Etiologies of Pericardial Diseases

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Introduction

There is a wide spectrum of conditions that affect the pericardium, including congenital defects and cysts, infectious, immune-mediated, metabolic, traumatic, neoplastic and drug-related causes [1] (Table 2.1). Most of these disorders result from an extrapericardial process (e.g., viral infections, uremia, chest radiation therapy), whereas a minority are isolated to the pericardium itself (e.g., cysts). Pathologically, the two most common disease processes are pericarditis (i.e., inflammation) and pericardial effusion. A less frequent development is pericardial constriction, a consequence of inflammatory insults that results in thickening, fibrosis and calcification [2]. Clinically, the presentation of pericardial disease is primarily determined by the degree and chronicity of the inflammatory process, the rate and amount of effusion accumulation, and the degree of pericardial thickening and fibrosis. The etiology of most cases of acute pericarditis is deemed "idiopathic" as no specific diagnosis is actively sought [3, 4]. The majority of such episodes are believed to be of viral origin.

Important questions in the history of patients with suspected pericardial diseases should focus on recent febrile illnesses, prior pericarditis episodes, recent procedures involving the chest, myocardial infarction (MI), the medication history (e.g., those associated with drug-induced lupus), tuberculosis exposure, travel history, a history of malignancy, previous radiation exposure, renal function, thyroid disease and the patient's immune status.

Infectious Pericardial Diseases

Viral Pericarditis

Viruses are the most common infectious agents that cause pericarditis. They may invade the pericardium directly, or may indirectly elicit an immune response. The most common viruses to cause pericarditis are echovirus and coxsackieviruses. Other important viral causes in the adult population include cytomegalovirus (CMV), herpesvirus (HSV), human immunodeficiency virus (HIV), and Ebstein-Barr virus (EBV). CMV pericarditis is more common in immune-compromised individuals including post-transplant and HIV patients [5]. In viral pericarditis, there is

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Table 2.1 Etiologies of diseases of the pericardium

1.	**Idiopathic** (acute and recurrent pericarditis)
2.	**Infectious**
	(i) **Viral** – Coxsackie A/B, echovirus, CMV,EBV, HSV, HBV, HCV, HIV/AIDS, Influenza, adenovirus, varicella, rubella, mumps, parvovirus, B19, HHV6
	(ii) **Bacterial** – Staphylococci, Streptococci, *Coxiella burnetti*, *Borrelia burgdorferi*, *Haemophilus influenzae,* meningococci, Chlamydia, Mycoplasma, Legionella, Leptospira, Legionella, Listeria, rickettsiae
	(iii) **Mycobacterial** – *Mycobacterium tuberculosis, Mycobacterium avium-intracellulare complex (*MAIC)
	(iv) **Fungal** – histoplasmosis, coccidioidosis, aspergillosis, blastomycosis, candidiasis
	(v) **Parasitic** – Chagas disease, African tripanosomiasis, echinococcosis, toxoplasmosis, amebiasis, schistosomiasis
3.	**Systemic inflammatory and autoimmune diseases**
	(i) **Connective tissue diseases –** systemic lupus erythematosus, rheumatoid arthritis, scleroderma, ankylosing spondylitis, mixed connective tissue disease, dermatomyositis
	(ii) **Vasculitides** – Takayasu arteritis, polyarteritis nodosa, Kawasaki disease, temporal arteritis, Churg-Strauss disease, Wegener granulomatosis
	(iii) **Rheumatic fever**
	(iv) **Granulomatous disease –** sarcoidosis
	(v) **Autoinflammatory diseases** – Familial Mediterranean Fever, inflammatory bowel diseases, TNF receptor-1 associated periodic syndrome (TRAPS)
4.	**Pericardial diseases secondary to diseases of surrounding organs** – pericarditis early after myocardial infarction, congestive heart failure, myocarditis, aortic aneurysm, pulmonary embolism, pulmonary hypertension, pneumonia, esophageal disease, paraneoplastic
5.	**Post cardiac injury syndrome** – Dressler syndrome (late post myocardial infarction syndrome), post-pericardiotomy syndrome, post heart transplant, pulmonary embolism
6.	**Neoplastic**
	(i) **Primary tumors** – mesothelioma, angiosarcoma
	(ii) **Secondary tumors** – metastatic or by direct extension e.g., lung cancer, breast cancer, Hodgkin's lymphoma, mesothelioma, gastric and colon cancer, melanoma and sarcoma
7.	**Mediastinal radiation therapy**
8.	**Hemopericardium and pericardial trauma**
	(i) Direct injury – penetrating thoracic injury, procedure related trauma (e.g., pacemaker, ablation, PCI, device placement), esophageal perforation
	(ii) Indirect injury – cardiopulmonary resuscitation, blunt trauma (e.g., automobile chest impact)
9.	**Aortic dissection**
10.	**Renal Disease** – uremic and dialysis pericarditis
11.	**Metabolic/Endocrine** – hypothyroidism (myxedema), scurvy, ovarian hyperstimulation syndrome
12.	**Congenital** – pericardial cysts, absence of pericardium
13.	**Drug induced pericarditis** – procainamide, hydralazine, isoniazid, methyldopa, phenytoin, penicillin, doxorubicin, daunorubicin, tetracyclines
14.	**Miscellaneous** – cholesterol pericardium, chylopericardium

