrome and, now, in the era of radiofrequency (RF) ablation, understanding of the pathophysiology of WPW syndrome has become refined in the wake of these elegant descriptions.

The first surgical division of an accessory pathway was performed at Duke University by Will C. Sealy, MD, in 1968. The first catheter ablation was reported in 1983, using DC energy; this was followed by the first successful RF ablation reported in 1987.

The underlying defect in WPW syndrome is the presence of an accessory pathway (AP) consisting of a myocardial connection at the atrioventricular (AV) junction. These are believed to be residual connections from the formation of the AV junction. The primary feature differentiating WPW syndrome from other AP-mediated supraventricular tachycardias (SVTs) is the ability of the AP to conduct antegradely (i.e. from atrium to ventricles) and retrogradely. The presence of this AP allows a reentrant tachycardia circuit to be established. In orthodromic SVT, the conduction is through the AV node to the ventricles, then back to the atria via the AP. Because the AP can conduct in both directions, it is also possible to experience antidromic tachycardia, in which the conduction from atrium to ventricle occurs via the AP, resulting in a broad complex tachycardia.

The presence of an antegrade AV connection also allows atrial arrhythmias to be conducted to the ventricles without passing through the AV node. Patients with WPW syndrome can more frequently develop atrial fibrillation, which can potentially be conducted to the ventricles rapidly (see Mortality/Morbidity). The different patterns of preexcitation have produced various classification systems. Classification by type is largely obsolete, and, currently, classification by anatomic location of the AP is used. The most common AP location is at the left free wall.

The incidence of the WPW pattern is unknown but is estimated to be 1–2 cases per 1000. This may be an underestimate, as it often represents an asymptomatic ECG finding. The incidence of newly diagnosed cases of WPW syndrome is approximately 4 per 100 000 population per year.

The incidence of sudden cardiac death (SCD) in WPW syndrome is approximately 1 in 100 symptomatic cases when followed for up to 15 years. Although relatively uncommon, SCD may be the initial presentation in as many as 4.5% of cases.

The cause of SCD in WPW syndrome is rapid conduction of atrial fibrillation (AF) to the ventricles via the AP, resulting in ventricular fibrillation (VF). AF develops in one fifth to one third of patients with WPW syndrome; the reasons for this and the effects of AP ablation on its development are unclear.

Certain factors increase the likelihood of VF, including rapidly conducting APs and multiple pathways. Cases also have been reported in association with esophageal studies, digoxin, and verapamil. A few reports document spontaneous VF in WPW syndrome, and SVT may degenerate into AF, thus leading to VF; however, both scenarios are rare in pediatric patients.

The morbidity in WPW syndrome results predominantly from AV reciprocating SVT. Even in the absence of VF, syncope is an occasional presenting complaint. However, in most patients, the SVT is well tolerated and not life threatening. If a patient experiences incessant tachycardia, cardiomyopathy may develop.

A male-to-female ratio of approximately 2:1 has been documented in some series. In other series, the syndrome was found to be more frequent in men (1.4 per 1000) than in women (0.9 per 1000). A recent Belgian study indicates a 3.5-fold higher prevalence of WPW in men than in women.

WPW syndrome may present at any age, with many cases presenting in infancy. A bimodal age distribution is observed in pediatric patients, with a second peak in school-aged children.

In several series, the incidence of associated congenital heart disease (CHD) is reported to be as high as 30%, most commonly Ebstein anomaly of the tricuspid valve and "corrected" transposition of the great arteries {S,L,L}. A genetic locus linking hypertrophic cardiomyopathy to WPW syndrome has been found on chromosome 7.

The findings of the underlying condition often become apparent only after the SVT has been terminated, although the hemodynamic consequences may be poorly tolerated in the presence of CHD.

APs are considered congenital phenomena, which are related to a failure of insulating tissue maturation within the AV ring. A proportion of patients with preexcitation may have a genetic predisposition. One example of such a predisposition is the association of preexcitation with a certain hypertrophic cardiomyopathy locus on chromosome 7.

Preexcitation can be created surgically, such as in certain types of Bjork modifications of the Fontan procedure, if atrial tissue is flapped on to and sutured to ventricular tissue. Certain tumors of the AV ring, such as rhabdomyomas, also may cause preexcitation.

Once identified and appropriately treated, WPW syndrome is associated with an excellent prognosis, including the potential for permanent cure through RF catheter ablation.

Concealed Wolff–Parkinson–White syndrome

Gillette studied 35 children with supraventricular tachycardia (SVT) and identified 8 with manifest or concealed "lateral anomalous pathway."[56] He describes these "concealed anomalous cardiac conduction pathways" as a frequent cause of supraventricular tachycardia. In a follow-up study of 103 children with SVT, a bypass tract was present in 51 and was concealed in 18.[5] These tachycardias are reentrant in nature and are included in the mechanisms underlying atrioventricular junctional tachycardias and atrioventricular reciprocating tachycardias. They are frequently initiated by a premature atrial or ventricular contraction,[76] and are a common cause of neonatal tachycardias.[77,78] Patients may have enhanced atrioventriicular conduction through the AV node facilitating tachycardia. In addition, a prolonged ventriculoatrial conduction time as demonstrated by a longer RP interval during tachycardia identifies infants whose SVT is more difficult to control.[79] The pathways may span the atrioventricular rings at any location, and can be abolished by surgical division along these areas.[80] The diagnosis can be verified by an esophageal atrial electrogram (AEGV) demonstrating a V-AEGM time of greater than 70 milliseconds, compared to V-AEGM times of less than 70 milliseconds in most cases of AV nodal reentry.[58] In addition to recording the AEGM, esophageal pacing can be used to initiate and terminate tachycardia.[81] A cycle length change of tachycardia when a bundle branch pattern occurs suggests that the pathway is ipsilateral to the bundle branch morphology.[82]

Several techniques have been used to ablate these pathways over the last two decades, including surgical division or cryoablation, DC shock catheter ablation,[83] radiofrequency catheter ablation[84,85] and catheter-delivered cryoablation.[86]

Permanent form of AV reciprocating tachycardia

In 1975, Coumel characterized the permanent form of junctional reciprocating tachycardia (PJRT), an entity which also bears his name (Coumel's tachycardia)[52,87] and is one of several mechanisms for incessant tachycardias in children.[88] Three years later, Gallagher demonstrated a number of features which characterize the mechanism of this tachycardia. The retrograde impulse was able to penetrate the atrium in two different areas, one near the region of the recorded His potential and the other near the orifice of the coronary sinus. Retrograde conduction persists after the creation of complete antegrade heart block (suggesting the existence of an accessory ventriculo-atrial connection). This provided supporting evidence that PJRT as an entity was likely different than atypical AV node reentry, which may present with a similar electrocardiogram. Para-Hisian pacing can also frequently separate PJRT from tachycardia mechanisms which do not rely on a septal accessory pathway.[89,90] The retrograde conduction has decremental properties suggesting that an accessory ventriculo-atrial nodal structure may be the underlying substrate of this arrhythmia.[91] Touboul described similar characteristics, as well as the surface ECG pattern of a relatively slow tachycardia, negative P waves in leads II, III and AVF, isobiphasic or negative P waves in the left precordial leads and a normal PR interval with long RP interval. The tachycardia started without lengthening of the PR interval or preceding extrasystoles.[92] An accessory pathway with a long conduction time is usually located in the posterior pyramidal space and provides the retrograde limb of the reentry circuit.[93] Such pathways conduct in a unidirectional retrograde fashion only, and have been demonstrated to be adenosine sensitive.[94] Other pathway locations along the AV groove and interatrial septum may occur,[95] as may multiple pathways.[96] P wave morphology may provide a clue as to PJRT pathway location.[97–99] Surgical ablation was a relatively successful therapy for patients presenting with PJRT in that era.[100] It could often be accomplished with a closed chest dissection, although occasionally an approach on cardiopulmonary bypass was required.[101] However, soon after this catheter ablation was applied,[102,103] and although early procedures were associated with complications of complete heart block or death,[102,104–107] the technique was eventually refined to utilize a radiofrequency energy source[108–111] and has become the standard therapy,[112,113] even in young children.[114,115] Medical therapy with amiodarone may be effective, and may allow for tachycardia-induced myocardial dysfunction to improve, but the tachycardia typically recurs with cessation of therapy.[116] Nevertheless, some authors recommend this conservative approach in infants and small children.[117,118]

The differential diagnosis of PJRT includes other accessory pathways with prolonged retrograde conduction times, but PJRT pathways should also show a decremental type of conduction and absence of antegrade conduction.[119,120] A subgroup of patients with slow or infrequent bursts of tachycardia can be identified and may not need treatment.[117]

Tachycardia-induced cardiomyopathy

The relatively slow tachycardia rates and normal PR interval of PJRT may occasionally be mistaken for sinus tachycardia if attention is not paid to the P wave morphology. In addition, prolonged incessant tachycardia may lead to a tachycardia-induced cardiomyopathy in these children. Occasional patients have been misdiagnosed as primary cardiomyopathy with sinus tachycardia and have been listed for transplantation.[121]

The majority of patients with PJRT and tachycardia-induced cardiomyopathy can be cured with radiofrequency ablation, following which their myocardial dysfunction usually resolves within approximately 6 months.[122–125] In one case, QT prolongation appeared to be a consequence of this tachycardia-induced cardiomyopathy, and an episode of torsades de pointes occurred following rate reduction by terminating the retrograde limb of tachycardia with RF ablation.[126]

Fetal PJRT

PJRT has been documented to occur *in utero*, where a long RP interval can be documented by measuring the ventriculo-atrial time interval on M-mode echocardiography.[127] Medical treatment *in utero* with amiodarone can be effective at reversing myocardial dysfunction.[128]

Mahaim tachycardias

The original descriptions of Mahaim were nodoventricular and fasciculoventricular fibers inserting within the right ventricle. It is now recognized that these fibers can also insert directly into the specialized conduction system of the right ventricle (right bundle branch). More importantly, it is now recognized that these structures most commonly arise from atrial tissue along the right atrioventricular ring. These pathways demonstrate decremental conduction, retrograde block and adenosine sensi-

tivity. It may be that "nodoventricular" fibers actually arise from the area of the slow pathway insertions to the AV node.

Mahaim fiber tachycardia typically involves antegrade conduction over this pathway with a resultant left bundle branch block and left axis deviation QRS morphology. The retrograde conduction is usually over the AV node, but occasionally over a second accessory pathway. In addition, Mahaim fibers may act as a bystander pathway to AV node reentry, not intrinsically being involved in the tachycardia but resulting in a broad-complex QRS morphology. A number of mapping strategies may be employed to localize and ablate Mahaim fibers participating in tachycardias. Atrial pace-mapping, introduction of late-coupled premature beats, "bump"-mapping and identification of accessory pathway potentials above or below the AV ring or deep in the right ventricular free wall have all been used with success.

Atrial ectopic tachycardia

Background: Atrial ectopic tachycardia (AET) is a rare arrhythmia; however, it is the most common form of incessant supraventricular tachycardia (SVT) in children. AET is believed to be secondary to increased automaticity of nonsinus atrial focus or foci. This arrhythmia, which also is known as ectopic atrial tachycardia or automatic atrial tachycardia, has a high association with tachycardia-induced cardiomyopathy. AET often is refractory to medical therapy and usually is not responsive to direct current (DC) cardioversion.

The diagnosis of AET is based on the presence of a narrow complex tachycardia (in the absence of aberrancy or preexisting bundle branch block) with visible P waves at an inappropriately rapid rate. The rates range from 120–300 and are typically higher than 200 bpm, although physiologic rates may be observed. The P wave axis is usually abnormal. Onset of the tachycardia occurs with a P wave identical to the subsequent P waves. The tachycardia may exhibit a "warming up," which refers to a progressively shortening P-P interval for the first few beats of the arrhythmia. Similarly, a "cool-down" period may be observed at its termination. First-degree atrioventricular (AV) block is typical and second-degree AV block is common. The tachycardia cycle length and degree of AV block are influenced by the autonomic tone.

Spontaneous depolarization is a phenomenon of automatic myocardium. The sinus node is usually the pacemaker of the heart because it has the most rapid spontaneous rate of firing. A small cluster of cells with abnormal automaticity is presumed to be responsible for AET. The conduction spreads from this cluster to the surrounding atrium and to the ventricles via the AV node. A conduction delay at the AV node often occurs, with most patients demonstrating first-degree AV block and some showing second-degree block.

Because AET often is incessant, tachycardia-induced cardiomyopathy is commonly observed. While the underlying mechanism of the development of cardiac dysfunction in the setting of chronic arrhythmias is unknown, numerous reports have documented improved cardiac function following ventricular rate control and treatment of the arrhythmia.

Although the exact incidence is unknown and few large series exist, AET is reported to comprise 5–10% of pediatric SVTs. Estimates of the incidence of pediatric SVTs vary greatly, but AET likely occurs with an incidence of approximately 1 in 10 000 children.

Tachycardia is generally well tolerated. Syncope is unusual, and cardiac arrest is rare, except when encountered as a complication of treatment. Tachycardia-induced cardiomyopathy is the most significant sequel of AET and may be insidious. The time it takes to develop is dependent on the rate and duration of the tachycardia, but dilatation may be present on initial presentation. This also can be reversed with successful treatment of the arrhythmia.

The arrhythmia is observed predominantly in infants and children; this accounts for a peak of 11–16% of tachycardias for which a mechanism is determined in young childhood. The adult form of AET may have a different etiology and natural history than the pediatric form.

AET is one of the incessant tachycardias, which may become associated with myocardial dysfunction if the average ventricular rate remains elevated over a long term.

