Seminar

Pericarditis

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Pericarditis is a common disorder that has multiple causes and presents in various primary-care and secondary-care settings. New diagnostic techniques have improved the sampling and analysis of pericardial fluid and allow comprehensive characterisation of cause. Despite this advance, pericarditis is most commonly idiopathic, and radiation therapy, cardiac surgery, and percutaneous procedures have become important causes. Pericarditis is frequently self-limiting, and non-steroidal anti-inflammatory agents remain the first-line treatment for uncomplicated cases. Integrated use of new imaging methods facilitates accurate detection and management of complications such as pericardial effusion or constriction. Differentiation of constrictive pericarditis from restrictive cardiomyopathy remains a clinical challenge but is facilitated by tissue doppler and colour M-mode echocardiography. Most pericardial effusions can be safely managed with an echo-guided percutaneous approach. Pericardiectomy remains the definitive treatment for constrictive pericarditis and provides symptomatic relief in most cases. In the future, the pericardial space might become a conduit for treatments directed at the pericardium and myocardium.

For more than a century, diseases of the pericardium have intrigued physicians. They have observed the wide range of clinical manifestations and begun to unravel the underlying anatomical and pathophysiological mechanisms. The normal pericardium cradles the heart within the middle mediastinum, protecting it from adjacent organs and providing constraint during diastolic filling. Pericarditis—inflammation of the pericardium—is a common disorder that presents in various settings, including primary care, accident and emergency departments, and subspecialty departments, such as cardiology, rheumatology, and nephrology.[1,2] Generally benign and self-limiting, pericarditis is occasionally complicated by pericardial effusion or constriction, which increase morbidity and mortality. Historically, eponymous physical signs, including those of Broadbent (systolic apical retraction), Friedreich (rapid y descent of the jugular venous waveform), and Kussmaul (an inspiratory rise or failure to fall in the jugular venous pulse) in constrictive pericarditis, and pulsus paradoxus (respiratory variation in systemic arterial pressure) and Beck's triad (hypotension, quiet heart sounds, and raised jugular venous pulse) in cardiac tamponade, reflected the underlying pathophysiology.

Despite the remarkable insights from clinical diagnosis, these signs lacked accuracy; modern imaging technologies allow more precise diagnosis. Still, however, detection and treatment of pericarditis, particularly its complications, remain a challenging problem in clinical practice, guided largely by the experience of a few referral centres, specialists, and mainly small retrospective studies. Furthermore, the prevalence of the pericardial diseases is not easily recorded because of referral bias, few prospective series, and inconsistent diagnostic criteria. The diagnoses of constriction and cardiac tamponade were previously made mostly by invasive haemodynamic tests. Now, however, non-invasive techniques, particularly echocardiography, with doppler, CT, and MRI, provide rapid, safe, and effective diagnostic methods to detect or confirm clinically suspected anatomical and pathophysiological abnormalities of pericardial disease.[3,4] There is hope that improved diagnostic testing will promote a clearer understanding of the epidemiology of disease and establish a standard diagnostic and management approach to this complex and intriguing group of disorders. We describe advances in the diagnosis and management of pericarditis and its major complications.

Anatomical considerations

The pericardium is a double-layered fibroserous sac that envelops the heart, covering nearly the entire cardiac surface and extending on to the great vessels. During development, as the embryonic heart tube advances into and invaginates the pericardial sac, the inner serosal layer of pericardium adheres to the myocardium, forming the visceral pericardium or epicardium, before reflecting back on itself to become contiguous with the outer fibroserous layer of parietal pericardium.[5] The two layers of the pericardial sac are 1–2 mm thick and are separated by a space that normally contains 15–35 mL pericardial fluid. The pericardium receives an independent blood supply from the internal mammary arteries and innervation from the phrenic nerve, and ligamentous attachments to the sternum, vertebral bodies, and diaphragm limit translation of the heart within the thorax.[1]

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Search strategy and selection criteria

We did a comprehensive MEDLINE search with the MeSH terms "pericarditis", "pericardium", "pericardial", "pericardial constriction", "pericardial effusion", "cardiac tamponade", and "diastolic function" from 1990 to January, 2004. Only papers published in English were retrieved. Papers with new or important insights or with useful further-reading lists are cited.

The parietal pericardium has an outer fibrous layer composed of multiple collagen layers interspersed with elastin fibrils, and an inner serous layer with a microvillous surface specialised for secretion of pericardial fluid.[6] Surfactant-like prostaglandins within pericardial fluid act as a lubricant during cardiac motion,[1] and prostacyclin and other substances regulate local sympathetic tone, cardiac contractility, and coronary vasodilatation.[7]

Physiological function of the pericardium

As well as protecting and restraining the heart, the normal pericardium is an important determinant of cardiac filling patterns.[1,2,8] Pericardial constraint limits chamber dilation, particularly of the thin-walled right atrium and ventricle, and equalises compliance between the right and thicker-walled left ventricle. The latter produces interdependence of filling between the ventricles, which normally is not physiologically important. When intrapericardial pressure is increased (as with pericardial effusion) or the pericardial cavity becomes fixed (as in constriction), ventricular interdependence is exaggerated and is frequently a key diagnostic feature.[1,2]

The pericardium exhibits an exponential stress-strain relation that reflects its microstructure and has a substantial reserve volume.[1] Physiological changes in circulating volume produce only minimum changes in intrapericardial pressure. With abrupt or large increases in intravascular volume that exceed the pericardial reserve volume, the pericardium exerts a notable constraint to filling.[1] Intrapericardial pressure is normally similar to pleural pressure, varying from −6 mm Hg at end inspiration to −3 mm Hg at end expiration. Lowering of pericardial pressure in inspiration raises transmural pressures in the right atrium and ventricle, leading to increased filling of the right heart, whereas left-heart output decreases slightly because of increased aortic transmural pressures and delayed pulmonary transit.

Pericarditis presentation

Inflammation of the pericardium presents in many clinical settings and has a wide range of causes.[2,9,10] The classic acute presentation is an important differential in the assessment of acute chest pain, but pericarditis can present in subacute or chronic forms. Presentations can include incidental effusion, cardiac tamponade, or constrictive pericarditis.[1,11] The diagnosis of acute pericarditis is based on the presence of typical symptoms of chest pain, pericardial rub, and characteristic electrocardiographic changes.

Epidemiology

The true incidence and prevalence of pericarditis are difficult to measure. A prevalence of around 1% in autopsy studies suggests that pericarditis might frequently be subclinical.[12] Pericarditis might account for around 5% of presentations to accident and emergency departments for non-acute myocardial-infarction chest pain.[10] Use of radiation therapy, percutaneous cardiac interventions, cardiac surgery, and the rising incidence of HIV have led to a shift in the type of causes.[1,13,14] By contrast, *Mycobacterium tuberculosis* pericarditis is now rare in developed countries, but remains more common in developing nations and in immunocompromised hosts.[15,16]

Causes

Pericarditis has a vast array of causes (panel) that can be separated into infectious and non-infectious categories. Non-infectious pericarditis can be subdivided into immunoreactive, neoplastic, traumatic, and metabolic causes.[17] Historically, most cases of pericarditis have been idiopathic.[1,2,17,18] Techniques such as pericardioscopy, immunohistochemistry, and PCR have improved the sampling and analysis of pericardial fluid and tissue and allowed more comprehensive classification of cause.[17] Nevertheless, the cause of pericarditis is not defined in up to 30% of patients, even when pericardial fluid or tissue samples are obtained.[14,17] Although antimyolemmal and sarcolemmal antibodies can be identified in idiopathic cases, the original stimulus is not confirmed and is typically assumed to be viral.[17] The usefulness of these tests in routine clinical practice is uncertain and they are frequently not done.

A wide range of organisms cause infectious pericarditis, but viral infection remains the most common probable or identifiable cause.[1,17,19] Organisms responsible for myocarditis are commonly implicated, particularly enteroviruses, adenoviruses, and influenza; herpes simplex and cytomegalovirus might be important in immunocompromised individuals.[17] Pericardial abnormalities are seen in up to 20% of patients with HIV infection,[20,21] but symptomatic pericarditis can frequently be due to secondary infection (commonly mycobacterial) or neoplasia (particularly lymphoma or Kaposi's sarcoma).[15] The frequency of pericardial involvement is lowered by

Cause of acute pericarditis

Idiopathic

Infections

Bacterial, tuberculous, viral (coxsackie, influenza, HIV, etc), fungal, rickettsial, mycoplasma, leptospiral, listeria, parasitic, and others

Vasculitis and connective-tissue disease

Rheumatoid arthritis, rheumatic fever, systemic lupus erythematosus, scleroderma, Sjögren's syndrome, Reiter syndrome, ankylosing spondylitis, Wegener's granulomatosis, giant-cell arteritis, polymyositis (dermatomyositis), Behçet's syndrome, familial Mediterranean fever, dermatomyositis, polyarteritis, Churg-Strauss syndrome, thrombohaemolytic thrombocytopenic purpura, leucoclastic vasculitis, and others

Diseases in adjacent structures

Myocardial infarction, aortic dissection, pneumonia, pulmonary embolism, empyema

Metabolic disorders

Uraemic, dialysis-related, myxoedema, gout, scurvy

Neoplastic disorders

Primary

Mesothelioma, sarcoma, fibroma, lipoma, and others

Secondary (metastatic or direct spread)

Carcinoma, lymphoma, carcinoid, and others

Trauma

Direct

Pericardial perforation (penetrating injury, oesophageal or gastric perforation) and cardiac injury (cardiac surgery, percutaneous procedures)

Indirect

Radiation, non-penetrating chest injury

Association with other syndromes

Postmyocardial and pericardial injury syndromes, inflammatory bowel disease, Loffler syndrome, Stevens-Johnson syndrome, giant-cell aortitis, hypereosinophilic syndromes, acute pancreatitis, others

Modified with permission from Spodick DH. Pericardial disease. In: Braunwald E, Zipes DP, Libby P, eds. Heart disease: a textbook of cardiovascular medicine, 6th edn. Philadelphia: WB Saunders, 2001 (reference 1).