commonly an upper respiratory tract infection prodrome preceding evidence of pericarditis. Assessment for rising serum viral titers has a limited role in diagnosis as it does not prove causality and most patients will have recovered before the results of such testing is available. Viral pericarditis is usually self- limiting, but may involve the myocardium (myopericarditis), or may lead to effusive or constrictive physiology.

HIV-Related Pericardial Disease

HIV may act on the pericardium by direct invasion, by related opportunistic pathogens, by an indirect immune response and by associated neoplastic involvement (e.g., Kaposi sarcoma and lymphoma). The most common pericardial presentation in HIV patients is simple pericardial effusion, which is present in 10–20 % of cases

and has been linked to shorter survival and lower CD4 counts [1–3]. The effusions are usually small, asymptomatic and non-progressive.

Pericardial effusion in HIV patients can also result from severe hypoalbuminemia due to AIDS related cachexia or capillary leak syndrome. The latter results from elevated cytokines (IL-2 and tumor-necrosis factor) that cause a systemic inflammatory response syndrome. HIV treatments, including nucleoside reverse transcriptase inhibitors (e.g., abacavir, lamivudine, zidovudine) and protease inhibitors (e.g., saquinavir, ritonavir) may additionally cause lipodystrophy; manifested by increased pericardial fatty tissue, visualized by echocardiography or MRI.

Bacterial Pericarditis

The most common pyogenic bacterial pathogens to invade the pericardium are staphylococci and streptococcal species [4–6] (Fig. 2.1). Less commonly implicated are *Haemophilus influenzae, Salmonella enteritidis, Niesseria meningitidis, Legionella pneumophila, Chlamydia pneumoniae, Coxiella burnetii, Treponema pallidum, Borrelia burgdorferi, Mycoplasma pneumoniae,* gram negative bacteria and rarely anaerobes. Bacterial pericarditis typically results in the accumulation of purulent fluid in the pericardial sac ranging from a thin layer to large quantities of frank pus. It is a life-threatening condition that presents as an acute febrile illness commonly complicated by tamponade. Though its prevalence has decreased since the advent of antibiotics, purulent pericarditis may result from local extension of suppurative pneumonia or cardiac ring abscess from endocarditis, following chest surgery or trauma, esophageal perforation, subdiaphragmatic abscess, or from hematogenous or lymphatic spread from a distant focus. In the developing world, tuberculous pericarditis remains the most common cause of chronic pericardial purulence. Patients with uremia, connective tissue disease and immune deficiency are more prone to this condition.

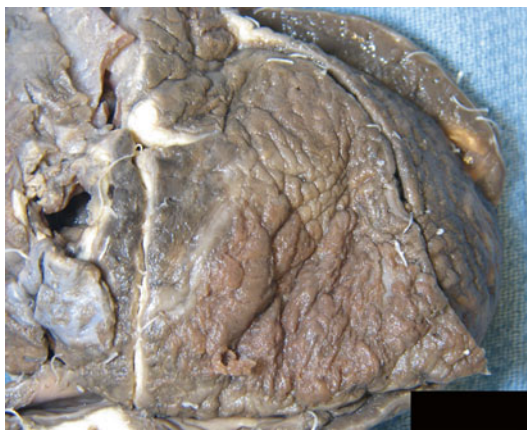

Fig. 2.1 Purulent pericarditis. The parietal pericardium has been removed to expose the purulent material covering the visceral pericardium (Courtesy of Dr. Stephen Sanders, Boston Children's Hospital, Harvard Medical School, Boston, MA)