Several reports have documented the spontaneous remission of AET in the pediatric population and in young adults. This may occur in as many as one third of patients following withdrawal of medication.[129]

Patients with AET should be monitored by a cardiologist. RF ablation can be curative and performed with a high degree of success, a low complication rate, and a low recurrence rate.

Junctional ectopic tachycardia

Background: Junctional ectopic tachycardia (JET) primarily occurs in two forms; idiopathic chronic junctional ectopic tachycardia is observed in the setting of a structurally normal heart, and transient postoperative junctional ectopic tachycardia occurs following repair of congenital heart disease. In addition, nonparoxysmal junctional tachycardia, which is a related but rare pattern of arrhythmia, can be observed in the setting of digoxin toxicity. JET is characterized by tachycardia for a person's age, which is being driven by a focus within or immediately adjacent to the atrioventricular (AV) junction of the cardiac conduction system (i.e. AV node–His bundle complex), but it does not have the features associated with reentrant tachycardia (e.g. AV node reentry). The tachycardia does not respond to a single extrastimulus and does not convert with programmed stimulation or cardioversion. The tachycardia may or may not have ventriculoatrial (VA) dissociation. Administration of adenosine results in VA dissociation without termination.

The pathophysiology of JET is unclear. Rare case reports have suggested that JET may be associated with progression to complete AV block. This does not appear to be the case in postoperative JET and has not been the author's experience in the rare cases of idiopathic JET. As implied by the synonym junctional automatic tachycardia, the mechanism may be automaticity. Others have suggested that triggered activity is responsible for this disorder.

The location of the responsible tissue probably is truly "ectopic" to the primary conduction pathway of the AV junction because JET has been treated successfully by the application of radiofrequency catheter lesions without the production of AV block. Junctional acceleration, albeit at a lesser rate than typical JET, is a recognized phenomenon during and following radiofrequency energy delivery for modification of slow pathway conduction in the therapy of AV node reentry.

Histamine, eosinophil cation protein, or other products of mast cell, eosinophil, or basophil degranulation that are liberated in response to cardiopulmonary bypass have been impli-

cated in the genesis of transient postoperative JET. The relative levels of various cytokines also may play a role. Low magnesium levels have been noted in children who develop JET following cardiopulmonary bypass surgery.

In one series, postoperative JET was identified in 7.5% of young patients undergoing Fontan procedures. In another series, postoperative JET requiring intervention was identified in 1.5% of infants undergoing the arterial switch procedure. JET is one of the most rare forms of supraventricular tachycardia in infants.

Postoperative JET usually occurs at an extremely vulnerable period following cardiac surgery, when nodal inflammation and/or ischemia may be present and ventricular function is often diminished. The additional insults of poor ventricular filling because of tachycardia and the loss of AV sequential contraction are considered to contribute significantly to morbidity and mortality. Congenital JET is an incessant tachycardia that usually results in tachycardia-induced cardiomyopathy.

Congenital JET is presumed to be present from birth but may not be identified until months or years later. Postoperative JET most commonly occurs in younger patients but also is known to occur in teenagers and adults following cardiopulmonary bypass surgery.

Congenital JET appears to be a chronic and unremitting condition. Curative attempts with radiofrequency catheter ablation therapy are probably warranted in patients with uncontrolled JET or if their size and age is sufficient to minimize procedural risks. Nevertheless, permanent AV block is a significant potential risk in the ablation of congenital JET.

Nonparoxysmal form of junctional tachycardia

The nonparoxysmal form of junctional reciprocating tachycardia is an extremely rare form of supraventricular tachycardia which may be seen clinically in significant digitalis toxicity. For this reason, it is suspected to be a triggered arrhythmia. Electrocardiographically it is characterized by a relatively slow, narrow-complex tachycardia with VA dissociation (Fig. 50-6).[130]

Chaotic atrial tachycardia

Chaotic atrial tachycardia has been defined as an irregularly irregular atrial tachycardia with three or more P wave mophologies and periods of isoelectric baseline (thus differentiating it from atrial fibrillation).[131] An adult disease, multifocal atrial tachycardia, has some similarities. Farooki and Green described multifocal atrial tachycardia in two neonates in 1977, and suggested that this was the first description of the entity in children,[132] although a number of prior reports existed.[133–137] The term "chaotic" is a general description of the irregular irregularity of both the atrial rhythm and its ventricular response, rather than a mathematical chaos in the rhythm, which has not so far been demonstrated.

Chaotic atrial tachycardia may occur in young children in isolation, in association with respiratory disease, or in association with specific entities such as Costello syndrome. One of the 9 patients described by Liberthson and Colan had bronchopulmonary dysplasia,[138] and in several patients with atrial tachycardias and respiratory syncytial virus infection, chaotic atrial tachycardia was documented.[139] Chaotic atrial tachycardia appears to be the typical arrhythmia of Costello syndrome.[140]

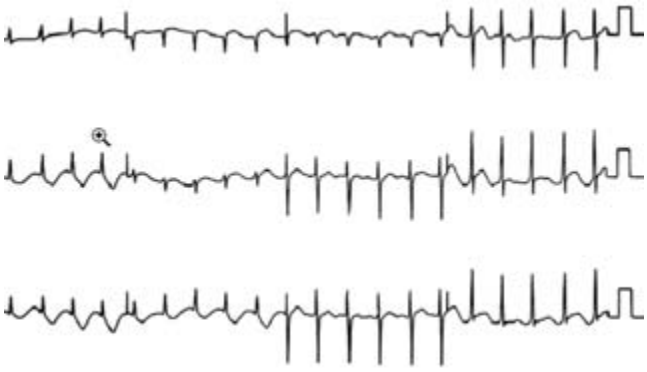

Fig. 50-6 Nonparoxysmal form of junctional tachycardia in a digoxin-toxic patient. (Reprinted from Ma *et al.*,[130] Copyright (2001), with permission from Elsevier.)

Atrial fibrillation

Atrial fibrillation has been a recognized arrhythmia in children for many years,[141,142] albeit rare in Europe and North America. Atrial fibrillation is more common in patients affected by rheumatic mitral valve disease, either primarily or following valve replacement.[143–145] Radford and Izukawa described a large series of 35 children identified in Toronto over 22 years.[146] The age of onset ranged from 1 day to 19 years (average, 8 years). Associated cardiac conditions were severe rheumatic mitral regurgitation (3 cases), cardiomyopathy (5), atrial tumors (2), infective endocarditis (1), paroxysmal atrial tachycardia of infants (4), idiopathic paroxysmal atrial fibrillation (1), Marfan's syndrome with mitral regurgitation (1), endocardial fibroelastosis (1), and structural congenital heart malformations (17). Surgical correction of congenital heart lesions was directly related to the development of atrial fibrillation in 14. The atrial fibrillation was paroxysmal or transient in 21 patients and persistent in 14. Digoxin was used in all cases and cardioversion attempted in ten. No patient was given anticoagulants in this series, and three children had cerebral emboli with residual defects. Within congenital heart disease patients, atrial fibrillation is frequently associated with severe systemic AV valve stenosis or insufficiency.[147]

The prolonged presence of an atrial septal defect is associated with the development of atrial flutter and atrial fibrillation. Patients who have delayed closure of atrial septal defects well into adulthood are more prone to these events.[148] Mitral valve insufficiency is a frequent associated finding. For those who have already developed atrial fibrillation or have a high risk of developing atrial fibrillation following surgery, performance of a Cox/Maze III procedure is a reasonable consideration at the time of repair.[149]

Atrial fibrillation can occur in children in the absence of obvious congenital or acquired structural heart disease.[150] Frequently, this has been reported as a familial occurrence in association with bradycardia and conduction disturbances.[151–154] Specific genetic defects predisposing to atrial septal defects and conduction system disease have been identified, as has a chromosomal locus for isolated familial atrial fibrillation.[155]

In the fetus and neonate, AF is almost always associated with an accessory AV connection. In this setting it is postulated that rapid AV reentry degenerates into AF; the natural history favors spontaneous resolution of tachycardia during the first year of

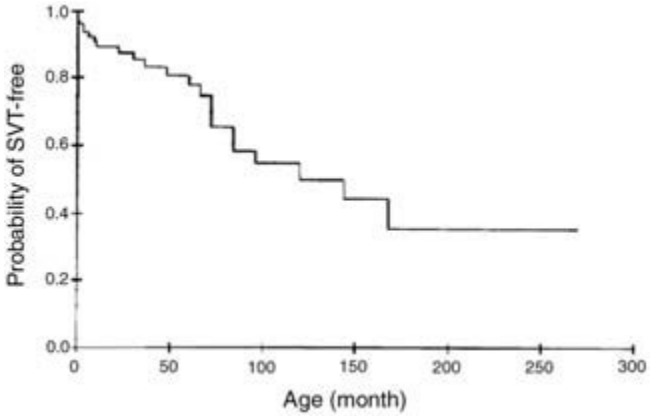

Fig. 50-7 Actuarial curve for the probability of being free from supraventricular tachycardia in 101 RAI patients. (Reprinted from Wu *et al.*,[159] Copyright (1998), with permission from The American College of Cardiology Foundation.)

life. A similar mechanism has been proposed for development of AF during paroxysmal supraventricular tachycardia in adolescents. Atrial fibrillation has been reported in association with dilated, restrictive and hypertrophic cardiomyopathies.

Supraventricular arrhythmias associated with structural heart disease

Atrial isomerism

Wren and colleagues reviewed electrocardiograms from 126 consecutive patients with atrial isomerism. Of 67 patients with left isomerism, 49 had sinus rhythm, 8 nodal rhythm and 10 atrioventricular (AV) block. Fifty-eight of 59 patients with right isomerism had sinus rhythm. Complete AV block was significantly more frequent in association with AV septal defect in left isomerism (5 of 45 patients) than in right isomerism (0 of 47 patients, $P = 0.049$). The P-wave axis was superior in 49% of patients with left isomerism. A significant shift of P-wave axis (> 90°) was seen on a subsequent electrocardiogram in 14 of 44 patients (32%) with left isomerism and 2 of 16 (13%) with right isomerism. Ambulatory electrocardiographic monitoring was performed in 17 patients. Based on these assessments, significant arrhythmias appeared to be rare, and did not appear to influence the natural history or affect the outcome of surgery.[156]

Momma and colleagues assessed the 15-lead electrocardiograms of 50 patients with left isomerism. In left isomerism, atrial rhythm with constantly normal P-wave axis was exceptional and the presence of atrial rhythm with abnormal P-wave axis was the rule. Slow atrial rates below the second percentile were observed in 50%, either transiently and recurrently (in 40%), or persistently (in 10%), and were associated with junctional escape in 42%. The number of patients with slow atrial rate increased with age. In right isomerism, multiple atrial rhythms were also frequent, but slow atrial rhythms was present in only 4%. Multiple atrial rhythms or bradycardia associated with junctional escape were rare in the group of patients with congenital heart disease and situs solitus. They concluded that multiplicity and progressive slowing of the atrial rhythm are characteristic in patients with left isomerism.[157] Wu documented Mahai-like pathways in two patients with left atrial isomerism.[158]

Wu and colleagues reviewed the prevalence and mechanism of supraventricular tachycardia in patients with right atrial isomerism. From 1987 to 1996, a total of 101 patients (61 male, 40 female) and four fetuses were identified with right atrial isomerism, with a median follow-up duration of 38 months. Supraventricular tachycardia was documented in 25 patients (24.8%) and one fetus (25%), with the age at onset ranging from prenatal to 14 years (median = 4 years). Actuarial analysis revealed that the probability of being free from tachycardia was 67% and 50% at 6 and 10 years of age, respectively. These tachycardias were converted by vagal maneuvers, verapamil, propranolol, digoxin, procainamide or rapid pacing. Seven cases had received electrophysiological studies, with reciprocating AV tachycardia induced in five and echo beats in one. The tachycardia in three patients was documented as incorporating a posterior AV node conducting in the antegrade direction, and an anterior or a lateral AV node conducting in the retrograde direction. Successful radiofrequency ablation was performed in two patients (Fig. 50-7).[159]

Cheung and colleagues also assessed that the conduction system in right atrial isomerism may be complicated by the presence of paired atrioventricular nodes. Symptomatic cardiac arrhythmia occurred in 15 of 85 patients (18%); 11 of the 15 patients had supraventricular tachycardia, and 1 patient each had atrial tachycardia, atrial flutter, ventricular tachycardia, and congenital complete heart block. The arrhythmias occurred before surgery in 4 patients, early after surgery in 5 patients, and late after surgery in 6 patients. Although 3 of the 7 patients who died suddenly had a history of symptomatic arrhythmia, arrhythmia was the documented cause of mortality in only 1 of the 32 fatalities (3.1%). Freedom from arrhythmia at 1, 5, 10, 15, and 20 years was 93% ± 3%, 86% ± 4%, 80% ± 6%, 73% ± 9%, and 48% ± 15% (mean ± SE), respectively (Fig. 50-8). No risk factors for symptomatic arrhythmia were identified by means of logistic regression. They concluded that although symptomatic cardiac arrhythmias are not uncommon, they do not seem to

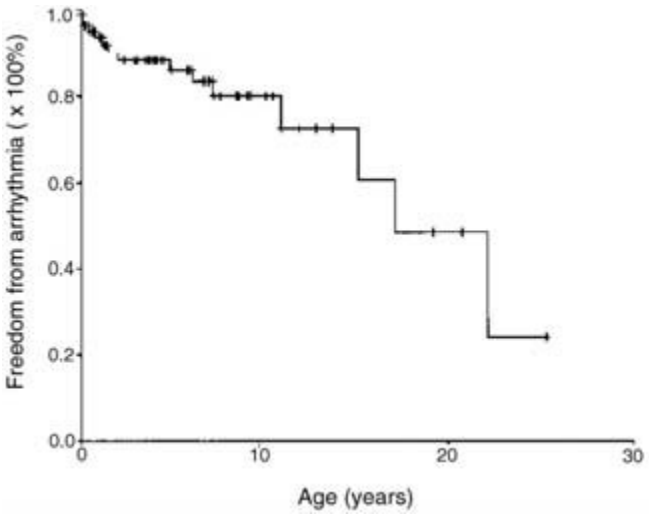

Fig. 50-8 Kaplan-Meier actuarial estimates of the probability of freedom from symptomatic cardiac arrhythmia in 85 patients who had undergone or were awaiting surgical interventions.