effective antiretroviral therapy, but when present denotes a worse outcome.[21]

Myopericarditis has been reported after smallpox vaccination in vaccinia-naive US military personnel.[22] Bacterial pathogens typically cause purulent pericarditis but are implicated in only around 5% of cases.[13,17] Bacterial spread to the pericardium may be haematogenous or by extension from adjacent organs, particularly the lungs or pleural space.[13] *M tuberculosis* causes up to 4% of acute pericarditis cases and 7% of tamponade presentations in developed countries, and remains important in developing nations and immunocompromised hosts.[15,16,23] Tuberculosis-related pericarditis might require pericardial biopsy for diagnosis and is complicated by pericardial effusion or constriction in up to 50% of cases.[24,25]

Neoplastic pericarditis is most frequently a secondary disorder, caused by local tumour invasion, or lymphatic or haematogenous spread. Primary malignant disease of the pericardium is rare.[26,27] Effusions (generally haemopericardium) are common and can be difficult to manage.[28] Pericarditis associated with transmural myocardial infarction has become less frequent with use of thrombolysis but still occurs in 5–10% of cases.[29,30] This disorder may be detected clinically by a rub[31] and on electrocardiography by ST segments or T-wave evolution and PR segment depression.[32,33] The PR segment depression suggests myopericarditis of the atria and might predict later atrial fibrillation.[34] Ventricular rupture should be considered in haemodynamically unstable patients with evidence of pericarditis.[35] Late postinfarction pericarditis (Dressler's syndrome) occurs in up to 5% of myocardial-infarction patients and typically presents more than 1 week after infarction with single or recurrent episodes of fever, raised inflammatory-marker concentrations, and pericardial pain.[2]

Pericarditis after cardiac surgery (postpericardiotomy syndrome) has been reported in up to 20% of cases at a median of 4 weeks after coronary bypass graft surgery.[1,36] Pericardial constriction has been reported in around 0·2% of cardiac surgical cases, occurring as early as 2 weeks after surgery.[37–39] A similar incidence is reported with minimally invasive surgery.[40] Any direct injury can cause traumatic pericarditis, which has been described after penetrating chest injury, needle embolus, and oesophageal fistula due to fish bones or toothpicks.[41–43]

Pericardial complications occur infrequently after percutaneous interventions—less than 0·2% in a large series of patients undergoing catheterisation, percutaneous transluminal angioplasty, pacemaker insertion, and catheter ablation.[44,45] Increased use of antiplatelet and anticoagulant treatments might raise the rate of these complications.[46] Active fixation pacemaker leads cause complications more frequently than passive leads.[47]

Radiation therapy for treatment of mediastinal tumours and breast cancers is an increasingly important cause of pericarditis or pericardial constriction.[37,48] Constriction occurs in around 4% of patients receiving radiation therapy for mediastinal Hodgkin's disease and might be predicted by the dose fraction.[49]

Presentation and diagnosis

Acute pericarditis classically presents with progressive, frequently severe, chest pain that is sharp and pleuritic. The pain is generally worse when lying supine, is relieved by sitting, and might radiate to the neck, arms, or left shoulder, making differentiation from myocardial ischaemia difficult. One distinction is that in pericarditis, pain can be referred to the trapezius muscle ridge because of phrenic-nerve innervation of these two regions.[9] Fever or features of sepsis might accompany viral or purulent pericarditis.[1]

A pericardial friction rub is pathognomonic for pericarditis, but is frequently not present. Best heard in end expiration when the patient is leaning forward, the sound is classically a rasping or creaking with a triple cadence but might be biphasic or monophasic. By contrast, a pleural rub is timed with the respiratory cycle.[1,50] A developing pericardial effusion might lessen the rub, but it is commonly still heard. Myocarditis is suggested by non-pleuritic pain, a rise in cardiac enzymes, conduction abnormalities, arrhythmias, or cardiac dysfunction on imaging, which might be evident only after drainage of an accompanying effusion.[1]

Electrocardiography is perhaps the most useful diagnostic test for acute pericarditis and classically shows widespread saddle-shaped or upward concave ST-segment elevation that reflects subepicardial inflammation.[1,51,52] PR-segment depression can accompany or precede ST changes. Electrocardiographic abnormalities may evolve through four phases: ST elevation and upright T waves (stage I) that typically resolve to normal (stage II) over several days or evolve further to T-wave inversion (stage III) and finally to normal (stage IV).[1] Unlike pericarditis, the ST-segment changes in myocardial ischaemia or acute myocardial infarction are characteristically regional.[53] There is no Q-wave formation or loss of R wave in acute pericarditis. The electrocardiographic changes of pericarditis can be differentiated from the early repolarisation pattern, which rarely shows PR-segment elevations (especially aVR) or ST elevation in V6.[9,54] A finding of the ratio of the height of the ST-segment-junction to the height of the apex of the T wave of more than 0·25 is suggestive of pericarditis.[1,51,52]

On laboratory findings, plasma troponin I may be raised in patients with ST elevation and acute pericarditis, reflecting myocardial involvement.[55] Elevation of troponin I in pericarditis does not seem to carry an adverse prognosis.[56] Leucocytosis, raised C-reactive protein concentration, and sedimentation rate are common findings. Serological studies might confirm the cause as infectious or autoimmune pericarditis, but are rarely of clinical relevance.[57]

Imaging of the heart has limited usefulness in uncomplicated acute pericarditis but is important in the assessment of sequelae such as effusion or constriction.[3,58] Chest radiography is frequently normal, but cardiomegaly can be seen in patients who have substantial pericardial effusion. More than 250 mL fluid is needed to enlarge the cardiac outline.[1] Echocardiography might be normal or show a small effusion, but provides a rapid, accurate, non-invasive assessment of pericardial and cardiac morphology and the physiological importance of complications.[59,60] Newer methods, such as tissue doppler imaging and colour M-mode of early left-ventricular flow propagation, help to define diastolic function and allow differentiation of constrictive pericarditis from restrictive cardiomyopathy.[44] Transoesophageal echo may be necessary when surface echo is suboptimum and there is evidence of complex diastolic dysfunction (mixed constriction and restriction) or postoperative pericardial haematoma. A paediatric transoesophageal echo probe inserted into a chest drain in the pericardial space allows rapid assessment of postoperative effusions.[61] Intracardiac echo has successfully guided pericardiocentesis in an experimental model and might be useful in the catheterisation laboratory.[62] CT and MRI provide excellent visualisation of the pericardium and pericardial space and have an important role in the assessment of

complications of pericarditis.[63–66] Radionuclide scanning can identify pericarditis as the source of an inflammatory syndrome, but is not routinely undertaken.[67]

Pericardiocentesis is indicated for pericardial effusion with clinical tamponade, purulent pericarditis, and a high suspicion of tumour, and should be considered for moderate or large effusions when acute illness is sustained and the diagnosis needs clarification.[1] A low yield for purely diagnostic taps has been reported, but newer techniques provide a diagnosis in up to 75% of cases.[17,68] In most cases percutaneous pericardiocentesis can be done safely, rapidly, and successfully under echocardiographic guidance.[69,70] A specialised needle that emits high-frequency sound waves can be used to accurately localise a needle tip with use of colour doppler imaging.[71]

If surgical drainage is necessary, a subxiphoid approach is almost always suitable and allows direct visualisation of the pericardium for a biopsy if indicated.[1] The complication rate is low (<1%) and recurrence of effusion is infrequent (around 8%).[11] A subdiaphragmatic laparoscopic technique and, more commonly, video-assisted thoracoscopic technique have been used for drainage of larger effusions.[72] A harmonic scalpel prevents bleeding with the laparoscopic technique.[73] Flexible pericardioscopy, although not available in all centres, is a less-invasive technique that allows inspection and targeted epicardial or pericardial biopsy.[74] This approach might increase the yield of biopsy and facilitate autofluorescence techniques for photodynamic diagnosis in suspected neoplastic effusion.[75]

Pericardial-fluid measurement should be done of glucose, protein, and lactic dehydrogenase, as well as cell-count, microscopy (including gram and Ziehl-Nielsen stain), bacterial (and occasionally viral) culture, and cytological examination.[1] PCR techniques can identify causative viruses and *M tuberculosis* from pericardial fluid or tissue.[68,76,77] Immunohistochemistry techniques can identify antibodies to myolemma and sarcolemma in immune-mediated pericarditis.[74] High concentrations of adenosine deaminase activity in pericardial fluid are specific for *M tuberculosis* and can predict constriction.[78] Carcinoembryonic antigen concentrations are higher in neoplastic than in benign effusions, with a carcinoembryonic antigen concentration of 5 ng/mL having 75% sensitivity and 100% specificity for malignant disease.[78]

Pericardial biopsy should be considered if malignant or granulomatous causes are suspected.[79,80] Histologically, pericarditis is characterised by hyperaemia, microvascularity, leucocyte accumulation, and fibrin deposition. In most cases, there is a trivial or small associated pericardial effusion. When present, pericardial fluid is typically hypercellular (polymorphs) and purulent in bacterial pericarditis, and is serous or serofibrinous in viral or immunoreactive pericarditis. Lymphocytes typically predominate in viral, tuberculous, and occasionally neoplastic pericarditis.[2] Haemorrhagic effusions are most commonly seen in tuberculous, neoplastic, or traumatic pericarditis but may also be due to radiation disease or idiopathic pericarditis.

Not all cases of pericarditis require the full series of available tests. We propose the following sequence as a rational approach to the investigation of pericarditis (figure 1).[14] For all patients a complete history should be taken, with physical examination, electrocardiography, chest radiography, complete blood count, measurement of sedimentation rate and plasma electrolytes, and renal-function testing. If clinically appropriate, diagnosis-specific tests might include tuberculin skin testing, rheumatoid factor, antinuclear antibody, and viral studies.

In more complex cases, with a long course, evidence of tamponade, or purulent pericarditis, echocardiography should be done and pericardiocentesis considered if a substantial effusion is detected. Additional imaging by transoesophageal echo, CT, or MRI should also be considered if surface echocardiography is inadequate or there is a suspicion of constriction or complex diastolic dysfunction.