The most common organism cultured in bacterial pericarditis is *Staphylococcus aureus* and its route of spread is typically hematogenous. *Streptococcus pneumoniae* is the most common organism causing purulence by direct extension from an adjacent pneumonia with empyema. Although suppurative foci complicating endocarditis may infiltrate the pericardial space, sterile pericardial effusion is more common in this situation. *Salmonella enteritidis* has been reported as a cause of purulent pericarditis in patients with HIV, lupus, malignancy and cirrhosis [7]. Esophageal perforation or mediastinal extension of peritonitis is associated with gram negative bacterial pericarditis, and penetrating trauma to the chest (e.g., knife wound) is often polymicrobial. The diagnosis of bacterial pericarditis is confirmed via pericardiocentesis and identification of the responsible pathogen by microscopy and culture. Effusion characteristics are exudative with high protein and low glucose concentrations. Treatment includes drainage of the purulent effusion and systemic antimicrobial therapy. Pericardiocentesis may serve both diagnostic and therapeutic purposes, but a thick effusion with fibrin stranding may prevent the complete drainage of purulent material [6]. Irrigation of the pericardial space with fibrinolytic agents such as urokinase or streptokinase may aid in drainage [8]. The creation of a window via the subxiphoid approach allows a surgeon to mechanically lyse

adhesions and more completely evacuate the effusion. In rare instances, a complete open pericardiectomy is required to disrupt adhesions and loculations to allow complete drainage.

Mycobacterial Pericardial Disease

Tuberculous pericarditis arises in approximately 4 % of patients with pulmonary tuberculosis (TB), and while now uncommon in the developed world, it remains an important cause of constrictive pericarditis in developing countries [9], where it is commonly diagnosed in association with AIDS. *Mycobacterium tuberculosis* infects the pericardium by direct invasion from adjacent tissues (primarily the lungs and the tracheobronchial tree), by hematogenous spread, or from reactivation from an extra-cardiac source. Pathologically four stages of development of pericardial disease occur: (1) granuloma formation with fibrinous exudation containing high concentrations of tuberculous bacilli; (2) serosanguinous effusion with a low concentration of bacilli, high protein and lymphocytic predominant exudate; (3) caseation of granulomas with early pericardial constriction including fibrosis and thickening; and (4) full pericardial constriction, scarring and calcification [10]. Progression among the stages is variable and generally the acute pericardial phase lasts between 2 to 4 weeks and the constriction component may take several years to develop.

Classically patients with tuberculous pericarditis present with fever, weight loss, night sweats and symptoms of right heart failure in the chronic phase, but at any stage may experience chest discomfort, cough and shortness of breath. Constrictive pericarditis can be dry or effusive and subsequently its presentation may vary from right-sided heart failure to tamponade, respectively.

Suspicion of mycobacterial disease starts by recognizing a history of TB exposure or HIV infection. Screening testing (e.g., tuberculin skin test or interferon gamma) may disclose exposure, but does not prove active disease. The diagnosis of TB pericarditis [11, 12] requires the identification of acid-fast bacilli (AFB) by stain or culture (40–60 % sensitive), a positive polymerase chain reaction for the DNA of *Mycobacterium tuberculosis* in the pericardial effusion, or demonstration of caseating granulomas in biopsied pericardial tissue (80–90 % sensitivity). The diagnostic yield is highest during the effusive stage. An increased level of adenosine deaminase (ADA) >40 units/l in pericardial effusion is 88 % sensitive and 83 % specific for TB. Imaging studies of the chest with CT or MRI may help detect pulmonary and other organ involvement. The mainstay of treatment is multidrug antituberculous therapy, which should be empirically administered when clinical suspicion is high in endemic areas of TB while awaiting conclusive diagnosis. Corticosteroid therapy for tuberculous pericarditis is controversial [13]. While such therapy may shorten the duration of symptoms, there has been no demonstrated survival benefit or prevention of progression to constriction. Surgical treatment of constrictive pericarditis with pericardiectomy is reserved for patients who exhibit persistent hemodynamic findings of constriction.

Fungal Pericarditis

Fungal pericarditis in the immune-competent patient is seen in endemic areas for *Histoplasma capsulatum* and *Coccidioides immitis*. Conversely, in the immunocompromised patient, candidiasis, aspergillosis and blastomyces infections are major fungal pathogens. Other patients predisposed to fungal infections are those who have chronic indwelling catheters, dialysis patients, alcoholics, burn victims and in individuals after prolonged antimicrobial therapy [14]. Diagnosis is made by fungal staining, positive cultures from pericardial effusion or tissue, and by measurement of serum titers of anti-fungal antibodies. Other than uncomplicated localized histoplasmosis, treatment usually requires antifungal antimicrobial therapy [15].