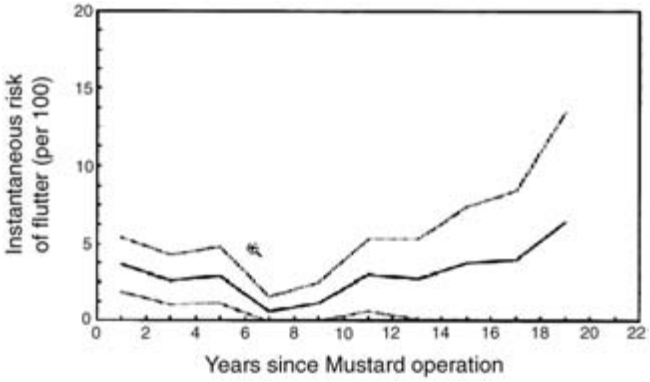

Fig. 50-9 (Reprinted from Gelatt, *et al.,*[164] Copyright (1997), with permission from The American College of Cardiology Foundation and Excerpta Medica.)

relate to the overall high mortality rate and occurrence of sudden death in this patient group.

Univentricular AV connections

IART in the Mustard/Senning patient

The Mustard and Senning atrial baffle repairs for correction of blood flow to repair transposition of the great vessels were devised several decades ago, yet we are still managing the electrophysiologic "fallout" of this operation. Late arrhythmias, particularly intra-atrial reentrant tachycardias previously termed "atrial flutter," have been recognized to be common for some time.[160,161] Over 50% of patients have inducible sustained atrial flutter at electrophysiologic study,[162] and at least a quarter of patients have clinical atrial flutter if assessed late postoperatively. Sudden death is frequent in this population, and associated with atrial flutter through recordings from case reports, as well as the similar bimodal pattern of risk that occurs for both atrial flutter and sudden death late after these repairs.[163,164] Impaired systemic right ventricular function is an additional risk factor for late death (Figs 50-9, 50-10).[164,165]

IART in the Fontan patient

Intra-atrial reentrant tachycardia, the name given to the complex atypical flutter often present in children following repair of congenital heart disease, is common following repairs utilizing the Fontan principle. However, IART can be reduced by modifying the type of Fontan operation, with fewer lateral tunnel Fontans having IART when compared to atriopulmonary connections.[166–168] The frequency of IART may be reduced even further by the use of a total extracardiac Fontan connection (Fig. 50-11).[169]

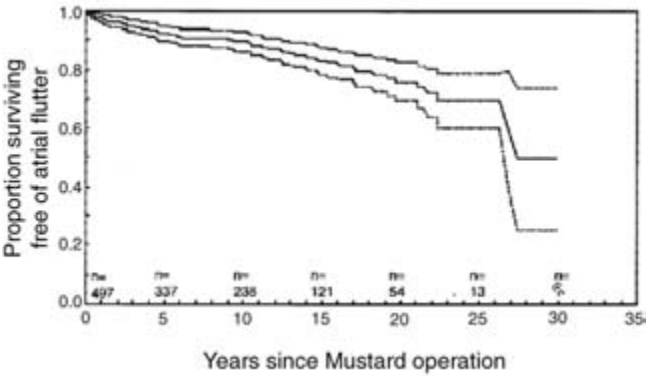

Fig. 50-10 (Reprinted from Gelatt, *et al.*[164], Copyright (1997), with permission from The American College of Cardiology Foundation and Excerpta Medica.)

IART in the other patients following congenital heart disease

TAPVD

Cardiac arrhythmias, particularly atrial flutter may occur late following repair of total anomalous pulmonary venous drainage in infancy, and are not predicted by age or adequacy of repair.[170] We have seen a high incidence of atrial flutter in our patients, as well as an occcasional patient with AV block.

Tetralogy of Fallot

Atrial arrhythmias, particularly atrial flutter, are common late following repair of tetralogy of Fallot, but usually occur beyond adolescence (Fig. 50-12).[170A]

Drug therapy

Most supraventricular arrhythmias will respond with a reduction but not abolition of symptomatic episodes. The appropriate medication depends on the underlying vulnerable substrate of the arrhythmia which can be targeted. This can often be identified from a 12-lead electrocardiogram in tachycardia. Atrioventricular node reentry responds well to digoxin, calcium-channel blockers or beta blockers, which slow conduction through the AV node. Accessory pathway mediated tachycardias are sensitive to Vaughan-Williams type 1 sodium channel blockers such as procainamide (1A) or flecainide or propafenone (1C), as well as type 3 potassium channel blockers such as sotalol or amiodarone.[171] Such pathway-specific medications may be particularly useful to reduce risk in patients with

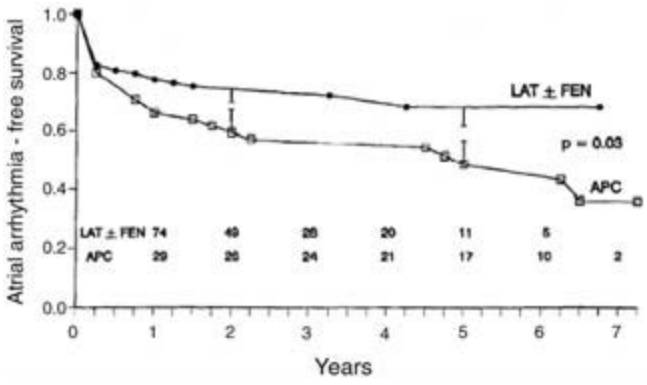

Fig. 50-11 Actuarial intermediate atrial arrhythmia-free survival after the Fontan procedure in patients with two different modifications: Lateral tunnel (LAT) with or without fenestration (FEN) versus atriopulmonary connection (APC). (Reprinted from Cecchin *et al.*,[168] Copyright (1995), with permission from Excerpta Medica, Inc.)

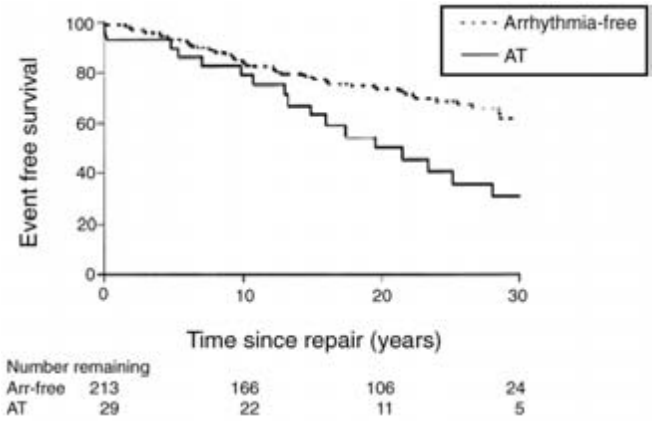

Fig. 50-12 Event-free survival compared between atrial arrhythmia and arrhythmia free patients with repaired tetralogy of Fallot. Events include death, heart failure, reoperation and stroke. (From Harris *et al.*[170A] with permission.)

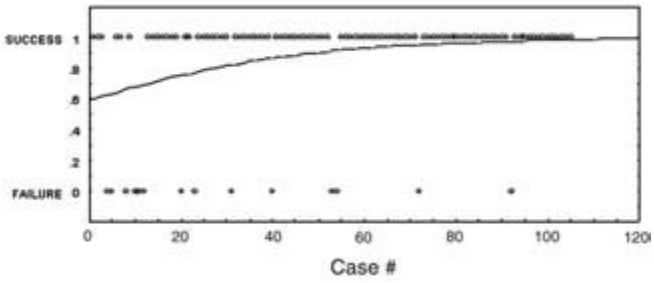

Fig. 50-13 Acute success rates for radiofrequency ablation of arrhythmias in children follow a negative exponential procedural learning curve which peaks at 95% in most centers.

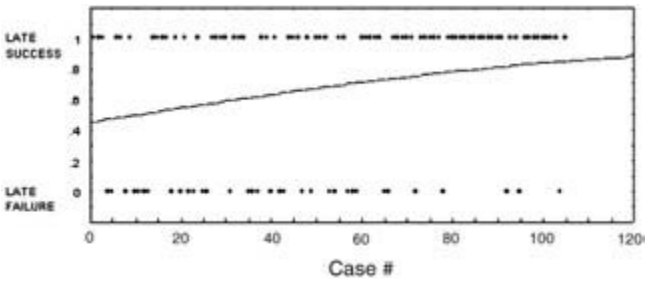

Fig. 50-14 Late (chronic) success following radiofrequency ablation of arrhythmias in children lags behind acute success in most centers.

Wolff–Parkinson–White syndrome with short antegrade refractory periods of the accessory pathway. On the other hand, digoxin and calcium channel blockers may accellerate the frequency of conduction over such pathways and increase the risk of frequent conduction of atrial fibrillation to the ventricle.

Automatic tachycardias appear to respond to procainamide with rate slowing, and may respond to propafenone, flecainide, sotalol or amiodarone with termination or reduction of the incessant tachycardia.

RFCA (Figs 50-13, 50-14)

Mapping methods

The majority of mechanisms of supraventricular tachycardia are amenable to curative catheter ablation. The potential success rate is likely related to the complexity of the anatomical substrate of the arrhythmia. If the vulnerable substrate of an arrhythmia can be localized to specific anatomical location, such as the slow pathway of AV node reentry or the accessory pathway of Wolff–Parkinson–White syndrome, ablation can often be accomplished using relatively simple imaging systems (biplane flouroscopy) and a limited number of recorded intracardiac channels. Anatomically, substrates such as the slow pathway of AV node reentry are limited to a limited number of locations on the surface of a complex three-dimensional structure (the posteroseptal space). When favorable anatomy guides the ablation catheter, such as in the substrate of a left-sided accessory pathway, one is essentially mapping sequentially along a curved line (the left AV groove). More complex anatomical substrates such as intra-atrial reentrant tachycardia (atrial flutter) may benefit from electroanatomical 3-D mapping systems to document areas of scar and critical isthmuses of conduction (Fig. 50-15).

Ablation methods

The mechanism for creation of an ablation lesion have evolved from relatively poorly controlled sources of energy (DC shock ablation) to finely controlled techniques (temperature-controlled radiofrequency catheter ablation) and now reversible mapping and ablation techniques (cryocatheter ablation). This new catheter ablation mechanism allows for a limited mapping and assessment of potential ablation outcome before creating a permanent lesion.

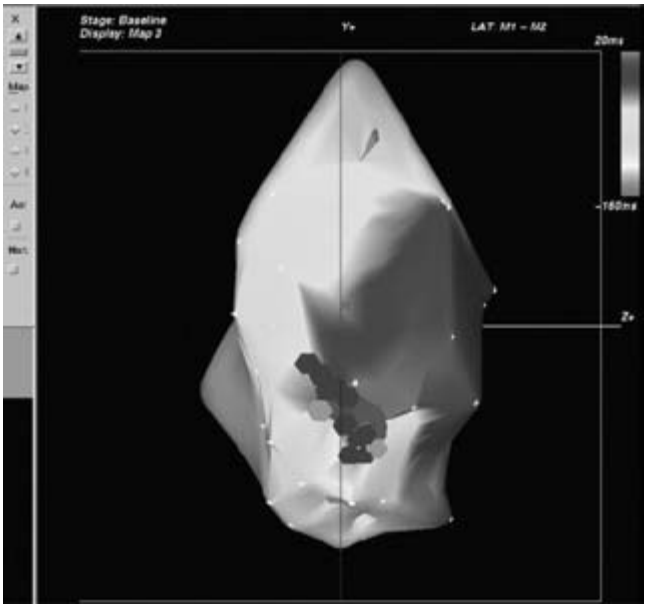

Fig. 50-15 Right lateral view of a right atriotomy flutter in a patient late following tetralogy of Fallot repair. The critical isthmus is identified above the area of breakout and between two marked points of double-potentials and was successfully ablated with a line of radiofrequency ablation lesions with no recurrence.

Outcomes

In a study of adults undergoing RF ablation, Cheng and colleagues demonstrated that radiofrequency ablation was the most effective and least expensive therapy for patients who have monthly episodes of supraventricular tachycardia.[172] Radiofrequency ablation improved quality-adjusted life expectancy by 3.10 quality-adjusted life-years and reduced lifetime medical expenditures by $27 900 compared with long-term drug therapy. Although the benefit of radiofrequency has not been studied in less symptomatic patients, a small improvement in quality of life is sufficient to give preference to radiofrequency ablation over drug therapy.

DeMaso and colleagues specifically studied children before and after radiofrequency ablation.[173] The patients showed reductions in the "fear of their heart problem" and increases in "the things that they enjoy," and those who had a successful ablation had better functioning than those who did not show improvement.

Pacing therapies

Pacing therapies can also be used successfully to treat atrial arrhythmias such as those following surgery for complex congenital heart disease. Rare complications or failures have decreased the enthusiasm for this technique.[174,175] Automatic overdrive pacemakers require excellent sensing of the atrial arrhythmia, an algorithm for identifying and discriminating the target arrhythmia and demonstration that repeated overdrive pacing is safe for the specific patient.