Management of acute pericarditis

The natural history of acute pericarditis is commonly benign and, therefore, management is largely supportive.[1] If a specific cause is identified, treatment should target the underlying cause, including appropriate antimicrobial treatment for any infectious organism.[1,81] Associated empyema or parapneumonic effusions should be drained.[2]

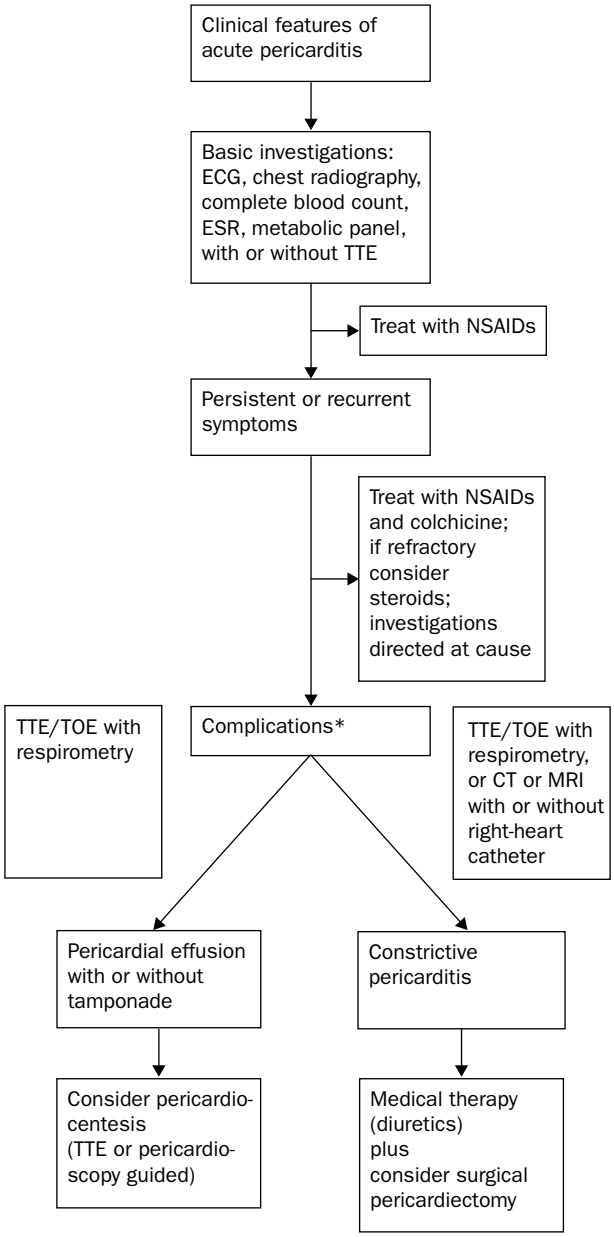

Figure 1: **Suggested approach to investigation and management of pericarditis and its complications**
TTE=transthoracic echo. TOE=transoesophageal echo. *Defined as haemodynamic instability, right-heart failure, volume overload, or both, or unexplained cardiovascular symptoms.

In uncomplicated cases, non-steroidal anti-inflammatory drugs (NSAIDS) are effective treatment for fever, pericardial pain, and inflammation.[82–84] As a first-line agent, we favour ibuprofen, which has a reasonable safety profile and can be titrated across a range of doses. Indometacin is an effective alternative especially for pain, but reduces epicardial coronary flow.[84] COX2-specific inhibitors offer a theoretical advantage but have not been studied in pericarditis.

Colchicine should be added in patients who have recurrent pericarditis. This drug is well tolerated and is often effective for recurrent pericarditis among patients who have already received NSAIDS and cortico-steroids.[85–87] Its efficacy is probably greatest in serositis due to familial Mediterranean fever.[88] Colchicine is an effective first-line treatment in NSAID-intolerant patients.[85–87]

The use of corticosteroid treatment is controversial. This approach is indicated for pericarditis with effusion due to *M tuberculosis*, in which it reduces the incidence of constriction.[89,90] In a study from Africa, steroid treatment improved clinical recovery and reduced complications in HIV-1-infected patients with effusive tuberculosis-related pericarditis.[91] However, in non-tuberculous pericarditis, systemic corticosteroids, although effective in reducing symptoms and recurrent episodes, should be reserved for severe cases not controlled by colchicine or NSAIDS because of their side-effect profile and a theoretical risk of reactivating infection or an increased incidence of chronic relapsing pericarditis.[1,92] Azathioprine or cyclophosphamide can be added to maintain remission while reducing steroid requirements.[93] Intrapericardial administration of steroids is effective and can reduce systemic side-effects.[94]

Pericardioscopy can facilitate direct instillation of treatments into the pericardial space.[95,96] This approach might be suitable for angiogenic and other gene-related treatments in the future.[95,96]

In our experience, most patients who have acute viral or idiopathic pericarditis do not require long-term surveillance. However, complicated cases should be followed carefully and may require repeat imaging if there is evidence of pericardial effusion or constriction.

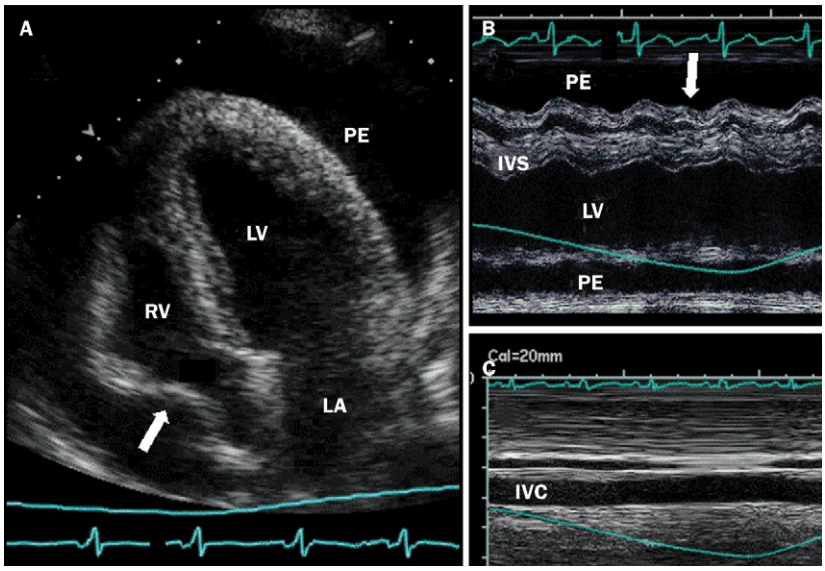

Figure 2: **Echocardiographic images of large pericardial effusion with features of tamponade**

PE=pericardial effusion. LV=left ventricle. RV=right ventricle. LA=left atrium. IVS=interventricular septum. IVC=inferior vena cava. A: Apical four-chamber view of LV, LA, and RV that shows large PE with diastolic right-atrial collapse (arrow). B: M-mode image with cursor placed through RV, IVS, and LV in parasternal long axis. The view shows circumferential PE with diastolic collapse of RV free wall (arrow) during expiration. C: M-mode image from subcostal window in same patient that shows IVC plethora without inspiratory collapse.

Complications of pericarditis

Recurrent pericarditis

Up to 30% of patients experience recurrent bouts of pericarditic pain accompanied by pericardial rub, fever, raised concentrations of inflammatory markers, or a combination of these. Episodes may recur for several years.[83,87] Pericardial effusion can accompany recurrences but tamponade and constriction are rare.[2] Primarily an immune-mediated process, recurrent pericarditis is most frequently idiopathic, but is also seen in postpericardotomy and Dressler's syndromes.[1] Raised titres of IgM to enterovirus in some cases implicates persisting viral infection.[57] Treatment of recurrent pericarditis is largely supportive. NSAIDs might be helpful, but colchicine offers the best prophylaxis against recurrent episodes and reduces symptoms during acute attacks.[87] Combined NSAIDs and colchicine might be necessary and in severe cases tapering courses of corticosteroids might be needed. Recurrent pericarditis in steroid-dependent patients is a notable management problem. Pericardiectomy can be considered as a last resort but is rarely successful, possibly due to persisting epitopes in the epicardium.[83]

Pericardial effusion and tamponade

Collection of pericardial fluid can occur in any form of pericarditis due to exudative secretion, lymphatic obstruction, or transudates.[11] Moderate or large effusions are more common in tuberculous, malignant, and pyogenic pericarditis.[11,97] A spectrum of haemodynamic abnormalities is possible,[98] small effusions generally being of minor consequence unless accumulation is rapid or constriction is also present. Once an effusion exceeds the pericardial reserve volume, intrapericardial pressure increases, causing a reduction in transmyocardial pressure gradient and, therefore, in chamber filling, particularly on the right side.[2] Increased intrapericardial pressure and pericardial constraint accentuate ventricular interdependence and respiratory variation in filling. As this pressure rises further, chamber collapse might occur, particularly of the thin walled atria and the right ventricle.[99] When fluid collection is slow, the pericardium can stretch to accommodate a large volume with minimum compromise of cardiac function, partly due to systemic neurohumoral responses that compensate for reduced cardiac filling.[1,11] Intravascular volume status greatly alters the haemodynamic importance of an effusion.[100,101]

Classically, haemodynamically important cardiac tamponade presents clinically with Beck's triad: hypotension, quiet heart sounds, and raised jugular venous pressure with prominent x descent (rapid filling during ventricular systole) and absent y descent (absent filling during diastole). Compensatory tachycardia and pulsus paradoxus (inspiratory fall in systolic blood

pressure >10 mm Hg) might occur because of respiratory interdependence of ventricular filling. Patients presenting subacutely might have signs of venous congestion. On electrocardiography in tamponade, electrical alternans might be seen due to the heart swinging within the effusion.[2]