Parasite-Related Pericardial Disease

Protozoans and helminthes may affect the pericardium during their migration in the body, or as

a target organ [16]. The most common parasitic infection that involves the heart is Chagas disease (American trypanosomiasis) caused by *Trypanosoma cruzi,* which is endemic to central and south America. It causes myopericarditis acutely and cardiomyopathy in the chronic phase. Conversely, the African form of trypanosomiasis ("sleeping sickness") caused by *T. gambiense or T. rhodesiense* may incite pericarditis even months to years following the initial infection. *Toxoplasma gondii* may result in acute pericarditis in the immune-compromised and progress to constrictive pericarditis. Other rare parasitic causes of pericarditis include *Entamoeba histolytica* (amebiasis), *Echinococcus granulosus*, *Trichinella spiralis* and *Schistosoma* species.

Pericardial Involvement in Systemic Inflammatory Diseases

Systemic inflammatory diseases encompass rheumatogic diseases, vasculitides, granulomatous conditions, and autoinflammatory diseases. Although pericardial involvement is not uncommon in these disorders, only rarely do patients present with primary cardiac symptoms. Pericardial conditions that can arise during the course of these systemic diseases include acute and recurrent pericarditis and pericardial effusions. Usual screening tests include antinuclear antibodies (ANA) and rheumatoid factor. The overall prognosis of pericardial involvement in systemic inflammatory diseases is good, and only rarely is there progression to cardiac tamponade or constrictive pericarditis.

Rheumatologic Diseases (Connective Tissue Diseases)

Systemic Lupus Erythematosus

Cardiac involvement in systemic lupus erythematosus (SLE) can occur in multiple forms, including premature and accelerated coronary atherosclerosis, venous thromboembolism and cardiac inflammation [17]. Pericardial involvement is common and usually benign. Although pericardial effusion develops in >40 % of patients during the course of disease, symptoms of pericarditis occur only occasionally, usually when the systemic disease involves other serosal surfaces (e.g., pleuritis) [18].

Rheumatoid Arthritis

Clinical acute pericarditis arises in approximately 25 % of patients with rheumatoid arthritis (RA) [19]. When present, pericarditis usually occurs with active rheumatoid disease and other extra-articular manifestations. Symptoms typically respond to high dose aspirin and other NSAIDs.

Systemic Sclerosis

Systemic sclerosis is characterized by the excess production of collagen, which results in fibrosis of involved organs. Although the most common cardiac manifestations are the development of systemic or pulmonary hypertension, it can also directly affect the myocardium, pericardium and conduction system. Symptomatic pericarditis occurs in up to 20 % of patients with systemic sclerosis, while evidence of pericardial involvement is found in >50 % of patients at autopsy [20]. Late constrictive pericarditis can also occur.

Acute Rheumatic Fever

Although rarely seen in the developed world, acute rheumatic fever remains prevalent in developing countries. Acute pericarditis is commonly seen in the first week of acute rheumatic fever, and is a sign of active rheumatic carditis. It usually manifests with a loud pericardial rub, and although pericardial effusion is commonly seen, pericardial tamponade is rare.

Other Rheumatologic Conditions

In patients with polymyostitis and dermatomyositis, pericardial involvement is not as common as other connective tissue disorders, occuring in <10 % of patients [21]. Pericarditis is more common (10–30 %) in patients with mixed connective tissue disorder, but complications such as pericardial tamponade are unusual [21].

Vasculitides

Vasculitides are characterized by inflammation and damage of vessel walls. Large vessel vasculitides include Takayasu arteritis and giant cell arteritis, while medium vessel vasculitis includes polyarteritis nodosa and Kawasaki disease. Small vessel vasculitides includes Churg-Strauss syndrome and Wegener's disease. Pericardial involvement is rare in the large vessel disorders compared to those with medium and small vasculitides [21].

Granulomatous Diseases

Sarcoidosis is the predominant granulomatous disease with clinically significant pericardial involvement. Although mild to moderate pericardial effusions are commonly detected, symptomatic pericarditis is rare [22].

Autoinflammatory Diseases

Familial Mediterranean fever (FMF) is an autosomal recessive disorder that occurs in specific ethnic groups of Mediterranean countries and presents with recurrent attacks of serositis, including pericarditis. TNF receptor-1 associated periodic syndrome (TRAPS) is a rare autosomal dominant disorder that arises from mutations in the gene that codes for a TNF alpha receptor. Protracted fever, eye, muscle, and pericardial inflammation are clinical manifestations [23].