Even in the absence of an automatic atrial overdrive pacemaker, many of the current standard atrial or dual chamber pacemakers are capable of manual overdrive pacing, and may be very useful for patients with only occasional episodes of atrial tachycardia with mild or moderate symptoms.[176]

Patients at risk for atrial arrhythmias probably benefit from concomitant drug therapy to reduce the frequency of conducted impulses through the AV node at the time of their arrhythmia and delivery of pacing therapy. Digoxin appears to reduce the severity of symptomatology during episodes of atrial flutter, at least in patients following Mustard repair.[164] However, the use of antiarrhythmic drugs other than digoxin, and the frequency of hospital admissions can both be reduced.[177]

All references can be found at the end of the book. See pp. 859–63 for Chapter 50.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Gil J. Gross, Wei Zhu, Christine Chiu, Robert M. Hamilton, and Joel A. Kirsh

Ventricular Tachycardia

Ventricular ectopy comprises a broad spectrum of cardiac rhythm abnormalities ranging from isolated ventricular premature beats to ventricular fibrillation (VF), and including ventricular tachycardia (VT). The feature common to all of these is activation of most or all of the ventricular myocardium independently of activity in cardiac tissue that normally takes precedence in the intrinsic pacemaking hierarchy; namely, the sinoatrial node, atria, atrioventricular node, and proximal elements of the His-Purkinje system. Isolated ventricular premature beats are common in children,[1–4] as in adults,[5,6] and are usually benign when unassociated with identifiable structural or functional heart disease.[7–11] At the other end of the spectrum, VF occurring beyond the setting of controlled induction in the electrophysiology laboratory or with implantable cardioverter-defibrillator (ICD) testing is almost uniformly fatal in the absence of prompt and effective cardiopulmonary resuscitation and defibrillation, although rare cases of spontaneous recovery have been documented.[12,13] This chapter will deal primarily with VT, defined as at least three consecutive beats of ventricular origin occurring at a rate higher than that of the rhythm that immediately precedes or follows them. VT is a relatively uncommon tachydysrhythmia in children, especially in the absence of known predisposing factors enumerated below. Because VT is actually a manifestation of a heterogeneous collection of disorders with variable substrates and mechanisms, there are few pediatric outcome studies offering data from uniform patient groups large enough to provide a clear evidence-based approach to management. In many instances, therapeutic decisions are guided by extrapolation of data obtained in adults, by small published series of pediatric cases, or by anecdotal institutional or personal physician experience. The resulting nonuniformity in management further frustrates attempts at systematic outcome analysis.

VT is often described in mechanistic and/or morphologic terms. Like their atrial and atrioventricular counterparts, ventricular tachydysrhythmias can be mechanistically based upon enhanced focal automaticity or reentrant circuits. Additionally, triggered automaticity is recognized as a mechanism mediating ventricular tachydysrhythmias more often than is the case with supraventricular tachycardias[14,15] The electrocardiographic QRS axis and morphology of individual beats in VT, as well as their propensity to remain the same (monomorphic VT) or to vary (as in bidirectional or polymorphic VT), can provide important clues regarding the mechanism and anatomic focus of the arrhythmia. These, in turn, often suggest potential etiologies, prognoses, and treatment strategies, especially when cardiac or systemic conditions that predispose to VT are apparent. Indeed, such predisposing conditions are present in a substantial majority of pediatric patients with VT, and they serve as a logical conceptual framework within which to consider pediatric VT in greater detail.

Table 51-1 presents a classification scheme for pediatric VT based on predisposing or associated factors. Those acute systemic conditions whose remediation leads directly to permanent VT resolution, such as acidosis and electrolyte abnormalities, will not be discussed further. Also, VT occurring in the setting of surgically palliated structural congenital lesions,[16–28] in dilated cardiomyopathy,[29–36] in transplanted hearts,[37,38] and in the congenital Long QT syndromes (LQTS),[39,40] is discussed in chapters dealing specifically with those topics, and will not be addressed here. This chapter will focus mainly on "primary" or idiopathic forms of VT, and on recognized myopathic conditions in which ventricular tachydysrhythmias are a major manifestation.

Pediatric VT: historical overview

The general rarity of pediatric VT, and the pitfalls inherent in approaching it as a unitary condition, are underscored by a relative paucity of peer-reviewed literature on this topic.

In one of the earliest reports dealing specifically with pediatric VT, Palaganas and colleagues in Kingston, Ontario summarized the published experience from 1943 to 1965 as the background for their own presentation of a 6½-year-old VT patient.[41] Their search of the English language literature turned up only 17 previous cases, in which key pieces of clinical data were frequently unavailable. Of historical interest, 3 of 17 patients were said to have had diphtheria, and all 3 of these died. Only one patient was listed as having "no evident heart disease," and this one also had a fatal outcome.

The first effort to isolate idiopathic or primary VT in children was by Hernandez and coworkers, who in 1975 published a series of 7 patients aged 1 day to 13½ years with VT and no obvious predisposing factors.[42] Importantly, however, this study predated the widespread availability of reliable noninvasive imaging, and cardiac catheterization with angiography was undertaken in only 1 of their patients who in fact was known to have tuberous sclerosis. Four patients had syncope, hypotension, palpitations and/or dyspnea, while 3 were asymptomatic. Medical therapy varied. All had benign outcomes at follow-up of 6 months to 3 years.

In 1977, Radford *et al.* presented a series of 8 patients aged 6–16 years with VT or VF from the Hospital for Sick Children in Toronto.[43] This was the first report incorporating echocar-

Table 51-1 A classification scheme for ventricular tachycardia (VT) in children

Predisposing or associated condition	Example(s)
None (primary or idiopathic VT)	Accelerated idioventricular rhythm (AIVR)
	Right ventricular outflow tract (RVOT) tachycardia
	Idiopathic left ventricular (Belhassen's) tachycardia (ILVT)
	Bundle branch reentry tachycardia (BBRT)
	Catecholamine sensitive polymorphic VT (PMVT)
	Congenital Long QT syndrome (LQTS)
	Brugada syndrome
Myopathic processes	Arrhythmogenic right ventricular dysplasia (ARVD)
	Hypertrophic cardiomyopathy (HCM)
	Myocarditis
	Dilated cardiomyopathy
	Metabolic disorders
	Degenerative muscle disease
	Myotonic dystrophy
Infiltrative or invasive heart muscle diseases	Hamartomas
	Rhabdomyoma
	Fibroma
	Metastatic malignancy
	Sarcoidosis
	Chagas disease
Conduction abnormality	Heart block
Native structural congenital heart disease	Left ventricular or septal aneurysm
	Left ventricular outflow tract obstruction
	Coronary artery anomaly
	Mitral valve prolapse
Palliated structural congenital heart disease	Tetralogy of Fallot
	Aortic stenosis
Myocardial ischemia	Kawasaki disease
Metabolic derangement	Electrolyte disturbance
	Acidosis
Drugs	Antiarrhythmic agents
	Nonsedating antihistamines
	Cisapride
	Cocaine
Cardiac transplantation	Rejection or coronary insufficiency in donor heart
Trauma	Commotio cordis

diographic assessment of all the patients. Six had syncope and one complained of palpitations. Follow-up durations were not specified. This small but heterogeneous group represented a microcosm of conditions that subsequently have come to be more widely recognized as correlates of VT or VF in young people. It included 2 patients with sinus node dysfunction and chronic bradycardia, 1 of whom had left ventricular dysfunction; 1 child each with mitral valve prolapse, surgically palliated tricuspid atresia, long QT syndrome, and familial hypertrophic cardiomyopathy; and 2 with "idiopathic" ventricular ectopy. Of the latter 2, one was a 7-year-old boy with recurrent syncope, isolated ventricular premature beats suppressed during sleep, and angiographically impaired left ventricular contractility who experienced the only fatal outcome in the series, dying suddenly 6 months after diagnosis. The other was a 12-year-old boy, the only asymptomatic patient in the group, who had exercise-suppressed VT against a background of sinus bradycardia, and an apparently benign outcome with beta-blocker therapy that did not eliminate his ectopy.

Shortly thereafter, Pedersen and colleagues reported a similar but slightly larger series of 18 patients with VT or VF aged 4 days to 24 years at presentation (mean 16.6 years) who were followed for up to 70 months (mean 22.4 months).[44] This mixed group included patients with a variety of myopathic and metabolic problems, but with no recognized structural lesions other than mitral valve prolapse (4 patients) or "possible VSD" (1 patient) in any of the 16 patients who underwent imaging studies comprising at least M-mode echocardiography. Among 3 patients who died, 2 were young adults with dilated cardiomyopathy who experienced sudden death. The third was an 11-year-old girl with "progressive cardiac decompensation" who died nearly 3 years after presentation and had post-mortem evidence of an inflammatory process of undetermined etiology. Four of the 18 patients, including the only one known to be asymptomatic, had no identified cardiac or systemic issues apart from VT or VF. All of these had a benign course either with or without antiarrhythmic therapy (2 patients each); of note, 2 of these 4 patients had "VT" rates of 66 and 68 per min, suggest-

ing the inclusion of escape-like rhythm phenomena that would not be classified as VT in the current era.

Bergdahl and colleagues described primary VT in 5 boys presenting at ages ranging from birth to 11 years, with follow-up durations of 6 months to 11 years.[45] All had benign outcomes including VT resolution, and therapeutic success with quinidine was claimed for all 4 patients in whom it was tried.

While symptomatic patients predominate in most reported pediatric VT series, a group in Boston led by Fulton described 26 largely asymptomatic VT patients aged 1 day to 15 years at presentation.[46] Among this cohort, only 4 had symptoms at presentation and another 4 developed symptoms during follow-up as long as 34 years, averaging nearly 5 years. Nineteen of the patients had echocardiographic exclusion of significant structural and functional abnormalities, while in the rest this was accomplished by clinical assessment. It is noteworthy that none of the 26 patients died, and that all had apparently satisfactory outcomes notwithstanding a variety of therapeutic approaches. Moreover, there was no observable difference in outcome between 9 patients whose VT was induced or exacerbated by exercise, and 7 in whom exercise suppressed the VT.

As the approach to and understanding of arrhythmias became steadily more sophisticated, Deal *et al.* presented their 12-year experience with VT in 24 patients aged 1–21 years, with a mean age of 14.9 years.[47] Although prominently billed as a homogeneous group "without overt heart disease," 6 of the patients in this series had echocardiographic evidence of chamber enlargement or ventricular dysfunction, while 16 of 23 who underwent hemodynamic catheterization had functional abnormalities. Apart from 2 patients with mitral valve prolapse, however, all were free of identifiable structural heart disease. Among 8 asymptomatic patients, all were alive and well at mean follow-up of 7.3 years, including 5 who were not treated. Among the 16 symptomatic patients, including 2 who had presented with resuscitated cardiac arrest, there were subsequently 3 sudden deaths during a mean follow-up period of 7.6 years. The authors observed the following common features in the 3 patients who died: multiple spontaneous episodes of symptomatic VT, at least one cardioversion, abnormal findings at hemodynamic catheterization or post-mortem, and easily inducible VT with programmed intracardiac stimulation. None of these 3 patients was receiving antiarrhythmic therapy at time of death. Two of 9 patients with exercise-related VT were among the 3 who died.

By the time Noh *et al.* published their series of 18 VT patients aged 1 to 16 years,[48] an investigative approach incorporating echocardiography and intracardiac electrophysiology study with programmed electrical stimulation had become somewhat standardized. The main apparent purpose of this report was to describe the invasive study protocol utilized by the authors and its diagnostic yield in their group of patients. Unfortunately, the follow-up data provided were extremely limited, such that the observations elicited in the clinical cardiac laboratory could not be related to long-term patient outcome. Among 14 patients for whom follow-up data of unspecified duration were offered, there was no mortality.

A second report from our institution was published by Davis and coworkers in 1996.[49] Already the largest such series at the time with 40 pediatric-aged VT patients, this study also shifted the spotlight to a younger subpopulation by limiting inclusion to children – and, for the first time, 7 fetuses – aged 5 years or less at presentation, with a median age of just 0.2 years. Moreover, none of the patients had a recognized structural cardiac defect, although 1 had an aortic coarctation. Half of the patients had identified predisposing factors for VT including myopathic or inflammatory processes, tumors, and long QT syndrome, and such data were unavailable for the other 20 patients. Nine cases of VT were detected incidentally in "asymptomatic" patients, although the preverbal status of many of these children would have precluded subjective symptomatic complaints. There were 6 VT-related deaths, including 3 in infants < 1 week old and 2 sudden deaths in older children, as well as unrelated mortality in 3 other patients during follow-up ranging up to 14.1 years for all but 1 patient who was followed for 28.1 years. Only the presence of symptoms predicted a fatal outcome. VT resolved in a substantial majority of the children, with a median time to resolution of 0.3 years in 29 patients. All but 4 of those who ultimately experienced VT resolution were treated with at least one antiarrhythmic medication, but 24 of 29 were free of VT while on no medication at latest follow-up.