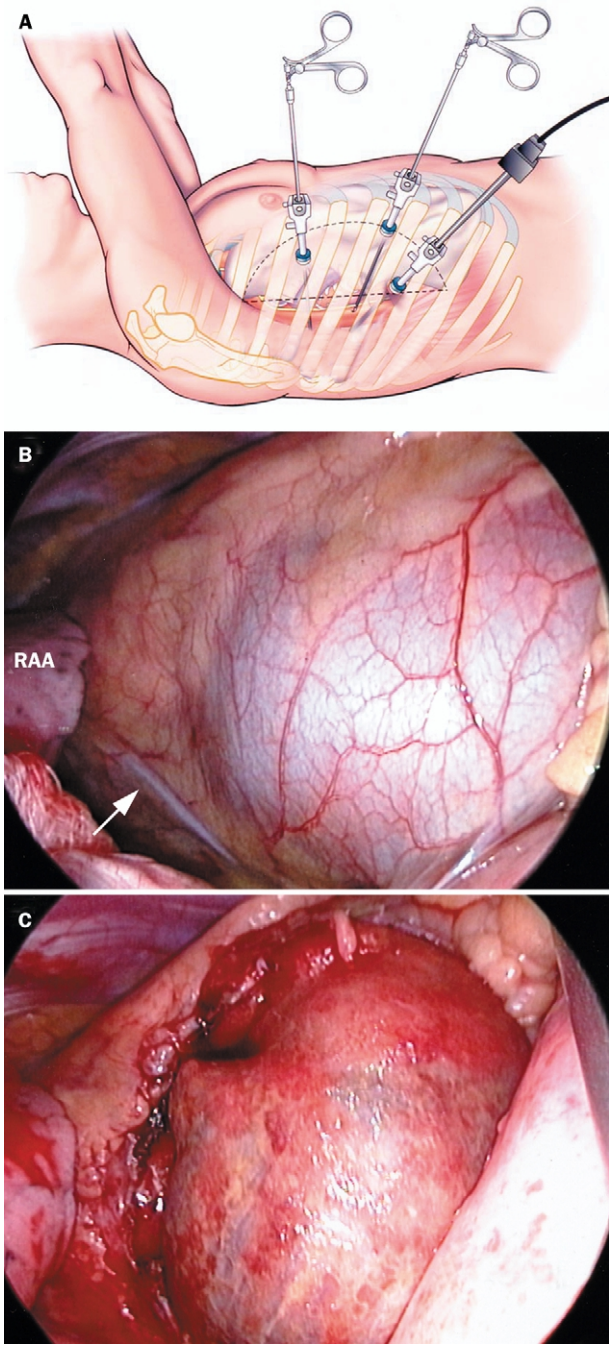

Figure 3: **Schematic representation (A) and view of inflamed and injected parietal pericardium in patient with effusive-constrictive pericarditis (B) on video-assisted thoracoscopic surgery, and view of inflamed visceral pericardium in same patient after video-assisted pericardiectomy (C)**
RAA=right-atrial appendage. A: Right lateral approach used for video-assisted thoracoscopic surgery with up to three ports for thoracoscope and instruments. B: RAA seen to left and phrenic nerve (arrow) seen coursing along right lateral border of heart. (Images courtesy of Sudish Murthy, Department of Thoracic Surgery, Cleveland Clinic Foundation).

Echocardiography is the test of choice for rapid and safe assessment of pericardial effusion (figure 2).[102–104] Tamponade is characterised by substantial respiratory variation in transmitral (>25%) and tricuspid (>50%) doppler inflow, diastolic collapse of the right atrium and right ventricle (>33% of the cardiac cycle) and inferior vena cava plethora.[102,105] Occasionally, hypovolaemia can cause chamber collapse without tamponade, whereas right-ventricular hypertrophy with decreased compliance, left ventricular hypertrophy with decreased compliance, and aortic valve disease can prevent chamber collapse. Regional collapse might occur in the case of loculated effusion.[106] Care should be taken to look for features of constriction, which can occur transiently in the resolution phase, after pericardiocentesis or with organised effusions.[107]

Cardiac catheterisation is rarely required, but in tamponade it classically shows raised central venous and right-atrial pressures with prominent x and diminished y descents, as well as equalisation of left-sided and right-sided diastolic pressures.[2] Cardiac catheterisation during pericardiocentesis might be helpful to identify effusive constrictive pericarditis.

Small to moderate effusions (<2 cm on echocardiography) should be followed up with repeat imaging studies.[11] Pericardial drainage is indicated for tamponade, purulent effusion, or for recurrent or large idiopathic effusions with haemodynamic compromise or suspicion of neoplastic or tuberculous causes.[11] Echocardiographically guided percutaneous pericardiocentesis should be done by a trained operator.[108] An apical, parasternal, or subcostal approach can be used dependent on the location of the effusion. The effusion should be drained dry and the fluid analysed as described above. Major complications such as right-ventricular or coronary laceration and pneumothorax are rare.[108] Surgical drainage can be reserved for the few occasions (around 1%) on which pericardiocentesis is unsuccessful or when the effusion is localised. Instillation of fibrinolytic agents has been described to aid the percutaneous drainage of purulent effusions or to maintain pericardial drain patency.[109]

For recurrent effusions for which repeat pericardiocentesis is unsuccessful, an alternative procedure is indicated.[110] Percutaneous options include balloon pericardial window formation[111] or instillation of sclerosing agents, such as minocycline,[112] which might be helpful in neoplastic effusion.[28] If surgical pericardial window formation is required, pericardioscopy or video-assisted thoracoscopic surgery offers the least invasive approach (figure 3).[113,114] Pericardiectomy is rarely indicated unless constriction is present.[112]

Constrictive pericarditis

Defined as chronic fibrous thickening, calcification of the pericardial sac, or both, constrictive pericarditis produces abnormal diastolic filling with raised filling pressures due to reduced compliance of a rigid pericardium. Pericardial constriction is most commonly idiopathic but can result from any cause.[1,115] Historically, and in developing countries, tuberculosis has been a major cause.[116,117] Cardiac surgery and radiation-induced pericarditis have become also important.[37,118] Pericardial thickening and calcification is sometimes less prominent in non-tuberculous constriction.[119] Systolic dysfunction might accompany constriction in radiation disease and is a marker of poor prognosis after pericardial stripping. Although typically a chronic process, constriction can also present more acutely (within days) or subacutely

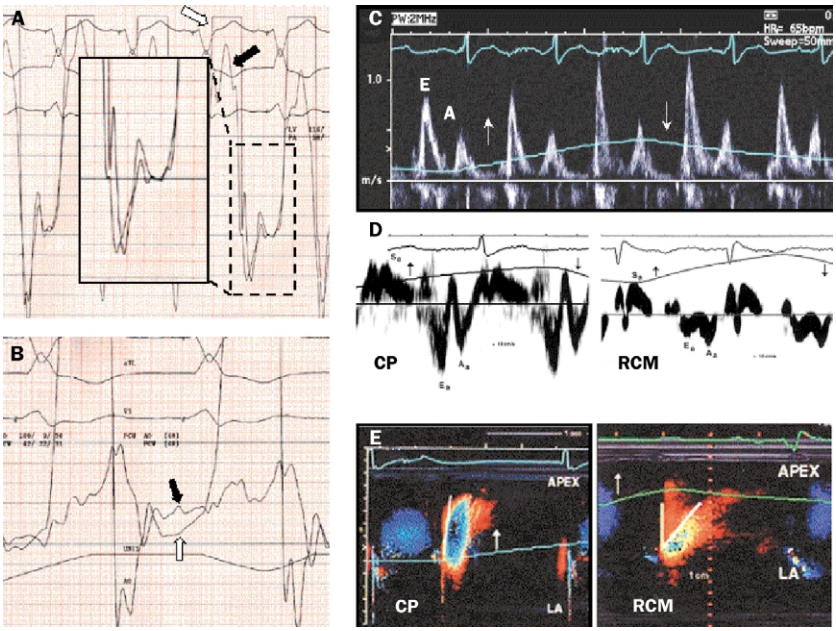

Figure 4: **Haemodynamic and echocardiographic findings in constrictive pericarditis**
CP=constrictive pericarditis. RCM=restrictive cardiomyopathy. LA=left atrium. Up arrow=onset of inspiration. Down arrow=onset of expiration. A: Simultaneous pressure tracings from left (white arrow) and right (black arrow) ventricles showing equalisation of diastolic pressures with typical dip and plateau or square-root pattern (enlarged in box). In cycle at left, pressure at plateau=27% of peak right-ventricular systolic pressure. B: Respiratory variation in simultaneous left ventricular (white arrow) and pulmonary capillary wedge (black arrow) pressure tracings due to dissociated intrathoracic and intrapericardial pressures. C: Respiratory variation in early diastolic transmitral flow velocities are measured by pulsed-wave doppler as consequence of increased interventricular interdependence and dissociation of intrathoracic and intrapericardial pressures. Velocities are 27% lower at onset of inspiration (up arrow) and higher at onset of expiration (down arrow). D: Tissue doppler imaging showing increased (15 cm/s) peak early diastolic mitral annular velocities (Ea) in CP. By comparison, peak annular velocities (Ea) are decreased (4 cm/s) in RCM due to abnormal longitudinal myocardial relaxation. E: Colour doppler M-mode echocardiography of diastolic flow from LA towards ventricular apex imaged in four-chamber view. Velocity of propagation of early left ventricular flow measured as slope of first aliasing contour (white line) is steep (110 cm/s; normal range 50–80 cm/s) in CP, but is delayed (25 cm/s) in RCM, reflecting abnormal myocardial relaxation. Adapted with permission of Excerpta Medica from Rajagopalan N, Garcia MJ, Rodriguez L, et al. Comparison of new Doppler echocardiographic methods to differentiate constrictive pericardial heart disease and restrictive cardiomyopathy. *Am J Cardiol* 2001; **87:** 86–94 (reference 126).

(3–12 months) after the initial insult, particularly after cardiac surgery.[120]

Constrictive pericarditis classically presents with debilitating chronic right-heart failure but might present as localised,[121] effusive (effusion present), occult (volume depleted), or transient constriction.[1,122,123] Symptoms may be present for some time before the diagnosis is made.[124,125] Constriction of coronary arteries or grafts after surgery might cause myocardial ischaemia.