Pericardial Diseases Secondary to Diseases of Surrounding Organs

Pericardial abnormalities may result from conditions that arise in adjacent structures such as the myocardium (e.g., heart failure, myocardial infarction, myocarditis), the great vessels (e.g., aortic dissection), the lungs (pneumonia and pulmonary embolism), the thoracic duct (e.g., chylopericardium) and the esophagus.

Congestive Heart Failure

Both pericardial and pleural effusions are commonly present in congestive heart failure and myocarditis. Pericardial effusions are related to increased right atrial pressure promoting transudation into the pericardial space [24].

Post Myocardial Infarction Pericarditis

Post myocardial infarction (MI) pericarditis exists in two forms. The first form presents in the first few days after a transmural infarction as a direct extension of inflammation to the pericardium [11, 25]. The incidence of post-infarction pericarditis has decreased to <5 % since the introduction of reperfusion therapies and limitation of infarct size. The classic ECG changes of pericarditis are usually not apparent and the diagnosis is based on clinical suspicion, fever, pleuritic chest pain, and the presence of an effusion by echocardiography. Recommended treatment is aspirin, as other nonsteroidal anti-inflammatory agents and steroids have been associated with delayed infarct healing [26]**.** The second form of pericarditis after MI occurs later and is known as Dressler syndrome. When present, it arises weeks after the MI and is presumed to have an autoreactive immune mechanism similar to the post-cardiac injury syndrome described later.

Pulmonary Hypertension

Pericardial effusion arises in up to 25 % of patients with group I pulmonary hypertension (i.e., idiopathic or primary). Larger effusions are associated with right heart failure, elevated right atrial pressures, poor hemodynamic status and worse prognosis [27–29]. These effusions are rarely of hemodynamic significance. Treatment should focus on the primary process and not on the pericardial effusion.

Post Cardiac Injury Syndrome (PCIS)

In addition to Dressler syndrome, pericarditis may occur weeks to months after other forms of cardiac injury including patients who have undergone cardiac surgery (postpericardiotomy syndrome), percutaneous cardiac procedures (e.g., percutaneous coronary interventions, pacemaker lead insertion, electrophysiology ablation procedures), or who have sustained chest trauma [25, 30, 31]. It is presumed that these conditions share a common pathway in which cardiac injury (ischemic, traumatic or iatrogenic) exposes myocardial antigens which incites a systemic inflammatory response. PCIS presents with fever, acute pleuritic chest pain, pericardial effusion and pleural infiltrates and effusions, with elevated inflammatory markers. Of note, colchicine was shown to prophylactically reduce the incidence of PCIS after cardiac surgery in the prospective randomized Colchicine for Post-Pericardiotomy Syndrome (COPPS) trial [32].

Pericardial Trauma

Injury to the pericardium can occur from blunt trauma (e.g., steering wheel impact during a motor vehicle accident or cardiopulmonary resuscitation) or penetrating trauma (e.g., stab or bullet wound, or iatrogenic during medical procedures). In such cases blood accumulates rapidly within the pericardial space such that a small volume of effusion can result in tamponade physiology (as little as 100–200 ml) [33]. In direct injuries to the pericardium with hemodynamic compromise, thoracotomy with surgical exploration is required for survival. As with all types of pericardial injury, PCIS may develop later in the course, and constriction may develop following an organized intra-pericardial hematoma.

Iatrogenic injuries to the pericardium have risen in frequency as the number and complexity of percutaneous interventions increase [11, 33]. Transseptal puncture to access the left heart appears to hold a high risk of wall perforation (1–3 %), especially if not performed under biplane fluoroscopy or intra-cardiac echocardiogram guidance. Other procedures or hardware that may traumatize the pericardium include pacemaker leads (0.3–3.1 %), guidewires for stent or other hardware placement (0.1–3 %), rotablation (0.1–5.4 %), atherectomy (0–2 %), high pressure stenting (<2 %), mitral valvulopasty (1–4 %), pulmonary artery catheters, endomyocardial biopsies (0.3–5 %), atrial fibrillation ablation (1–6 %) and atrial septal occluder (1.8–3 %). Rescue pericardiocentesis in these situations has a very high success rate (95 %) and the mortality rate is low (<1 %).