The largest, most recent and probably the most contemporarily relevant series of pediatric VT cases is that of Pfammatter and Paul, presented on behalf of the Working Group on Dysrhythmias and Electrophysiology of the Association for European Pediatric Cardiology.[50] This is the only multicenter study of pediatric VT to date, reporting retrospectively on 98 patients aged 0.1 to 15.1 (mean 5.4) years at presentation, with reasonably rigorous exclusion of all children with known factors predisposing to VT. Thus, it is arguably the only currently available study involving a substantial number of pediatric-aged patients with primary VT. Magnetic resonance imaging (MRI), increasingly considered to be an important diagnostic modality in VT patients, contributed to the exclusion of significant structural abnormality in 9 patients in this series. However, no biopsy data were presented. No cases of polymorphic VT were observed, possibly because catecholaminergic VT was specifically excluded. This could perhaps help to explain the remarkably benign courses and outcomes of the children in this study, as well as their relatively poor response to beta-blocker therapy. During 12–182 (mean 47) months of follow-up, there was no mortality, and all 98 patients had echocardiographically normal left ventricular function at last assessment. Moreover, 96 of the patients were asymptomatic at last follow-up, as compared with 36% who had symptoms either at presentation or at other times in the study period. VT resolved in 79 patients, including 63 who were on no antiarrhythmic medication. Seven of these had undergone successful transcatheter radiofrequency ablation of their VT focus, including 5 in the right ventricular outflow tract and 2 on the left ventricular aspect of the interventricular septum. Sixteen patients enjoyed complete VT control on chronic antiarrhythmic therapy, with amiodarone showing the greatest effectiveness (*c.* 80% total VT suppression plus *c.* 10% partial suppression) in comparison with verapamil, sotalol, propafenone, flecainide, and β-blockers, which were the least effective (*c.* 25% total suppression plus *c.* 10% partial suppression). Although not rigorously assessed, presumably because virtually all of the patients did well, the variable that appeared most highly predictive of a particularly good outcome such as early spontaneous VT resolution was presentation during infancy. Patients in the infant age group more often exhibited a left bundle branch block pattern electrocardiographic QRS morphology in VT, suggestive of a right ventricular focus, which itself was associated with a greater chance of VT resolution and lower incidence of symptoms even among the older patients.

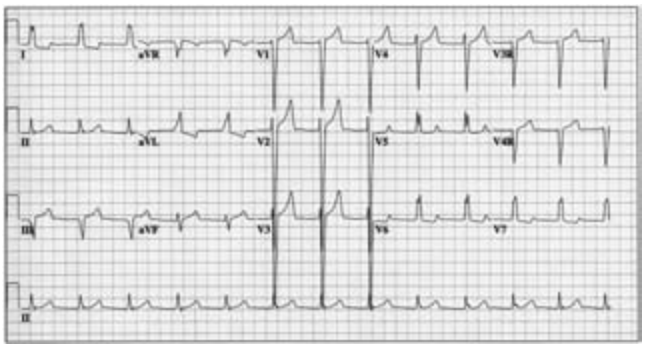

Fig. 51-1 This 12 lead ECG recording was obtained from an 8-year-old girl 2 years after repair of a secundum type atrial septal defect. It shows accelerated idioventricular rhythm (AIVR) with left bundle branch block morphology and left axis deviation at 74 beats/min.

Primary or idiopathic VT

There is still some variability in the diagnostic classification of patients with VT occurring in the absence of identifiable systemic, structural or functional heart disease. However, incremental steps forward in our understanding of VT substrates and mechanisms have yielded a growing consensus in diagnostic categorization, accompanied by refinements in prognostication and management.

Patient records recovered through a computerized cardiology database search at the Hospital for Sick Children, Toronto, were reviewed and assigned to one of the following diagnostic categories wherever possible. Available data were inadequate for VT classification in 25 of the 73 records reviewed.

Accelerated idioventricular rhythm (AIVR)

AIVR is characterized by a regular monomorphic ventricular rhythm (Fig. 51-1) with rates that are just slightly more rapid than the prevailing sinus rate (Table 51-2). This apparently benign diagnostic entity is encountered in patients of all ages, but is decidedly rare in patients who fall outside the neonatal and infant age group.[51] In adults, AIVR is typically associated with postischemic reperfusion or with other types of myocardial pathology.[32] The distribution of AIVR in children follows the maturational transition from infancy, when associated heart disease is typically absent, to adulthood,[52] in other words, the older the child is at presentation with AIVR, the greater is the likelihood of discovery of myocardial disease. The association with myocardial disease has prognostic implications, in that the course of AIVR in such patients tends to track that of their underlying pathology. AIVR has a greater tendency to persist in patients with no apparent heart disease. AIVR is rarely dangerous in either group, however, and mortality is virtually unknown. Moreover, AIVR rarely responds to conventional antiarrhythmic therapy, such that the natural history is not significantly altered by treatment.

Among 12 identified patients with AIVR at our institution, mean age at presentation was 3.8 years. Symptoms were present in 16% of these children, but none experienced syncope, apparent life-threatening events, or cardiac mortality during an average 2.1 years of follow-up. Moreover, complete VT resolution was documented in all of them.

Right ventricular outflow tract (RVOT) tachycardia

RVOT tachycardia is one of the more common and benign types of idiopathic VT,[53] but diagnostic differentiation between RVOT tachycardia and the potentially more malignant myopathy known as arrhythmogenic right ventricular dysplasia (ARVD, discussed below) can be difficult, and is not always unequivocal.[54,55] RVOT tachycardia is most often characterized by paroxysmal runs of uniform nonsustained VT with an inferior QRS axis and left bundle branch block morphology (Fig. 51-2). It is often inducible with exercise and/or sensitive to adenosine. Lerman *et al.* have suggested that a mechanism based on cyclic AMP-mediated triggered activity could account for all of these characteristics.[56] Magnetic resonance imaging studies of RVOT tachycardia have revealed mild structural abnormalities in approximately 75% of patients,[57,58] but single-photon emission computed tomography (SPECT) using technetium-99m sestamibi/tetrofosmin might be more sensitive and specific in discriminating noninvasively between RVOT tachycardia and ARVD.[59] RVOT tachycardia usually maps electrically to the septal region of the RVOT, and transcatheter radiofrequency ablation of the VT focus has been applied safely and effectively in both adults[60] and patients in the pediatric age group.[61] VT ablation is usually undertaken to alleviate symptoms including palpitations, presyncope or syncope, as the natural history of untreated RVOT VT is almost invariably benign with respect to mortality or serious complications.[53] Moreover, RVOT VT is often sensitive to a wide variety of antiarrhythmic agents including simple beta blockers.[53]

Our database yielded records on 13 patients with RVOT VT, diagnosed at a mean of 3.5 years of age, and followed for 3.3 years on average. While symptoms were present in 63%, including 25% with syncope, there were no incidents of cardiac mortality, and all patients eventually experienced VT resolution including two who received no treatment. Among 10 patients for whom detailed documentation of medical therapy was available, 8 were successfully withdrawn from therapy and free of tachycardia at latest follow-up. Our RVOT VT ablation experience has thus far been limited to one success in three attempts.

Idiopathic left ventricular (Belhassen's) tachycardia

Another type of episodic VT occurring in otherwise normal hearts is commonly known as idiopathic left ventricular tachycardia (ILVT). This condition, whose ECG hallmark is a leftward QRS axis with right bundle branch pattern, was originally described by Zipes *et al.* in 1979[14] (Fig. 51-3). However,

Table 51-2 Diagnostic features of accelerated idioventricular rhythm (AIVR)

Diagnostic features
Monomorphic ventricular rhythm (usually LBBB morphology)
VT rate within 10–15% of prevailing sinus rate
VT runs begin with a fusion beat or with a "late" ventricular premature beat
Regular VT rhythm with mild acceleration or deceleration, especially before termination
Variable retrograde conduction resulting in suppression of the sinus mechanism

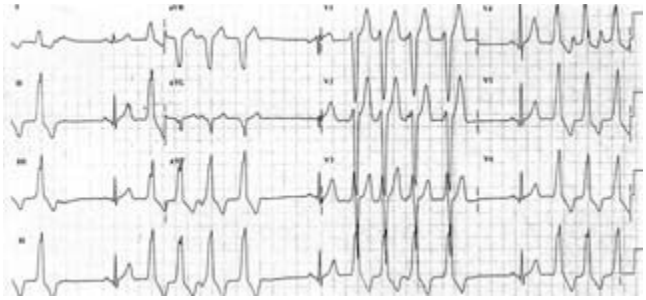

Fig. 51-2 Right ventricular outflow tract tachycardia (RVOT VT) in a minimally symptomatic 15-year-old male with a structurally normal heart. Typical features include short bursts of VT with inferior QRS axis and left bundle branch block morphology. He eventually underwent successful transcatheter radiofrequency ablation of an RVOT focus.

Belhassen's name is the one that became eponymously linked with ILVT after he and his colleagues characterized its striking susceptibility to suppression with verapamil.[62] In their original report, Zipes and coauthors presented evidence that the mechanism underlying ILVT is likely to be either reentry or triggered automaticity, most prominently including their observation that ILVT could be induced by atrial stimulation or sinus tachycardia.[14] Subsequent studies in isolated cases and small series of patients have supported either or both of these tachycardia mechanisms,[15;63–66] although more recent studies, cited below with respect to radiofrequency ablation, appear to favor reentry as the predominant mechanism.

The largest preablation era series involved 16 patients with a mean age of 33 years including 2 who were within the pediatric age range at 12 and 13 years old.[65] All 16 patients were symptomatic with palpitations at presentation, and 13 who received long-term oral verapamil therapy enjoyed significant or complete symptomatic relief during 1–6 (mean 2.8) years of follow-up. The same group subsequently reported long-term follow-up data from a larger group of 37 patients during a transitional period when transcatheter radiofrequency ablation was just becoming established as a therapeutic option.[67] Patients in this study had a mean age of 33 years at diagnosis and were followed for 1–13 (mean 5.8) years. They were classified by degree of initial symptomatic limitation into mild, moderate, and severe categories. None of the 14 patients with ILVT categorized as mild was treated, and none showed any significant deterioration during follow-up. ILVT was considered moderate in 17 patients, all of whom enjoyed a favorable symptomatic response to medical therapy which consisted of verapamil in the great majority of cases. All 6 patients with severe ILVT failed to respond to medication. Of these 6 patients, 4 subsequently underwent transcatheter radiofrequency ablation and one had cryosurgery. The only fatality among all 37 patients was the remaining patient with severe ILVT who died suddenly after implantation of an antitachycardia pacemaker.[67] Diltiazem appears to be as effective as verapamil in controlling ILVT.[68]

Because ILVT is usually symptomatic and there are reports of its culmination in tachycardia-mediated cardiomyopathy, transcatheter radiofrequency ablation has been readily embraced as a definitive cure,[69] with the first pediatric case report appearing in 1997.[70] The tachycardia focus or exit site usually maps to the left posterior fascicle,[71–73] although radiofrequency energy has been successfully applied at other sites on the septal surface of the left ventricle as well.[74–76]

Our institutional database search yielded 11 pediatric patients meeting diagnostic criteria for ILVT. They had a mean age at diagnosis of 4.4 years and were followed for an average of 1.8 years, during which there was no cardiac mortality, with apparent VT resolution in 90% of cases. Symptoms were present in 81% of this group, including syncopal events in 2 of the patients. Transcatheter radiofrequency ablation has been successful in five of six attempts.

Bundle branch reentry tachycardia (BBRT)

Bundle branch reentry is an unusual clinical entity most commonly associated with ventricular enlargement in the setting of dilated cardiomyopathy or other myocardial or valvular dysfunction.[77] BBRT is also associated with myotonic dystrophy.[78] It has only rarely been described in the absence of these functional or anatomic substrates,[79] with no published literature relating specifically to children. The right bundle branch forms the antegrade limb while the left bundle branch serves as the retrograde limb of a reentrant circuit which also incorporates the His bundle.[60] Electrocardiographic evidence of intraventricular conduction delay in sinus rhythm is the rule, and the QRS morphology in VT typically resembles that in sinus rhythm[60] (Fig. 51-4). Transcatheter radiofrequency ablation applied to the right bundle branch is usually successful in abolishing BBRT.[80]

Our cardiology database search yielded 4 patients with a diagnosis of BBRT in the absence of recognized functional or structural heart disease, presenting at a mean age of 4.7 years and followed for 2 years on average. Transcatheter radiofrequency ablation was attempted in 2 of these patients and was successful in 1. None of the 4 patients experienced cardiac mortality during the follow-up period, and BBRT apparently resolved spontaneously in 2 of them, with only the patient who underwent unsuccessful ablation continuing to experience episodic VT with palpitations.

Catecholamine sensitive polymorphic VT (PMVT)

Although relatively rare, catecholamine sensitive PMVT stands apart from other types of primary VT in three important aspects: it often has a malignant course and prognosis, it is

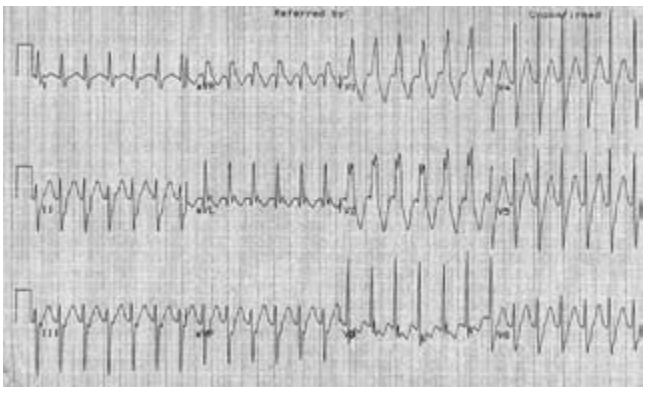

Fig. 51-3 Surface ECG recording showing ventricular tachycardia with RBBB morphology and left axis deviation characteristic of idiopathic left ventricular tachycardia (ILVT) at 191 beats/min in a 10-year-old boy with a structurally normal heart. There is evidence of VA dissociation most clearly shown in ECG leads I and II.