Differentiation of constrictive pericarditis from restrictive cardiomyopathy remains a difficult but important clinical challenge. Constriction is potentially correctable with pericardiectomy whereas in restrictive cardiomyopathy, treatment is largely palliative and prognosis is poor.[37,119] These two disorders are characterised by abnormal diastolic filling. In restrictive cardiomyopathy, this finding reflects primary abnormalities in myocardial relaxation and compliance. However, in pure constriction, myocardial relaxation is normal and diastolic dysfunction results from impaired compliance and a finite cardiac diastolic volume.[119] These key features can be detected with current echocardiographic methods.[4,119,126]

An understanding of the pathophysiological abnormalities is pivotal to the accurate diagnosis of constrictive pericarditis.[119] Encasement of the heart by a rigid pericardium isolates the heart from normal respiratory changes in intrathoracic pressure. As described originally by Hatle and colleagues,[127] this symptom produces two fundamental abnormalities: dissociation of intracardiac and intrathoracic pressures during respiration[128,129] and interdependence of ventricular filling.[130] On inspiration, intrathoracic pressure decreases but is not transmitted to the left atrium. A reduced pulmonary vein to left atrium pressure gradient produces a fall in flow into the left atrium and across the mitral valve into the left ventricle. Decreased left-ventricular filling during diastole allows more room for right-ventricular filling, which leads to a septal shift and an increase in right-sided inflow. The exact opposite sequence occurs in expiration. These findings are readily detected by doppler echocardiography with respirometry.[127]

Clinical clues to the diagnosis of constrictive pericarditis include pulsatile hepatomegaly, a decreased apical impulse, and an early diastolic heart sound, also called a pericardial knock.[124,131,132] The jugular venous pressure is commonly raised, might have a prominent y descent (Friedreich's sign), and may rise or fail to fall with inspiration (Kussmaul's sign).[124] However, none of these signs is specific for constrictive percarditis.[124] On electrocardiography, low voltages with non-specific T-wave changes can be seen, as can so-called egg-shell pericardial calcification on chest radiography in chronic cases and pleural effusions.

At catheterisation, low cardiac output, despite reflex tachycardia, can be seen.[133] Prominent x descent (occasionally absent) and y descents on the atrial waveform producing M or W waveforms, and the diastolic dip and plateau pattern of the ventricular waveform reflect abrupt termination of ventricular filling due to rigid pericardial constraint, but are not specific for constrictive pericarditis.[128,134] Haemodynamic features that suggest constrictive pericarditis include equalisation of right-ventricular and left-ventricular end-diastolic pressures (<5 mm Hg difference), ventricular interdependence, exhibited by respiratory discordance in right-ventricular and left-ventricular peak systolic pressure, and dissociation of intrathoracic and intracardiac pressures (figure 4).[128,135] This dissociation of pressures results in the lowering of the pulmonary capillary wedge pressure compared with left-ventricular end-diastolic pressure during inspiration.[128] A right-ventricular systolic pressure higher than 50 mm Hg is rare in isolated constrictive pericarditis compared with restrictive cardiomyopathy.[135]

Advances in cardiac imaging allow the diagnosis of constrictive pericarditis to be made non-invasively in nearly all patients. In most cases, this disorder can be confirmed by echocardiography, which allows assessment of the key pathophysiological abnormalities.[119,129] Characteristic two-dimensional echo features include pericardial thickening, myocardial tethering, a septal bounce, and inferior vena cava plethora.[136] Doppler

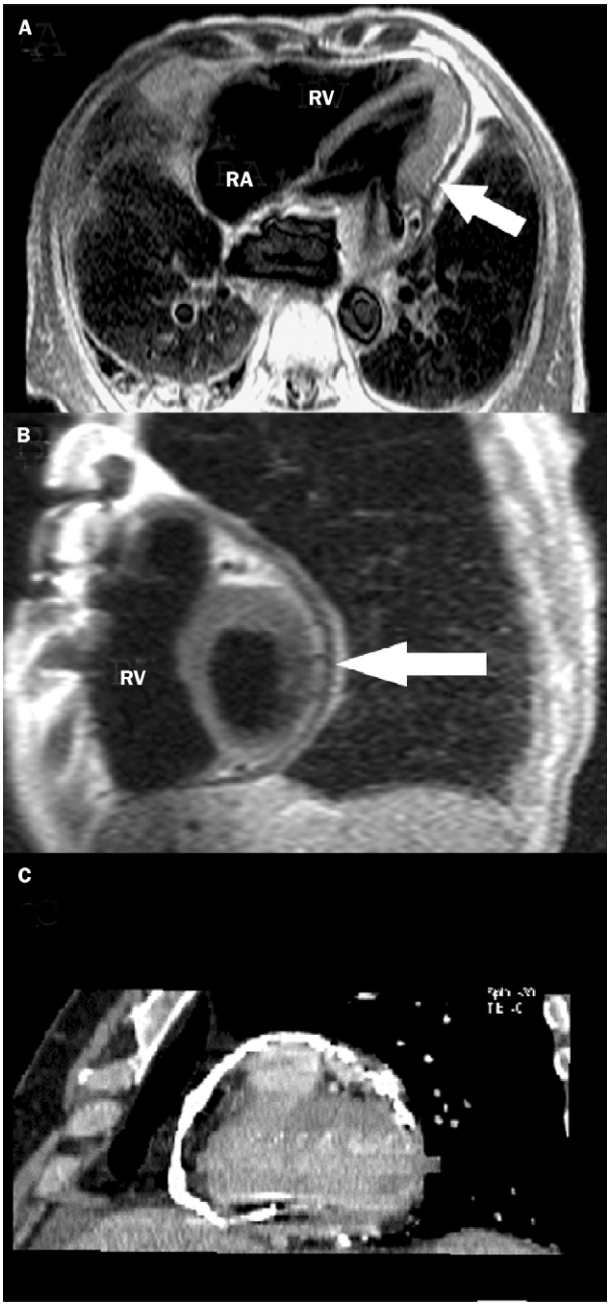

Figure 5: **MRI and CT images showing features of constrictive pericarditis**

RV=right ventricle. RA=right atrium. A: MRI dark=blood image (spin-echo; axial projection) from patient with constrictive pericarditis showing pericardial thickening, calcification, or both, along posterolateral wall represented by curvilinear signal void (arrow) separated by bright signal of epicardial and pericardial fat. Associated conical or tubular compression deformity of left ventricle can be seen. B: MRI image (spin echo; sagittal projection) from same patient again showing thickened pericardium (arrow). C: Short-axis CT image of heart in another patient, showing calcification of pericardium. (Image provided by Richard D White, Cleveland Clinic Foundation.)

echocardiography with respirometry shows increased respiratory variation in transmitral and pulmonary venous flow velocities (>25% at onset of inspiration and expiration).[127,137] Preload reduction might be required to unmask respiratory variation when left-atrial pressure is high, or volume loading if filling pressures are low.[101,134,138] Atrial fibrillation makes doppler assessment difficult, but a similar respiratory variation of pulmonary venous and mitral inflow is seen.[139] Trans-tricuspid flow velocities decrease and hepatic-vein-flow reversals increase in expiration.[127,129] Respiratory variation in systolic flow in the superior vena cava suggests chronic obstructive lung disease rather than constrictive pericarditis.[140]

Newer echocardiographic methods such as colour M-mode and tissue doppler imaging provide important additional information that can accurately differentiate constrictive pericarditis from restrictive cardiomyopathy (figure 4), especially when substantial respiratory variation is not seen.[4,126,141] The velocity of propagation of early ventricular inflow from colour M-mode and the early mitral annular velocity from tissue doppler imaging are markers of myocardial relaxation. Values of early mitral annular velocity and velocity of propagation are generally normal or supranormal in pure constrictive pericarditis, in which myocardial relaxation is normal or raised. By contrast, these values are decreased in restrictive myocardiopathy, in which myocardial relaxation is impaired.[4,126,141,142] Occasionally the early mitral annular velocity may be decreased if the annulus is involved with the constrictive process.[143] There is an inverse relation between the ratio of early transmitral to annular velocities and filling pressures (annular paradoxus) in constriction.[142] If transthoracic echocardiography is sub-optimum, transoesophageal echocardiography frequently allows more accurate measurement of pericardial thickness and can facilitate assessment of transmitral and pulmonary vein flows.[136]

In summary, the key echocardiographic features that differentiate constrictive pericarditis from restrictive cardiomyopathy are thickened pericardium, significant respiratory variation in transmitral, pulmonary vein, and tricuspid inflows and preserved indices of myocardial relaxation (velocity of propagation and early mitral annular velocity).[119,126,127,135]

CT and MRI allow accurate measurement of pericardial thickness (figure 5) and some assessment of diastolic filling patterns.[3,144,145] Ancillary diagnostic findings include conical narrowing of the ventricles, atrial dilation, enlargement of the inferior vena cava, hepatomegaly, and ascites. Excellent overall sensitivity (88%), specificity (100%), and accuracy (93%) have been reported for MRI.[144,146] Increased pericardial thickening may not always imply constriction, and conversely, constrictive pericarditis can present with normal pericardial thickness on non-invasive imaging, histology, or a combination of these.[119,147]

Even with modern imaging techniques, the diagnosis of constrictive pericarditis can be difficult, particularly in complex cases with mixed features of constriction and restriction. No one method is completely reliable.[119] Data from more than one imaging method should be considered to provide an integrative assessment of anatomical and physiological function. Correlation with invasive haemodynamics might also be necessary.[119] Rarely, when the diagnosis remains uncertain and clinical suspicion is high, endomyocardial biopsy or explorative thoracotomy might be necessary.