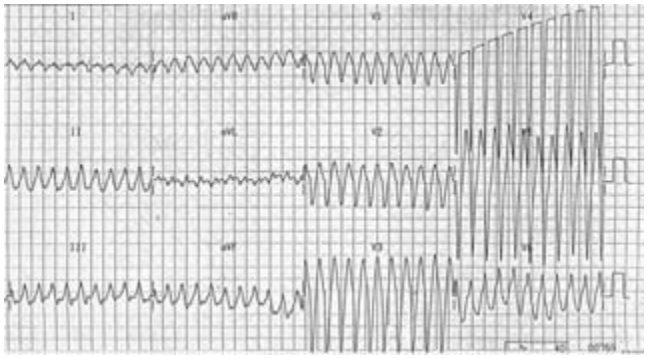

Fig. 51-4 ECG recording obtained from an 8-year-old boy with dilated cardiomyopathy and bundle branch reentry tachycardia (BBRT). There is a wide QRS complex tachycardia at 240 beats/min with left bundle branch block morphology, rightward QRS axis deviation and 1:1 VA relationship as evidenced by retrograde P waves in the inferior limb leads. Confirmation of tachycardia mechanism was obtained during electrophysiologic study which showed prolonged HV interval during ventricular tachycardia with this same morphology and VA dissociation. Subsequent ablation of the right bundle branch successfully abolished this patient's tachycardia circuit.

frequently familial, and its familial pattern of occurrence has in turn enabled the recent elucidation of its underlying cellular and molecular pathophysiology. PMVT features polymorphic or bidirectional (alternating QRS polarity) VT that is most often induced by exercise, emotional stress, or catecholaminergic stimulation of any source including isoproterenol infusion (Fig. 51-5). There had apparently been very few cases in the literature, including a series of 4 children reported by Coumel and coauthors,[81] when Leenhardt *et al.* published the first series establishing this condition as a unique diagnostic entity in 1994.[82] They described 14 young adult patients aged 35 ± 10 years who presented with syncope and were further characterized by a marked predisposition to ventricular fibrillation (10 patients) and sudden death (4 patients) during mean follow-up of 7 years. Their polymorphic ventricular ectopy was remarkable for strikingly short coupling to the preceding sinus beat, and for noninducibility with programmed stimulation.

As recently as 1997, Coumel puzzled over the cause of catecholamine sensitive PMVT and speculated about a possible etiologic relationship with the congenital LQTS.[83] Since 1999, however, when Swan and colleagues mapped autosomal dominant PMVT in two unrelated Finnish families to chromosome 1q42-q43,[84] major strides in molecular genetics have revealed that the key to this condition lies not in abnormal myocyte repolarization, as is the case in LQTS, but in intracellular calcium handling. Marks and colleagues[85] have summarized the rapid progress made subsequent to Swan *et al.*'s report,[84] culminating in the identification, to date, of 11 mutations clustered in three regions of the gene encoding the human cardiac ryanodine receptor known as RyR2.[86,87] This fruitful field of investigation is yielding exciting links not only between molecular abnormalities and their clinical cardiac phenotypic correlates, but also with diseases extrinsic to the cardiovascular system. RyR2 is the channel protein located in the sarcoplasmic reticular (SR) membrane that enables calcium-mediated calcium release, a key event in myocyte excitability and excitation–contraction coupling. Adrenergic stimulation results in RyR2 phosphorylation by protein kinase A, leading to increased release of calcium from SR stores. Abnormal calcium "leak" through RyR2 can induce delayed afterdepolarizations, which can in turn precipitate triggered tachydysrhythmias of the type seen in PMVT.[85] The 3 RyR2 regions thus far implicated in autosomal dominant PMVT are homologous to 3 regions in the skeletal muscle ryanodine receptor, RyR1, in which mutations associated with malignant hyperthermia (MH) and the degenerative neurologic disorder central core disease (CCD) have been identified.[85] Lahat and associates further consolidated the pathophysiologic connection between PMVT and impaired myocyte calcium handling. Having mapped a particularly lethal autosomal recessive form of PMVT found in Israeli Bedouin families to chromosome 1p13–21,[88] they went on to pinpoint a missense mutation in a highly conserved region of calsequestrin 2 (CASQ2), the protein that serves as the major SR calcium reservoir in cardiac myocytes.[89]

Leenhardt *et al.* reported on outcomes in 21 children with PMVT followed for an average of 7 years.[90] These patients had a mean age of 9.9 ± 4 years at presentation. All but 1 were symptomatic with exercise-induced syncope, and 30% had a family history of syncope or sudden death. Treatment with beta blockers resulted in complete symptom resolution, and a total of 3 syncopal events and 2 sudden deaths occurring in 3 treated patients during follow-up were attributed by the authors to probable or proven medication compliance issues. Fisher and colleagues described their 25 year experience involving 4 surviving affected members (father and 3 siblings) of a single family with PMVT and prior sudden death in 2 other siblings. Among the affected survivors, beta blocker therapy was effective in preventing untoward events during the extended follow-up period.[91]

With more recent advances in molecular diagnosis of PMVT, it should become possible to define outcomes in relation to specific mutations. Priori *et al.* investigated 4 families with autosomal dominant PMVT.[86] Among 11 individuals proven or presumed to be affected by RyR2 mutations, there were 2

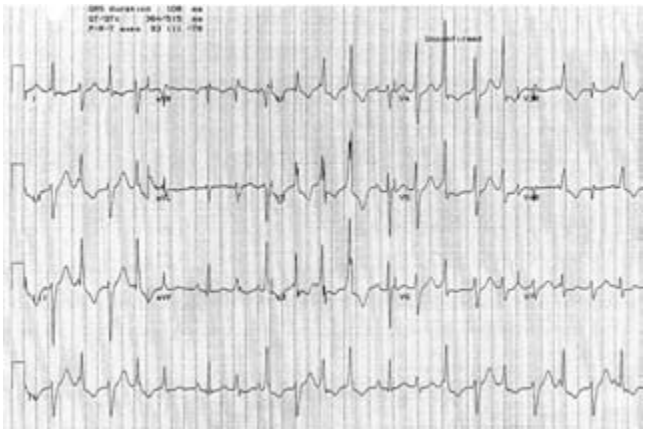

Fig. 51-5 Surface ECG recording from a 16-year-old girl with structurally normal heart who presented after a syncopal episode. She had nonsustained runs of bidirectional VT with a cycle length of 320 ms (note alternating QRS morphology in inferior leads). She responded well to beta-blocker therapy.

sudden deaths in typical circumstances, in sisters aged 14 and 16 years, and another in an unrelated 7-year-old boy whose identical twin presented with recurrent syncope. The authors provided 1–9 year follow-up data for 4 of 7 survivors, 3 of whom were treated with beta blockers, and 2 of whom underwent ICD implantation. All 3 medically treated patients enjoyed symptomatic relief from recurrent syncope. The 1 patient receiving both therapies continued to have short runs of VT documented by the ICD, but none apparently meeting criteria for device discharge. This was in contrast to the only ICD patient not treated with beta blockers, who experienced 2 ICD discharges in stressful settings during the first year of follow-up.[86] Bauce and colleagues recently demonstrated the feasibility and advocated the implementation of genetic screening in PMVT families with RyR2 mutations.[92] Patients from Lahat *et al.*'s Bedouin tribe, encompassing 7 related families with autosomal recessive PMVT, exhibit symptoms that are particularly severe and early in onset. Among 22 patients with proven or presumed PMVT, there were 9 sudden deaths occurring at age 7 ± 4 years, and 12 of 13 survivors have experienced recurrent syncope and/or seizures beginning at age 6 ± 3 years. Most of the survivors have responded favorably to beta-blocker therapy.[88]

Four of the patients in the Hospital for Sick Children cardiology database met our diagnostic criteria for PMVT. They presented at an average age of 9.5 years and were followed for a mean of 4.1 years, during which 1 patient (25%) experienced cardiac death. Two others had syncope or acute life-threatening events, and all 4 suffered from VT-related symptoms.

Brugada syndrome

The Brugada syndrome, first described in 1992 by 2 of the 3 brothers whose name it bears[93] and subsequently characterized more fully by all 3 of them in 1998,[94] is a novel ion channelopathy whose electrocardiographic hallmark is right bundle branch block QRS morphology and right precordial ST segment elevation in sinus rhythm. Sodium channel blocking agents such as flecainide and ajmaline are utilized diagnostically to accentuate the ECG abnormality in borderline cases,[95] and can also be arrhythmogenic in these patients.[96] Brugada syndrome is now known to be due to at least 3 autosomal dominant mutations in the cardiac myocyte sodium channel SCN5A with variable phenotypic manifestations involving loss of channel function and altered kinetics of recovery from inactivation.[97,98] These predispose the heart to sudden episodes of ventricular fibrillation, with predictably high mortality. The disease is typically one of adult males of Southeast Asian origin, although increased physician awareness has led to its recognition in other populations as well[95] None the less, the number of well-documented pediatric cases remains extremely small.[96,99,100] This is probably owing to age-dependent penetrance, with phenotypic expression in males, who account for 80–90% of affected individuals, peaking in the third and fourth decades of life.[101] The clinical heterogeneity of Brugada syndrome is increasingly well recognized,[102,103] and risk stratification strategies based on relatively substantial patient numbers are just beginning to emerge.[95,102] However, the applicability of recommendations arising from these reports to the pediatric population cannot be evaluated at this time. The issue of risk stratification is nontrivial, because no effective pharmacologic therapy has been identified to date, and ICD implantation represents the only life prolonging intervention presently available.[95,101]

VT associated with cardiomyopathies

Arrhythmogenic right ventricular dysplasia (ARVD)

ARVD is an uncommon condition which has nevertheless inspired a great deal of interest and numerous publications in recent years for the following reasons: (1) it is an increasingly recognized cause of arrhythmic mortality in otherwise healthy young people, accounting for one-quarter of cases of cardiac arrest or sudden death in athletes according to one Italian study;[104] (2) it can be difficult to differentiate from RVOT VT, a more common and usually benign condition; (3) its cellular and molecular underpinnings are the subject of a fruitful field of ongoing investigation. From the perspective of this chapter, ARVD is of added interest because it is the prototypical structural cardiomyopathy in which VT serves as the cardinal clinical manifestation.

Although earlier publications probably hinted at ARVD as a distinct clinical entity, the most widely cited benchmark case series is that of Marcus in collaboration with Fontaine and others, published in 1982.[105] These two authors have continued to write prolifically on the topic, generating, among other important contributions, a series of review articles chronicling many of the key steps leading to our current understanding of ARVD.[106–114] The interested reader is referred to these helpful resources, as all but a superficial survey of the copious ARVD literature is beyond the scope of this chapter.

Transmural fibrofatty replacement of RV myocardium is the pathologic *sine qua non* of ARVD,[105] and its demonstration at surgery or necropsy was defined as the diagnostic gold standard for ARVD in the criteria proposed by McKenna *et al.* in 1994.[115] However, fatty infiltration of RV myocardium can apparently occur in the absence of ARVD.[116] While ARVD was initially considered to be a disease specifically affecting the right ventricle, there are now numerous published examples of biventricular involvement.[117–123] The cause of progressive fibrofatty replacement of the myocardium in ARVD remains unknown. Recent identification of several seemingly unrelated pathogenetic factors including RV myocyte apoptosis,[124,125] mutations in novel genes of uncertain function,[126–133] and the presence of cardiotropic viruses in affected tissue[134,135] suggest that the pathologic features of ARVD might represent a final common pathway for a diverse group of etiologic agents, or the result of synergistic interaction among them. Familial cases, accounting for an unclear percentage of all ARVD patients, have been mapped to at least six different autosomal dominantly transmitted chromosomal loci, yielding a classification system (ARVD1–6)[136] that has yet to find general clinical acceptance or application. Among these subtypes, ARVD2 has the most clearly defined gene product, which interestingly happens to be the RyR2 ryanodine receptor implicated in PMVT (see above).[85,92,136] This link might provide an early clue regarding the propensity of ARVD to manifest clinically with ventricular arrhythmias, which otherwise remains unexplained.

The clinician faced with a suspected case of ARVD must often deal sequentially with two conundrums: first, differentiation of ARVD from RVOT VT, which features electrocardiographically indistinguishable VT and is considered to be far more common and more benign than ARVD; and second, an attempt at risk stratification based on fragmentary clinical outcome data in this heterogeneous disorder or group of disorders. In addition to relatively routine cardiac investigations

including standard electrocardiography, echocardiography[137,138] and cardiac catheterization with right ventriculography,[111] a number of more esoteric tests have been promoted as useful tools in establishing the diagnosis of ARVD. These include signal averaged ECG,[139–142] detection of so-called epsilon waves[111] and/or quantification of QT[143] or QRS[144] dispersion on standard 12-lead ECG recordings, Fourier phase analysis of gated blood pool single-photon emission computed tomography (GBP SPECT),[145] SPECT using technetium-99m sestamibi/tetrofosmin,[59] and even the measurement of plasma brain natriuretic peptide (BNP) levels, which have been shown to be elevated in patients with ARVD but not in those with RVOT VT.[146] Endomyocardial biopsy is not free of risk, and its diagnostic sensitivity can be confounded by the patchy nature of fatty RV myocardial infiltration and its typical distribution in the RV free wall rather than along the septal surface where tissue can be sampled most safely. A positive biopsy is none the less considered to be diagnostic of ARVD in the presence of other supportive findings.[115,147] In recent years, there has been great interest in the use of MRI which, in addition to being noninvasive and hence safer than cardiac biopsy, is quite sensitive and specific for detection of fibrofatty replacement of myocardium with fat.[148–151] Unfortunately, the sensitivity of this imaging modality also reveals myocardial fat deposition in a significant proportion of patients with presumed RVOT VT,[58,152] thus bringing into question its utility in differentiation between the two conditions, not to mention an as yet undefined degree of clinical overlap between them.

Outcome studies in ARVD are limited in number and the older ones are cited in reviews mentioned above. They are confounded by heterogeneity of the disease itself, of the diagnostic criteria employed in gathering data, and of the therapeutic interventions that have been utilized in its treatment.[153–158] No outcome information pertaining specifically to children is currently available. Berder and coauthors presented retrospective outcome data on a cohort of 49 men and 23 women presenting with ARVD at age 40 ± 13 years and followed for a mean of 4.5 (range 1–14.3) years.[159] According to the authors, 57 of their patients (79%) met the ARVD diagnostic criteria that were then just newly proposed by McKenna *et al*.[115] Three patients died, with 2 of the deaths attributed to complications of therapy. All but 11 of the surviving patients received treatment with a variety of antiarrhythmic medications given alone or in combination, direct current or radiofrequency ablation, and surgery comprising ICD implantation, right ventriculotomy or right ventricular disarticulation (also used in one of the patients who died). Meaningful conclusions are difficult to extract from these data, but it is noteworthy that most of the surviving patients were asymptomatic at latest follow-up, including 8 of those without treatment. In another retrospective analysis involving 121 ARVD patients of sex and age distribution similar to that of Berder *et al.*'s study, Peters and colleagues identified male sex, a variety of ECG measures of abnormal QRS dispersion and ventricular repolarization, RV enlargement, and left ventricular regional wall motion abnormalities as predictors of arrhythmic events severe enough to precipitate near or actual sudden death.[160] However, they did not describe actual patient outcomes or specify follow-up durations. Niroomand and coworkers recently compared electrophysiologic findings and outcomes in 15 patients presenting with ARVD meeting the McKenna criteria at 37.4 ± 16.4 years of age, and 41 patients assigned a default diagnosis of RVOT VT by exclusion of ARVD at age 40.1 ± 13.4 years.[161] In general, the ARVD patients were found to have more severe symptoms including syncope in 33% vs. 5% in the RVOT VT group, and cardiac arrest in 14% as compared with none among the RVOT VT patients. There were no deaths in either group, but VT and associated symptoms tended to be more resistant to therapy in the ARVD group than in the RVOT VT group. While this study is of some interest in the absence of more definitive data, its value is diminished by small patient numbers, by variable therapy and intervention, and especially by a very brief follow-up interval described by the authors as "around two years in both groups."

Hypertrophic cardiomyopathy (HCM)

VT is a well recognized and sometimes lethal complication of HCM. Citing an annual sudden death incidence of 1–4% in HCM patients, Elliott and coauthors assessed mid-term survival in 16 HCM patients aged 19 ± 8 years with documented sustained VT with syncope or resuscitated VF.[162] Excluding 1 patient who succumbed to neurologic complications of his initial cardiac arrest, there were 2 subsequent sudden deaths in patients treated with amiodarone, while 3 other patients received appropriate ICD discharges for VT during mean follow-up of 6.1 ± 4.0 years. Thus, only 10 of 15 patients were free of actually or potentially life-threatening arrhythmias during this relatively brief time frame.

The pathogenesis of life-threatening ventricular arrhythmias in HCM is likely multifactorial and risk stratification is acknowledged to be challenging, particularly in young patients.[163] Syncope and a family history of sudden death have long been considered markers of sudden death risk in young HCM patients.[162] Nonsustained VT on ambulatory ECG monitoring portends an increased risk of sudden death in adults with HCM.[164,165] The significance of this finding in children is less clear; one study involving 53 pediatric-aged HCM patients reported no apparent association between ambulatory VT and increased sudden death risk over a mean of 3 years of subsequent follow-up,[166] while a more recent retrospective evaluation of 99 children with HCM at our own institution with longer mean follow-up duration (4.8 years) showed VT detected on ambulatory monitoring to be highly predictive of future life-threatening events.[167]

Maki *et al.* performed a retrospective multivariate analysis to identify hemodynamic variables at rest and with exercise predictive of sudden death in 28 members of their 309 patient HCM study population followed over a mean of 9.4 years.[168] Higher resting left ventricular outflow tract gradient and blunted systolic blood pressure response to exercise independently predicted sudden death in the entire group. Of note, the mean age of 8 patients experiencing sudden death in the setting of exercise (28 years) was much lower than that of 20 patients who died suddenly at rest (47 years). Yetman *et al.* proposed that myocardial bridging of the left anterior descending coronary artery (LAD) could cause dynamic occlusion followed by myocardial ischemia. They demonstrated that among 36 children with HCM, 10 patients with myocardial LAD bridging had substantially higher incidences of VT (80% vs. 8%) and cardiac arrest (50% vs. 4%) than did those without myocardial bridging.[169] Aside from its novelty, this finding is of considerable interest because myocardial bridging is often amenable to surgical relief. However, the observation has been challenged by Mohiddin and colleagues, who argued that myocardial bridging

is merely a marker for severe left ventricular hypertrophy, and that it does not independently predict arrhythmias or sudden death in children with HCM.[170]

Recent studies have considered histopathologic and genetic factors as correlates of VT and sudden death in HCM. Varnava and coworkers demonstrated a greater degree of cardiac myocyte disarray in patients dying suddenly and aged younger than 21 years than in those dying of heart failure and at older ages. However, a history of nonsustained VT correlated directly with myocardial fibrosis and inversely with the extent of myocyte disarray among the 75 cases studied post-mortem.[171] Because of its reliance on substantial amounts of tissue for analysis, this approach is unlikely to achieve clinical applicability in HCM risk stratification. Among over 150 genetic mutations thus far linked to HCM, 4 affecting the cardiac β-myosin heavy chain and one involving the cardiac troponin T gene are considered particularly malignant with respect to their association with sudden life-threatening events. Ackerman and colleagues reasoned that screening for these particular mutations in HCM patients might be helpful in risk stratification. They found, however, that only 3 of the 293 unrelated HCM patients whom they tested were affected by any of the 5 mutations, notwithstanding that one-quarter of them had a family history of sudden death. The investigators concluded that this particular screening approach is unlikely to be of value in identifying patients at increased risk due to the marked genetic heterogeneity in HCM.[172]

VT associated with various other conditions

This section is intended to provide some elaboration and references with respect to selected conditions associated with VT in children as listed in Table 51-1. For the most part, there are no published outcome data relating specifically to pediatric VT in these conditions.

Myopathic processes

Inborn errors of fatty oxidation provide an example of congenital metabolic disorders featuring VT. In a series of 107 children with an inherited mitochondrial fatty acid β-oxidation disorder reported by Bonnet *et al.*, 24 had arrhythmias as the predominant presenting clinical abnormality, and 15 of these had VT described as polymorphic with degeneration to VF in 6 of 15. Mortality among the 24 arrhythmia patients was extremely high, with only 4 surviving beyond 2 years of follow-up.[173]

Corrado and colleagues recently presented data on noninvasively detected rhythm disturbances and echocardiographically determined ventricular function in 84 patients with Duchenne muscular dystrophy followed for a median of 76 months from age 18.6 ± 4.8 years. Among 81 patients undergoing Holter monitor recording, 19% had ventricular couplets and 7% had VT. There was 27% mortality in this group, and just over one-third of the deaths were described as sudden. The only variables found to predict mortality were the presence of at least six ventricular ectopic beats per hour on ambulatory monitoring, and left ventricular systolic dysfunction.[174]

Myotonic dystrophy has long been linked with arrhythmias and an increased risk of sudden death. Merino *et al.* performed invasive electrophysiologic testing, followed in most cases by transcatheter radiofrequency ablation, in 6 patients with myotonic dystrophy. All 6 were found to have BBRT, notwithstanding that 5 of 6 had no overt evidence of myocardial or valvular dysfunction.[78] A 17-year-old patient with myotonic dystrophy reported elsewhere had documented ILVT.[175]

Infiltrative or invasive heart muscle diseases

A number of years ago, Garson and coauthors generated considerable interest with their report of surgically resectable myocardial hamartomas serving as VT foci in infants.[176] Apart from a subsequent report of 2 cases from the Mayo Clinic,[177] however, this observation does not seem to have been reproduced at other centers. Indeed, primary cardiac tumours of most types are associated with ventricular arrhythmias[178,179] and should always be sought in newly diagnosed pediatric VT patients, but only rarely is an invasive lesion actually found to underlie ventricular ectopy.

Conduction abnormality

There is a well established association between complete heart block and VT which most often manifests as *torsades de pointes*.[180,181] Evidence obtained from animal heart block models indicates that bradycardia-mediated ventricular remodeling with downregulation of cardiac myocyte repolarizing currents likely underlies the predisposition to VT.[182,183]

Native structural congenital heart disease

There is an extensive literature documenting the association between mitral valve prolapse and various arrhythmias including VT. La Vecchia *et al.* performed extensive functional and anatomic studies in 28 consecutive adult patients with idiopathic VT. They echocardiographically diagnosed mitral valve prolapse in 7 (25%) of these patients, all of whom had VT of right bundle branch block QRS morphology, and all of whom had benign outcomes at mean follow-up of approximately 5 years.[184] Mechanisms by which the other lesions listed in Table 51-1 could predispose to ventricular arrhythmias include myocardial ischemia and imposition of anatomic or functional conduction barriers enabling development of reentrant circuits.

Drugs

Most drug-induced VT is due to cardiac potassium current inhibition, impaired cardiac myocyte repolarization and *torsades de pointes*.[185] This is certainly well demonstrated with respect to the "proarrhythmic" properties of many antiarrhythmic agents, as well as for certain antibiotics, antifungals, nonsedating antihistamines, and cisapride, all of which have been used extensively in children. There are, however, other pathways by which drugs can precipitate VT, including neurally mediated mechanisms that have been implicated with cocaine.[186]

The impact of newer interventions on pediatric VT outcomes

As indicated in the foregoing sections, the natural history of pediatric VT is often benign, particularly in most categories of primary VT. With increasing refinement in our understanding of the distinctions among various types of VT, physicians have a growing obligation to diagnose the cause and mechanism of VT with the greatest possible precision before recommending

therapy that can sometimes be more dangerous than the arrhythmia itself. Treatment should be directed at specific therapeutic endpoints, namely symptomatic relief or the prevention of adverse outcomes in settings of recognized risk. The temptation to aggressively treat asymptomatic patients with "ugly" VT on ECG or Holter tracings should be resisted when potentially life-threatening conditions such as PMVT, ARVD, and HCM have been convincingly excluded.

For many years, antiarrhythmic medications were the sole refuge for clinicians managing pediatric VT. A wide range of drugs has been used in pediatric VT with varying claims of success in trials that typically fail to meet currently accepted standards of randomization and control. Evaluation of these data is further complicated by small and heterogeneous patient populations, the subjective nature of symptomatic reporting, especially in children, and a lack of discrete differences in outcome between treated and untreated cases of many types of VT. Compelling exceptions to this general rule include the widely recognized beneficial effects of calcium channel blockers in ILVT[65,67,68] and beta blockers in PMVT,[88,90,91] although even these have not been subjected to rigorously controlled clinical trials. Antiarrhythmic agents continue to be a mainstay of pediatric VT therapy. Beyond beta blockers and calcium-channel blockers, medications most often found to be effective in chronic VT management are those belonging to Vaughan Williams classes 1c[187,188] and 3.[189,190]

Transcatheter radiofrequency ablation of supraventricular tachydysrhythmia substrates has gained widespread acceptance and achieved considerable success among pediatric cardiologists since 1990,[191] but experience with VT ablation in children remains limited and no large-scale outcome studies have been published as of this writing. A Dutch group recently reported their adult VT ablation results in a group of 122 men and 29 women aged 57 ± 16 years who were followed for an average of just under 3 years post-procedure. Their results are of interest because the 151 patients included 30 (20%) with primary VT and 32 (21%) with ARVD. Major procedural complications occurred in 7% of the patients, including death in 2%. The procedure was considered successful in 83% of cases, and VT subsequently recurred in 19% of successful cases and 64% of unsuccessful cases.[192]

Implantable cardioverter-defibrillator devices (ICD) undoubtedly represent the most significant advance in life-saving therapy for patients with dangerous ventricular arrhythmias,[193] and progressive miniaturization of these devices is making them increasingly accessible to infants and young children. ICD therapy is of clearly demonstrated benefit in high-risk HCM patients,[194] and there is a growing familiarity with its advantages and pitfalls in other conditions featuring life-threatening VT, such as ARVD[158] and PMVT.[86]

The earliest collected pediatric ICD experiences appeared in 1990.[195,196] Kron and colleagues' international survey identified just 40 patients aged <20 years who had undergone device implantation, with generally favorable results including 82% survival at 33 months of follow-up.[195] By 1993, the Pediatric Electrophysiology Society investigators were able to present 31 ± 23 months' worth of multicenter follow-up data on 125 of 177 identified patients who had received ICDs at ages ranging from 1.9 to 19.9 (mean 14.5) years. Indications for device implantation included resuscitated sudden cardiac death in 76%, drug refractory VT in 10%, and syncope with inducible sustained VT in 10%. The actuarial 5 year survival post-implantation was 85%, and ventricular dysfunction was the primary correlate of mortality among the 9 patients who died.[197] Hamilton and co-authors reported on the 5-year ICD experience of our own institution involving 11 patients aged 4–16 years in 1996. While relating a favorable experience overall including no mortality in follow-up ranging to 3.5 years, they also drew attention to the problem of inappropriate device discharges which occurred in 6 of the patients and were not completely controlled by the routine administration of beta blockers to prevent sinus tachycardia.[198] Recently, Love *et al.* reviewed the single center ICD experience of Children's Hospital, Boston, involving 81 implantation procedures up until December 1999, and focusing on the incidence of supraventricular tachycardias that could contribute to the occurrence of inappropriate device discharges in these patients. Of note, this series included a substantial number of adults, with patient ages ranging between 15 months and 48 years (median 16.5 years). In keeping with continuous improvements in device technology and physician experience in ICD management, there were only 2 deaths among 54 patients during a median follow-up duration of 38 months, and one of these deaths occurred in a patient who had refused replacement of a depleted generator. Three other patients underwent cardiac transplantation with ICD removal.[199] The increasingly routine use of ICDs in patients of all ages with life-threatening ventricular arrhythmias will almost certainly have a substantial impact on these patients' outcomes, with implications for life expectancy that are most profound in the pediatric population.