Medical management of constrictive pericarditis, especially in less-severe cases, is aimed at relief of fluid overload with diuretics, and is at best palliative. Surgical pericardiectomy remains the only definitive management and should be done before calcification and myocardial involvement progresses.[37,113,148,149] In one report, pericardiectomy was done safely and with good symptomatic outcome in selected patients.[37] In that group, functional class improved in most patients, and 30-day, 5-year, and 10-year survival values were 94%, 78%, and 57%, respectively. Predictors of poor prognosis included advanced age, New York Heart Association class, and

postradiation cause.[37] In another series, higher New York Heart Association functional class, radiation, myocardial involvement, and older age predicted a worse outcome after pericardiectomy.[148] In our own series of 163 patients,[150] overall survival after pericardiectomy for constriction differed significantly among the major cause subgroups and was best for patients with idiopathic, intermediate for postsurgical, and poor for postradiation constriction. Other key predictors of survival were related to cardiac function (left-ventricular systolic function, pulmonary-artery systolic function) and renal function (creatinine and sodium).[150] Improvement in doppler profiles on echocardiographic examination correlates with improved clinical status and may be a useful way to track outcome.[151,152]

Conclusions

Pericarditis remains a common disorder, particularly as a complication of modern treatments such as cardiac surgery, percutaneous interventions, and radiation therapy. Pericardial effusion and constrictive pericarditis are infrequent sequelae that can be diagnosed accurately in most cases by use of modern imaging methods. Management of uncomplicated pericarditis rests largely on NSAID agents with the addition of colchicine for relapses. Pericardial effusion can be managed percutaneously in most cases, whereas definitive treatment for constriction remains surgery.

Conflict of interest statement

None declared.

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References

1 Spodick DH. Pericardial diseases. In: Braunwald E, Zipes DP, Libby P, eds. Heart disease: a textbook of cardiovascular medicine, 6th edn. Philadelphia: WB Saunders, 2001: 1823–76.
2 Klein AL, Asher CR. Diseases of the pericardium, restrictive cardiomyopathy and diastolic dysfunction. In: Topol EJ, ed. Textbook of cardiovascular medicine, 2nd edn. Philadelphia: Lippincott, Williams and Wilkins, 2002: 595–646.
3 Breen JF. Imaging of the pericardium. *J Thorac Imaging* 2001; **16:** 47–54.
4 Garcia MJ, Rodriguez L, Ares M, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy: assessment of left ventricular diastolic velocities in longitudinal axis by Doppler tissue imaging. *J Am Coll Cardiol* 1996; **27:** 108–14.
5 Manner J, Perez-Pomares JM, Macias D, et al. The origin, formation and developmental significance of the epicardium: a review. *Cells Tissues Organs* 2001; **169:** 89–103.
6 Spodick DH. Macrophysiology, microphysiology, and anatomy of the pericardium: a synopsis. *Am Heart J* 1992; **124:** 1046–51.
7 Spodick DH. Microphysiology of the pericardium: substrate for intrapericardial therapeutics. *Herz* 2000; **25:** 720–23.
8 Frais MA, Bergman DW, Kingma I, et al. The dependence of the time constant of left ventricular isovolumic relaxation (tau) on pericardial pressure. *Circulation* 1990; **81:** 1071–80.
9 Spodick DH. Acute pericarditis: current concepts and practice. *JAMA* 2003; **289:** 1150–53.
10 Launbjerg J, Fruergaard P, Hesse B, et al. Long-term risk of death, cardiac events and recurrent chest pain in patients with acute chest pain of different origin. *Cardiology* 1996; **87:** 60–66.
11 Soler-Soler J, Sagrista-Sauleda J, Permanyer-Miralda G. Management of pericardial effusion. *Heart* 2001; **86:** 235–40.
12 Friman G, Fohlman J. The epidemiology of viral heart disease. *Scand J Infect Dis Suppl* 1993; **88:** 7–10.
13 Sagrista-Sauleda J, Barrabes JA, Permanyer-Miralda G, et al. Purulent pericarditis: review of a 20-year experience in a general hospital. *J Am Coll Cardiol* 1993; **22:** 1661–65.
14 Permanyer-Miralda G, Sagrista-Sauleda J, Soler-Soler J. Primary acute pericardial disease: a prospective series of 231 consecutive patients. *Am J Cardiol* 1985; **56:** 623–30.
15 Estok L, Wallach F. Cardiac tamponade in a patient with AIDS: a review of pericardial disease in patients with HIV infection. *Mt Sinai J Med* 1998; **65:** 33–39.
16 Wragg A, Strang JI. Tuberculous pericarditis and HIV infection. *Heart* 2000; **84:** 127–28.
17 Maisch B, Ristic AD. The classification of pericardial disease in the age of modern medicine. *Curr Cardiol Rep* 2002; **4:** 13–21.
18 Zayas R, Anguita M, Torres F, et al. Incidence of specific etiology and role of methods for specific etiologic diagnosis of primary acute pericarditis. *Am J Cardiol* 1995; **75:** 378–82.
19 Fairley CK, Ryan M, Wall PG, et al. The organisms reported to cause infective myocarditis and pericarditis in England and Wales. *J Infect* 1996; **32:** 223–25.
20 Barbaro G, Klatt EC. HIV infection and the cardiovascular system. *AIDS Rev* 2002; **4:** 93–103.
21 Pugliese A, Isnardi D, Saini A, et al. Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect* 2000; **40:** 282–84.
22 Halsell JS, Riddle JR, Atwood JE, et al. Myopericarditis following smallpox vaccination among vaccinia-naive US military personnel. *JAMA* 2003; **289:** 3283–89.
23 Dye C, Scheele S, Dolin P, et al. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country: WHO global surveillance and monitoring project. *JAMA* 1999; **282:** 677–86.
24 Sagrista-Sauleda J, Permanyer-Miralda G, Soler-Soler J. Tuberculous pericarditis: ten year experience with a prospective protocol for diagnosis and treatment. *J Am Coll Cardiol* 1988; **11:** 724–28.
25 Fowler NO. Tuberculous pericarditis. *JAMA* 1991; **266:** 99–103.
26 Meng Q, Lai H, Lima J, et al. Echocardiographic and pathological characteristics of cardiac metastasis in patients with lymphoma. *Oncol Rep* 2002; **9:** 85–88.
27 Warren WH. Malignancies involving the pericardium. *Semin Thorac Cardiovasc Surg* 2000; **12:** 119–29.
28 Vaitkus PT, Herrmann HC, LeWinter MM. Treatment of malignant pericardial effusion. *JAMA* 1994; **272:** 59–64.
29 Tofler GH, Muller JE, Stone PH, et al. Pericarditis in acute myocardial infarction: characterization and clinical significance. *Am Heart J* 1989; **117:** 86–92.
30 Correale E, Maggioni AP, Romano S, et al. Comparison of frequency, diagnostic and prognostic significance of pericardial involvement in acute myocardial infarction treated with and without thrombolytics: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). *Am J Cardiol* 1993; **71:** 1377–81.
31 Wall TC, Califf RM, Harrelson-Woodlief L, et al. Usefulness of a pericardial friction rub after thrombolytic therapy during acute myocardial infarction in predicting amount of myocardial damage: the TAMI study group. *Am J Cardiol* 1990; **66:** 1418–21.
32 Nagahama Y, Sugiura T, Takehana K, et al. Clinical significance of PQ segment depression in acute Q wave anterior wall myocardial infarction. *J Am Coll Cardiol* 1994; **23:** 885–90.
33 Oliva PB, Hammill SC, Talano JV. T wave changes consistent with epicardial involvement in acute myocardial infarction: observations in patients with a postinfarction pericardial effusion without clinically recognized postinfarction pericarditis. *J Am Coll Cardiol* 1994; **24:** 1073–77.
34 Nagahama Y, Sugiura T, Takehana K, et al. The role of infarction-associated pericarditis on the occurrence of atrial fibrillation. *Eur Heart J* 1998; **19:** 287–92.
35 Figueras J, Juncal A, Carballo J, et al. Nature and progression of pericardial effusion in patients with a first myocardial infarction: relationship to age and free wall rupture. *Am Heart J* 2002; **144:** 251–58.
36 Miller RH, Horneffer PJ, Gardner TJ, et al. The epidemiology of the postpericardiotomy syndrome: a common complication of cardiac surgery. *Am Heart J* 1988; **116:** 1323–29.
37 Ling LH, Oh JK, Schaff HV, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. *Circulation* 1999; **100:** 1380–86.
38 Kutcher MA, King SB 3rd, Alimurung BN, et al. Constrictive pericarditis as a complication of cardiac surgery: recognition of an entity. *Am J Cardiol* 1982; **50:** 742–48.
39 Matsuyama K, Matsumoto M, Sugita T, et al. Clinical characteristics of patients with constrictive pericarditis after coronary bypass surgery. *Jpn Circ J* 2001; **65:** 480–82.
40 Calafiore AM, Di Giammarco G, Teodori G, et al. Midterm results after minimally invasive coronary surgery (LAST operation). *J Thorac Cardiovasc Surg* 1998; **115:** 763–71.
41 LeMaire SA, Wall MJ Jr, Mattox KL. Needle embolus causing cardiac puncture and chronic constrictive pericarditis. *Ann Thorac Surg* 1998; **65:** 1786–87.
42 Choi JB, Lee SY, Jeong JW. Delayed diagnosis of purulent pericarditis

caused by esophagopericardial fistula by computed tomography scan and echocardiography. *Eur J Cardiothorac Surg* 2001; **20:** 1267–69.
43 Meyns BP, Faveere BC, Van de Werf FJ, et al. Constrictive pericarditis due to ingestion of a toothpick. *Ann Thorac Surg* 1994; **57:** 489–90.
44 Von Sohsten R, Kopistansky C, Cohen M, et al. Cardiac tamponade in the "new device" era: evaluation of 6999 consecutive percutaneous coronary interventions. *Am Heart J* 2000; **140:** 279–83.
45 Scheinman MM, Huang S. The 1998 NASPE prospective catheter ablation registry. *Pacing Clin Electrophysiol* 2000; **23:** 1020–28.
46 Vasquez A, Butman SM. Pathophysiologic mechanisms in pericardial disease. *Curr Cardiol Rep* 2002; **4:** 26–32.
47 Sivakumaran S, Irwin ME, Gulamhusein SS, et al. Postpacemaker implant pericarditis: incidence and outcomes with active-fixation leads. *Pacing Clin Electrophysiol* 2002; **25:** 833–37.
48 Piovaccari G, Ferretti RM, Prati F, et al. Cardiac disease after chest irradiation for Hodgkin's disease: incidence in 108 patients with long follow-up. *Int J Cardiol* 1995; **49:** 39–43.
49 Martel MK, Sahijdak WM, Ten Haken RK, et al. Fraction size and dose parameters related to the incidence of pericardial effusions. *Int J Radiat Oncol Biol Phys* 1998; **40:** 155–61.
50 Oakley CM. Myocarditis, pericarditis and other pericardial diseases. *Heart* 2000; **84:** 449–54.
51 Spodick DH. Diagnostic electrocardiographic sequences in acute pericarditis: significance of PR segment and PR vector changes. *Circulation* 1973; **48:** 575–80.
52 Ginzton LE, Laks MM. The differential diagnosis of acute pericarditis from the normal variant: new electrocardiographic criteria. *Circulation* 1982; **65:** 1004–09.
53 Brady WJ, Perron A, Ullman E. Errors in emergency physician interpretation of ST-segment elevation in emergency department chest pain patients. *Acad Emerg Med* 2000; **7:** 1256–60.
54 Spodick DH. Differential characteristics of the electrocardiogram in early repolarization and acute pericarditis. *N Engl J Med* 1976; **295:** 523–26.
55 Bonnefoy E, Godon P, Kirkorian G, et al. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. *Eur Heart J* 2000; **21:** 832–36.
56 Imazio M, Demichelis B, Cecchi E, et al. Cardiac troponin I in acute pericarditis. *J Am Coll Cardiol* 2003; **42:** 2144–48.
57 Muir P, Nicholson F, Tilzey AJ, et al. Chronic relapsing pericarditis and dilated cardiomyopathy: serological evidence of persistent enterovirus infection. *Lancet* 1989; **1:** 804–07.
58 Karia DH, Xing YQ, Kuvin JT, et al. Recent role of imaging in the diagnosis of pericardial disease. *Curr Cardiol Rep* 2002; **4:** 33–40.
59 Chandraratna PA. Echocardiography and Doppler ultrasound in the evaluation of pericardial disease. *Circulation* 1991; **84:** I303–10.
60 Hinds SW, Reisner SA, Amico AF, et al. Diagnosis of pericardial abnormalities by 2D-echo: a pathology-echocardiography correlation in 85 patients. *Am Heart J* 1992; **123:** 143–50.
61 Furnary AP, Siqueira C Jr, Lowe RI, et al. Initial clinical trial of substernal epicardial echocardiography: SEEing a new window to the postoperative heart. *Ann Thorac Surg* 2001; **72:** S1077–82.
62 Clark CB, Davies LR, Kerber RE. Intracardiac echocardiography identifies pericardial fluid and can monitor the success of pericardiocentesis: experimental studies. *J Am Soc Echocardiogr* 2001; **14:** 712–14.
63 Lawler LP, Horton KM, Corl FM, et al. Review: the pericardium—a computed tomography perspective. *Crit Rev Diagn Imaging* 2001; **42:** 229–58.
64 Sechtem U, Tscholakoff D, Higgins CB. MRI of the normal pericardium. *AJR Am J Roentgenol* 1986; **147:** 239–44.
65 Sechtem U, Tscholakoff D, Higgins CB. MRI of the abnormal pericardium. *AJR Am J Roentgenol* 1986; **147:** 245–52.
66 Smith WH, Beacock DJ, Goddard AJ, et al. Magnetic resonance evaluation of the pericardium. *Br J Radiol* 2001; **74:** 384–92.
67 Coupland DB, Terriff B, Fung AY, et al. The 'hot halo' sign: pyogenic pericarditis on In-111 leukocyte scintigraphy. *Clin Nucl Med* 1992; **17:** 579–80.
68 Fujioka S, Koide H, Kitaura Y, et al. Molecular detection and differentiation of enteroviruses in endomyocardial biopsies and pericardial effusions from dilated cardiomyopathy and myocarditis. *Am Heart J* 1996; **131:** 760–65.
69 Callahan JA, Seward JB, Nishimura RA, et al. Two-dimensional echocardiographically guided pericardiocentesis: experience in 117 consecutive patients. *Am J Cardiol* 1985; **55:** 476–79.
70 Spodick DH. Acute cardiac tamponade. *N Engl J Med* 2003; **349:** 684–90.
71 Armstrong G, Cardon L, Vilkomerson D, et al. Localization of needle tip with color doppler during pericardiocentesis: in vitro validation and initial clinical application. *J Am Soc Echocardiogr* 2001; **14:** 29–37.
72 Totte E, Hee R, Brabant P, et al. Laparoscopic transabdominal pericardial window: new standard in the treatment of recurrent pericardial effusion complicated by cardiac tamponade. *Surg Endosc* 2002; **16:** 859–63.
73 Pataki N, Szelig L, Horvath OP, et al. Pericardial drainage using the transdiaphragmatic route: refinement of the laparoscopic technique. *Surg Endosc* 2002; **16:** 1105.
74 Maisch B, Bethge C, Drude L, et al. Pericardioscopy and epicardial biopsy: new diagnostic tools in pericardial and perimyocardial disease. *Eur Heart J* 1994; **15** (suppl C)**:** 68–73.
75 Seferovic PM, Ristic AD, Maksimovic R, et al. Flexible percutaneous pericardioscopy: inherent drawbacks and recent advances. *Herz* 2000; **25:** 741–47.
76 Maisch B, Schonian U, Crombach M, et al. Cytomegalovirus associated inflammatory heart muscle disease. *Scand J Infect Dis Suppl* 1993; **88:** 135–48.
77 Godfrey-Faussett P, Wilkins EG, Khoo S, et al. Tuberculous pericarditis confirmed by DNA amplification. *Lancet* 1991; **337:** 176–77.
78 Koh K, Kim E, Cho C, et al. Adenosine deaminase and carcinoembryonic antigen in pericardial effusion diagnosis, especially in suspected tuberculous pericarditis. *Circulation* 1994; **89:** 2728–35.
79 Posner MR, Cohen GI, Skarin AT. Pericardial disease in patients with cancer: the differentiation of malignant from idiopathic and radiation-induced pericarditis. *Am J Med* 1981; **71:** 407–13.
80 Millaire A, Wurtz A, de Groote P, et al. Malignant pericardial effusions: usefulness of pericardioscopy. *Am Heart J* 1992; **124:** 1030–34.
81 Trautner BW, Darouiche RO. Tuberculous pericarditis: optimal diagnosis and management. *Clin Infect Dis* 2001; **33:** 954–61.
82 Hoit BD. Management of effusive and constrictive pericardial heart disease. *Circulation* 2002; **105:** 2939–42.
83 Fowler NO, Harbin AD 3rd. Recurrent acute pericarditis: follow-up study of 31 patients. *J Am Coll Cardiol* 1986; **7:** 300–05.
84 Minuth AN, Nottebohm GA, Eknoyan G, et al. Indomethacin treatment of pericarditis in chronic hemodialysis patients. *Arch Intern Med* 1975; **135:** 807–10.
85 Millaire A, de Groote P, Decoulx E, et al. Treatment of recurrent pericarditis with colchicine. *Eur Heart J* 1994; **15:** 120–24.
86 Adler Y, Finkelstein Y, Guindo J, et al. Colchicine treatment for recurrent pericarditis: a decade of experience. *Circulation* 1998; **97:** 2183–85.
87 Guindo J, Rodriguez de la Serna A, Ramio J, et al. Recurrent pericarditis: relief with colchicine. *Circulation* 1990; **82:** 1117–20.
88 Zemer D, Cabili S, Revach M, et al. Constrictive pericarditis in familial Mediterranean fever. *Isr J Med Sci* 1977; **13:** 55–58.
89 Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clin Infect Dis* 1997; **25:** 872–87.
90 Strang JI, Kakaza HH, Gibson DG, et al. Controlled trial of prednisolone as adjuvant in treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987; **2:** 1418–22.
91 Hakim JG, Ternouth I, Mushangi E, et al. Double blind randomised placebo controlled trial of adjunctive prednisolone in the treatment of effusive tuberculous pericarditis in HIV seropositive patients. *Heart* 2000; **84:** 183–88.
92 Stubbs DF. Post-acute myocardial infarction symptomatic pericarditis (PAMISP): report on a large series and the effect of methylprednisolone therapy. *J Int Med Res* 1986; **14** (suppl 1)**:** 25–29.
93 Marcolongo R, Russo R, Laveder F, et al. Immunosuppressive therapy prevents recurrent pericarditis. *J Am Coll Cardiol* 1995; **26:** 1276–79.
94 Quigg RJ Jr, Idelson BA, Yoburn DC, et al. Local steroids in dialysis-associated pericardial effusion: a single intrapericardial administration of triamcinolone. *Arch Intern Med* 1985; **145:** 2249–50.
95 Maisch B, Ristic AD, Seferovic PM, et al. Intrapericardial treatment of autoreactive myocarditis with triamcinolon: successful administration in patients with minimal pericardial effusion. *Herz* 2000; **25:** 781–86.
96 Spodick DH. Intrapericardial therapy and diagnosis. *Curr Cardiol Rep* 2002; **4:** 22–25.
97 Olsen PS, Sorensen C, Andersen HO. Surgical treatment of large pericardial effusions: etiology and long-term survival. *Eur J Cardiothorac Surg* 1991; **5:** 430–32.
98 Shaver JA, Reddy PS, Curtiss EI, et al. Noninvasive/invasive correlates of exaggerated ventricular interdependence in cardiac tamponade. *J Cardiol* 2001; **37** (suppl 1)**:** 71–76.
99 Armstrong WF, Schilt BF, Helper DJ, et al. Diastolic collapse of the right ventricle with cardiac tamponade: an echocardiographic study. *Circulation* 1982; **65:** 1491–96.
100 Antman EM, Cargill V, Grossman W. Low-pressure cardiac tamponade. *Ann Intern Med* 1979; **91:** 403–06.
101 Oh JK, Tajik AJ, Appleton CP, et al. Preload reduction to unmask the