All references can be found at the end of the book. See pp. 863–8 for Chapter 51.

The Natural and Modified History of Congenital Heart Disease
Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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Professor Jane Somerville

Epilogue

The senior author of this work (RMF) and I have been friends for more than 30 years. We have witnessed most of the advances, developments and disasters in the understanding and management of congenital heart diseases. We have shared medical education at home and abroad, enjoying ourselves over the decades with the "world as our oyster," trying to make contributions and exchanging thoughts, some original, some crazy, some excellent and even useful as well as extraordinary. Despite differences in backgrounds and training we share the same sense of humor and have discovered similar perceptions of truth, facts and observations of the world of pediatric cardiology and the people players in it – good and bad. Our ideals have been maintained and goals remained the same. Bob has always been concerned with understanding the hearts, anatomy, angiography correlated with pathology and managing events in infants and children, particularly the complex anomalies. I, trained as an adult cardiologist, have been concerned with the outcomes of claimed surgical triumphs as their blemished futures unfolded, their care, diagnosis and the establishment of correct clinical services to give optimal medicine for life. Our aims were complementary. Neither of us became hooked on nomenclature nor embryological mythology. To us "what does it do?" was more important than "where does it come from?" All this and more was debated over many good meals, often with great wine and laughter. I am honoured to be "told" to write the last words in this encyclopedia of congenital heart disease.

Bob has always written papers and chapters and books, contributing so much to the dissemination of knowledge about congenital abnormalities of the heart as he swept in everybody's contributions, with full descriptions as shown so clearly in this book. There is no point in referencing this final chapter, all the relevant references are here. References for almost every condition and solution can be found somewhere in this tome. He has been my one encourager for ideas and "lateral" thoughts, constantly pressurizing me to write a book, which I would neither finish nor probably ever start. There was a suggestion we should combine in his last work and for a brief period it was agreed we would write together on "outcomes." He would bring knowledge and perspectives up to date, inserting his own views and I would address the long-term adult data and experience of clinical management and results of further surgery over decades. Our styles of thinking and writing are so different and with my lack of discipline and too many interests it did not happen.

This is Bob's book and that's how it's planned and executed. Yet the contributions of Shi-Joon Yoo, Haverj Mikailian and Bill Williams and the other contributors all add to the completion of this opus, and should not be underestimated or undervalued. I have followed the production with enthusiasm. Bob often showed and shared his contributions, always ignoring my criticisms and cries that this was not about "outcomes" and all attempts to change his English. What is there left to say about congenital heart disease after he has analysed all the referenced writing on all the anomalies which affect the heart and circulation at birth, and the evolution of management strategies witnessed to date?

What to call Chapter 52? I suggested Epilogue (not Epitaph!). He did not tell me. All I had was "please write it." Epilogue is, according to the *Oxford English Dictionary*, "the concluding part of a literary work," "a speech or short poem addressed to the spectators by one of the actors after the play is over." Epilogue is the correct title.

This book is "all ye know and all ye need to know" as Keats wrote when a medical student at Guy's Hospital (where I trained) and of greater importance where Blalock first visited across the ocean to speak of his success in treating cyanotic patients. I was a medical student, raw and playful. This initiated my intrigue and enthusiasm about congenital heart disease which has remained. Entranced and amazed by the "antics" of cardiac surgery, or was it surgeons, I was a "dresser" on the firm and subsequently the house surgeon to Sir Russell Brock. I so wanted to be a cardiac surgeon and part of all this excitement. It was one long thrill and many long days and nights of struggle for survival – the patient's and mine.

Finding my hands were not connected to my head, the need for reoperation, often so soon and very tedious long hours holding a retractor, I decided medical cardiology and observation of surgeons and their eccentricities in cardiac surgery could be a better professional path. Despite warnings of likely personal failure, cardiology was exciting as was the man of my "dreams" – both achieved.

This book is a whole "Ring Cycle" of congenital heart disease and pediatric cardiology explained in all its magnificence and weaknesses, available in one volume. It includes the triumphs of Wotan(s), the cardiac surgeons, the Niebelungs (pediatric cardiologists) developing over years into an organized and recognized group with a difficult start to establish themselves as a specific specialty, particularly in Europe. This development was inevitable since the need to treat infants and newborns, and now fetuses, with heart disease became clear. There are the strong Walkyrie (nurses) vital to success and their development into an influential force, and there were the naughty gnomes (guess who) and the occasional interventions of strong Brunhilde to solve, support and perhaps increase dissent. Like Wagner's

Ring, it tells of triumphs, greed, sadness, mistakes, misunderstandings and unexpected events and contains much of the author's philosophy and wisdom, as well as useful folklore. It is as amazing as Wagner, providing a chronicle of different eras, moods and thinking. Like Wagner the story is both simple, human and in parts complex and is equally compelling as the reality of what has been achieved over 50 years. The surgeons' triumphs have created the new medical community of grown up congenital hearts (GUCH) or "adults" as North America wishes to call them. "Adults" takes no account of the adolescents' care whose needs change as they "grow up." The management of the "transition" is fundamental. The arrival and advance of therapeutic medical interventions via catheter, to the Valhalle of pediatric cardiology will cause disruption to the surgeons but hopefully not destroy the practice and training of cardiac surgeons so needed for complex congenital heart disease, at least until successful prevention.

"This is not the end. It is not even the beginning of the end. It is perhaps the end of the beginning," so wrote Winston Churchill in 1942 and this applies to Chapter 52. What matters to us both is what happens to the patient and lesions over three score years and ten. Mostly we do not know but we are learning all the time as the new problems in the GUCH show themselves. The wide variety of abnormalities and innovative solutions by man have produced a constellation of different problems to be solved decades later.

There have been enough long-term survivors reaching adulthood over the last 40 years of surgical and medical progress to provide adequate information to demonstrate the need for specialist expertise to care for the long-term survivor, establishing the importance of informed medical care beyond childhood and pediatrics. Soon there will be more GUCHs than children with congenital heart disease in the population but fewer GUCH patients needing expert care since surgery helped so much. Total numbers do not reflect the medical needs of the GUCH community, although these are frequently used to demonstrate the growth and demands of the group. Freedom has profoundly influenced this development by supporting services for GUCH in Toronto General Hospital across the bridge and road; separate services, each with their autonomy, sharing surgeons and facilities but keeping healthily apart. Truly an exemplary development initiated by John Keith – a man of vision.

There are many long-term survivors with simple and severe lesions who have done well. Reparative surgery better performed in infants has evolved since the courageous and refined surgery by Dr Aldo Castaneda at the Boston Children's Hospital, who started his contributions to the surgical management of congenital heart disease where C Walton Lillehei took an immense risk using the mother as the bypass "machine" to repair a ventricular septal defect. Would the moralists and managers of today allow such spectacular risks which paved the way for the use and safety of cardiopulmonary bypass?

We know that radical repair of Fallot's tetralogy, the commonest cyanotic congenital heart disease has been a success over 40 years. Results are excellent with maintained long-term results with increasing "grandaddies." Large numbers of patients have been seen with good lives although but there are 10–15% with important residua. Discussions about pulmonary regurgitation, often inevitable to relieve the right ventricular tract obstruction, have occupied research and conference space for 30 years continuing with attractive solutions. Attention has been diverted to a small "layby" track with attention of a few to the dangers of widened QRS, frightening patients and physicians when QRS > 0.16. As part of a constellation of more important factors involving pulmonary regurgitation it can herald problems. It is the change that matters. There are many patients from yesteryears' surgery aging quietly, static with such findings and well. Attention is now returning to the straight path to concentrate on pulmonary valve leak and when it should be treated. Now we have nonsurgical means using Bonhoeffer's valve placed through a cardiac catheter. It is too soon to know if this new triumph will last. The life of the new valve will determine this but it does delay the first reoperation.

It could be as important as Ross's use of the cadaver aortic homograft to replace the diseased pulmonary valve placed in the right ventricular outflow for pulmonary atresia in 1966. An operation modified to treat many other forms of complex congenital heart diseases which has stood the text of time. A major advance for congenital heart diseases. Many factors influence longevity of homografts and the urgent need for something to prevent calcification and degeneration remains.

The dramatic reversal of the once disastrous fate of classic transposition with atrial septation by Mustard and Senning has seen many patients "grow up," still with problems yet often able to lead normal lives. Such problems are arrhythmias, baffle obstructions and systemic ventricular failure, the latter requiring a later arterial switch or cardiac transplantation to be salvaged. The long-term future of the "switched" transpositions for which the patients have to thank Adib Jatenes' ingenuity and courage in Sao Paulo has yet to unfold. What will happen to the neoaortic valve, the implanted coronary orifices and the multiple suture lines? So far it has been a real advance in restoring normality of circulation in patients with transposition and when applied to neonates as shown by Aldo Castaneda and which with Magdi Yacoub is now routine practice. The more recent evolution from physiological to anatomical repair of congenitally corrected transposition demands ingenious surgery; time will tell whether these new "double" switches are justified and when they should be undertaken.

Coarctation, one of the earliest lesions to have surgical repair, initiated by Clarence Crafoord, is a success story with many subsequent technical modifications which influence long-term complications and survival. Possibly now surgery may not be needed. Time will show. This simple condition provides the best example of diffuse "congenital cardiovascular disease" involving not only many other disorders of structure of the heart and valves but also the need to understand that there is congenital disease in conducting arteries and myocardium. This concept of structural congenital heart anomalies being part of congenital cardiovascular disease was proposed and demonstrated by a remarkable pathologist, Luis Becu in the early 1970s. Interest and rediscovery has been recently stimulated by Joe Perloff, a pioneer in GUCH management who must have felt, at times, that he cried in "the wilderness" to establish such services. The footprints of congenital cardiovascular disease give subtle signs or even dramatic events in adults. It is more frequent than realized and often undiscovered because of the shortage of informed and interested cardiac pathologists. The vital investigation of necropsy is often neglected in the millennium.

The consequences of failures in old Fontan patients, despite the occasional outstanding success, at least one grandfather known, provide extraordinary difficulties for those caring for GUCH patients. The misery and solutions for protein losing enteropathy, attrition of the long starved systemic ventricle, now

referred to as "restricted preload," dangerous and disasterous atrial arrhythmias confirm the imperfections of this once hailed answer for complex heart diseases. Without the efforts and ingenuity of Frances Fontan there might not have been the need for specialists in grown up congenital heart disease: cardiologists do not understand and do not want to understand the Fontan circulation. This does not prevent their attempts to manage and not refer. Those who pioneered the subspeciality of caring for outcomes are grateful to Fontan.

We have yet to learn the fate of long-term survivors of repaired hypoplastic hearts, cavopulmonary connections, interventional devices, new valves, and often new techniques. We need to know what is good and lasting. Already the study of GUCH patients calls for modification or even stopping some of the established techniques used in childhood. The solutions for the "ills" of the panacea may be more testing for surgeons and cardiologists than the primary intervention or replacement. "Total correction" is a dream but radical repair of many abnormalities has been an extraordinarily successful surgical endeavor. The continued scourge of arrthymias, progressive pulmonary vascular disease, destructive myocardial changes with terminal apoptosis, degeneration in biological and native valves still begs for solutions to better the outcomes for patients.

Pediatric cardiology, created by necessity to increase and strengthen success of cardiac surgery must change and we the "grown up cardiologists" must learn and care for the survivors. The specialty of congenital heart disease and its management has arrived at a point of maturity and understanding as shown with particular clarity by this book. It needs more time for cardiologist and patients to grow older with grace, style and more understanding before the true and complete final story of this Ring can be written.

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CHAPTER 1

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CHAPTER 4

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CHAPTER 5

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CHAPTER 6

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CHAPTER 10

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CHAPTER 11A

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CHAPTER 13A

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CHAPTER 13B

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CHAPTER 14B

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CHAPTER 14C

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CHAPTER 15A

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CHAPTER 15B

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CHAPTER 16

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CHAPTER 22

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CHAPTER 23

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CHAPTER 24A

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CHAPTER 24B

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CHAPTER 24C

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CHAPTER 25B

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CHAPTER 25C

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CHAPTER 28

Part I: Double-Outlet Right Ventricle

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CHAPTER 33

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CHAPTER 34

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CHAPTER 35

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CHAPTER 37

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CHAPTER 39

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CHAPTER 40

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CHAPTER 41G

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CHAPTER 41H

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CHAPTER 41I

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CHAPTER 45

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CHAPTER 46

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CHAPTER 48

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CHAPTER 49

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CHAPTER 50

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CHAPTER 51

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Edited by Robert M. Freedom, Shi-Joon Yoo, Haverj Mikailian, William G.Williams

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