characteristic Doppler features of constrictive pericarditis: a new observation. *Circulation* 1997; **95:** 796–99.
102 Levine MJ, Lorell BH, Diver DJ, et al. Implications of echocardiographically assisted diagnosis of pericardial tamponade in contemporary medical patients: detection before hemodynamic embarrassment. *J Am Coll Cardiol* 1991; **17:** 59–65.
103 Appleton CP, Hatle LK, Popp RL. Cardiac tamponade and pericardial effusion: respiratory variation in transvalvular flow velocities studied by Doppler echocardiography. *J Am Coll Cardiol* 1988; **11:** 1020–30.
104 Himelman RB, Kircher B, Rockey DC, et al. Inferior vena cava plethora with blunted respiratory response: a sensitive echocardiographic sign of cardiac tamponade. *J Am Coll Cardiol* 1988; **12:** 1470–77.
105 Leeman DE, Levine MJ, Come PC. Doppler echocardiography in cardiac tamponade: exaggerated respiratory variation in transvalvular blood flow velocity integrals. *J Am Coll Cardiol* 1988; **11:** 572–78.
106 Chuttani K, Pandian NG, Mohanty PK, et al. Left ventricular diastolic collapse: an echocardiographic sign of regional cardiac tamponade. *Circulation* 1991; **83:** 1999–2006.
107 Sagrista-Sauleda J, Permanyer-Miralda G, Candell-Riera J, et al. Transient cardiac constriction: an unrecognized pattern of evolution in effusive acute idiopathic pericarditis. *Am J Cardiol* 1987; **59:** 961–66.
108 Callahan JA, Seward JB. Pericardiocentesis guided by two-dimensional echocardiography. *Echocardiography* 1997; **14:** 497–504.
109 Winkler WB, Karnik R, Slany J. Treatment of exudative fibrinous pericarditis with intrapericardial urokinase. *Lancet* 1994; **344:** 1541–42.
110 Sagrista-Sauleda J, Angel J, Permanyer-Miralda G, et al. Long-term follow-up of idiopathic chronic pericardial effusion. *N Engl J Med* 1999; **341:** 2054–59.
111 Di Segni E, Lavee J, Kaplinsky E, et al. Percutaneous balloon pericardiostomy for treatment of cardiac tamponade. *Eur Heart J* 1995; **16:** 184–87.
112 Spodick DH. Minocycline sclerosis for malignant pericardial effusions. *Chest* 1997; **111:** 524.
113 Chen EP, Miller JI. Modern approaches and use of surgical treatment for pericardial disease. *Curr Cardiol Rep* 2002; **4:** 41–46.
114 Luison F, Boyd WD. Three-dimensional video-assisted thoracoscopic pericardiectomy. *Ann Thorac Surg* 2000; **70:** 2137–28.
115 Ling LH, Oh JK, Breen JF, et al. Calcific constrictive pericarditis: is it still with us? *Ann Intern Med* 2000; **132:** 444–50.
116 Suwan PK, Potjalongsilp S. Predictors of constrictive pericarditis after tuberculous pericarditis. *Br Heart J* 1995; **73:** 187–89.
117 Bashi VV, John S, Ravikumar E, et al. Early and late results of pericardiectomy in 118 cases of constrictive pericarditis. *Thorax* 1988; **43:** 637–41.
118 Cameron J, Oesterle SN, Baldwin JC, et al. The etiologic spectrum of constrictive pericarditis. *Am Heart J* 1987; **113:** 354–60.
119 Nishimura RA. Constrictive pericarditis in the modern era: a diagnostic dilemma. *Heart* 2001; **86:** 619–23.
120 Spodick DH. Pericarditis, pericardial effusion, cardiac tamponade, and constriction. *Crit Care Clin* 1989; **5:** 455–76.
121 Hasuda T, Satoh T, Yamada N, et al. A case of constrictive pericarditis with local thickening of the pericardium without manifest ventricular interdependence. *Cardiology* 1999; **92:** 214–16.
122 Akdemir I, Davutoglu V, Aksoy M. Constrictive pericarditis localized to left ventricle presented with left pleural effusion: a case report. *Echocardiography* 2002; **19:** 329–32.
123 Haley JH, Tajik AJ, Danielson GK, et al. Transient constrictive pericarditis: causes and natural history. *J Am Coll Cardiol* 2004, **43:** 271–75.
124 Myers RB, Spodick DH. Constrictive pericarditis: clinical and pathophysiologic characteristics. *Am Heart J* 1999; **138:** 219–32.
125 Killian DM, Furiasse JG, Scanlon PJ, et al. Constrictive pericarditis after cardiac surgery. *Am Heart J* 1989; **118:** 563–68.
126 Rajagopalan N, Garcia MJ, Rodriguez L, et al. Comparison of new Doppler echocardiographic methods to differentiate constrictive pericardial heart disease and restrictive cardiomyopathy. *Am J Cardiol* 2001; **87:** 86–94.
127 Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation* 1989; **79:** 357–70.
128 Hurrell DG, Nishimura RA, Higano ST, et al. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. *Circulation* 1996; **93:** 2007–13.
129 Oh JK, Hatle LK, Seward JB, et al. Diagnostic role of Doppler echocardiography in constrictive pericarditis. *J Am Coll Cardiol* 1994; **23:** 154–62.
130 Santamore W, Bartlett R, Van Buren S, et al. Ventricular coupling in constrictive pericarditis. *Circulation* 1986; **74:** 597–602.
131 Nicholson WJ, Cobbs BW Jr, Franch RH, et al. Early diastolic sound of constrictive pericarditis. *Am J Cardiol* 1980; **45:** 378–82.
132 Manga P, Vythilingum S, Mitha AS. Pulsatile hepatomegaly in constrictive pericarditis. *Br Heart J* 1984; **52:** 465–67.
133 Anand I, Ferrari R, Kalra G, et al. Pathogenesis of edema in constrictive pericarditis: studies of body water and sodium, renal function, hemodynamics, and plasma hormones before and after pericardiectomy. *Circulation* 1991; **83:** 1880–87.
134 Bush CA, Stang JM, Wooley CF, et al. Occult constrictive pericardial disease: diagnosis by rapid volume expansion and correction by pericardiectomy. *Circulation* 1977; **56:** 924–30.
135 Vaitkus PT, Kussmaul WG. Constrictive pericarditis versus restrictive cardiomyopathy: a reappraisal and update of diagnostic criteria. *Am Heart J* 1991; **122:** 1431–41.
136 Ling LH, Oh JK, Tei C, et al. Pericardial thickness measured with transesophageal echocardiography: feasibility and potential clinical usefulness. *J Am Coll Cardiol* 1997; **29:** 131723.
137 Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flow. *J Am Coll Cardiol* 1993; **22:** 1935–43.
138 Abdalla IA, Murray RD, Lee JC, et al. Does rapid volume loading during transesophageal echocardiography differentiate constrictive pericarditis from restrictive cardiomyopathy? *Echocardiography* 2002; **19:** 125–34.
139 Tabata T, Kabbani SS, Murray RD, et al. Difference in the respiratory variation between pulmonary venous and mitral inflow Doppler velocities in patients with constrictive pericarditis with and without atrial fibrillation. *J Am Coll Cardiol* 2001; **37:** 1936–42.
140 Boonyaratavej S, Oh JK, Tajik AJ, et al. Comparison of mitral inflow and superior vena cava Doppler velocities in chronic obstructive pulmonary disease and constrictive pericarditis. *J Am Coll Cardiol* 1998; **32:** 2043–48.
141 Palka P, Lange A, Donnelly JE, et al. Differentiation between restrictive cardiomyopathy and constrictive pericarditis by early diastolic doppler myocardial velocity gradient at the posterior wall. *Circulation* 2000; **102:** 655–62.
142 Ha J-W, Oh JK, Ling LH, et al. Annulus paradoxus: transmitral flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. *Circulation* 2001; **104:** 976–78.
143 Arnold MF, Voigt JU, Kukulski T, et al. Does atrioventricular ring motion always distinguish constriction from restriction? A Doppler myocardial imaging study. *J Am Soc Echocardiogr* 2001; **14:** 391–95.
144 Masui T, Finck S, Higgins CB. Constrictive pericarditis and restrictive cardiomyopathy: evaluation with MR imaging. *Radiology* 1992; **182:** 369–73.
145 Kojima S, Yamada N, Goto Y. Diagnosis of constrictive pericarditis by tagged cine magnetic resonance imaging. *N Engl J Med* 1999; **341:** 373–74.
146 Olson MC, Posniak HV, McDonald V, et al. Computed tomography and magnetic resonance imaging of the pericardium. *Radiographics* 1989; **9:** 633–49.
147 Talreja DR, Edwards WD, Danielson GK, et al. Constrictive pericarditis in 26 patients wih histologically normal pericardial thickness. *Circulation* 2003; **108:** 1852–57.
148 DeValeria PA, Baumgartner WA, Casale AS, et al. Current indications, risks, and outcome after pericardiectomy. *Ann Thorac Surg* 1991; **52:** 219–24.
149 Uchida T, Bando K, Minatoya K, et al. Pericardiectomy for constrictive pericarditis using the harmonic scalpel. *Ann Thorac Surg* 2001; **72:** 924–25.
150 Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. *J Am Coll Cardiol* (in press).
151 Sun JP, Abdalla IA, Yang XS, et al. Respiratory variation of mitral and pulmonary venous Doppler flow velocities in constrictive pericarditis before and after pericardiectomy. *J Am Soc Echocardiogr* 2001; **14:** 1119–26.
152 Senni M, Redfield MM, Ling LH, et al. Left ventricular systolic and diastolic function after pericardiectomy in patients with constrictive pericarditis: Doppler echocardiographic findings and correlation with clinical status. *J Am Coll Cardiol* 1999; **33:** 1182–88.