Aortic Dissection and Hemopericardium

Hemopericardium is a life-threatening complication of ascending aortic dissection (type A) and pre-operative tamponade is a leading cause of mortality in this condition. A presentation of acute aortic regurgitation with pericardial effusion should raise the suspicion of an ascending aortic dissection, the presence of which can be confirmed by CT or transesophageal echocardiography [34]. Prompt surgical repair of the dissection is required. Preoperative pericardiocentesis with control of intravascular volume has been performed successfully in patients who could not otherwise survive awaiting surgical intervention [35].

Neoplastic Pericardial Disease

Pericardial tumors are uncommon, with metastatic involvement occurring more frequently than primary neoplasms. Neoplastic effusions tend to be large and hemorrhagic. In general autopsy studies of cancer patients, malignant involvement of the pericardium is detected in up to 20 % [36] (Fig. 2.2).

Primary Tumors of the Pericardium

Mesothelioma is the most common primary malignant neoplasm of the pericardium, accounting for ~50 % of all primary pericardial tumors.

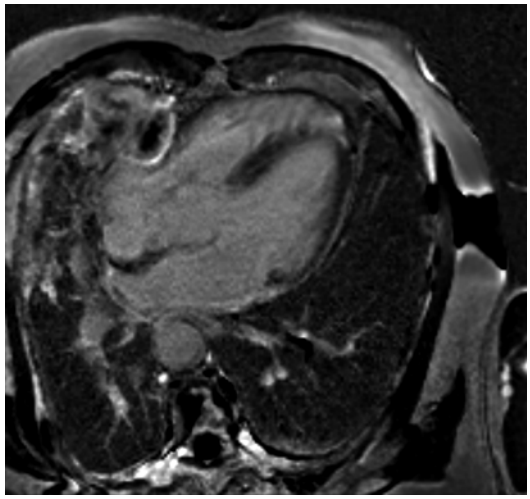

Fig. 2.2 Metastatic disease. MRI delayed enhancement image demonstrating mesothelioma penetrating the pericardium through a pericardial patch (Courtesy of Dr. Michael L. Steigner, Brigham and Women's Hospital, Harvard Medical School, Boston, MA)

As compared to pleural mesothelioma, no definite association with asbestos exposure has been established. It may arise in children or adults, with a preponderance for males (2:1 male: female ratio) [37]. Typically at presentation, patients present with diffuse pericardial involvement and signs and symptoms of constrictive pericarditis may be present. Other primary malignant pericardial tumors include sarcomas (fibrosarcoma and liposarcoma), lymphoma and malignant teratomas. These malignancies usually present as large masses with hemorrhagic pericardial effusion. Benign pericardial tumors include lipomas, teratomas, and fibromas.

Secondary or Metastatic Malignant Pericardial Disease

Metastases to the heart and pericardium are far more common than primary tumors and portend a poor prognosis. Noncardiac tumors may invade the heart and pericardium by means of lymphatic or hematogenous dissemination or local extension. Pulmonary primary tumors are the most common source of pericardial neoplastic disease, accounting for approximately 40 % of malignant effusions [38, 39]. Other primary tumors that spread to the pericardium include breast, melanoma, and hematologic malignancies, including lymphoma and leukemia. Tumors below the diaphragm, such as from the gastrointestinal tract and the renal system, rarely extend to the pericardium. Pericardial Kaposi sarcoma or lymphoma may appear in patients with HIV disease.

Radiation Pericarditis

Therapeutic radiation for malignancy is an important cause for acute pericarditis, pericardial effusion and constrictive pericarditis (Fig. 2.3). Most cases are secondary to irradiation of the chest for Hodgkin lymphoma, breast or lung cancer [40]. Pericardial inflammation may present during acute radiation treatment or findings of constrictive pericarditis may arise many years thereafter. Constriction related to radiation therapy increases the surgical risks of pericardiectomy and worsens post-operative outcomes.

Renal Related Pericardial Disease

Pericardial involvement in advanced renal disease includes uremic pericarditis (6–10 % of patients, prior to initiation of dialysis), dialysis-related pericarditis, large pericardial effusions and rarely constrictive pericarditis [11, 41]. The incidence of pericarditis rises with greater levels of azotemia and uremic pericarditis is an indication for acute initiation of dialysis. Pericarditis arising in patients already on dialysis may result from inadequate intensity of dialysis treatments. Pathologically, there are adhesions bridging a thickened pericardium in a "bread and butter" appearance. The pericardial effusion may range from serous fluid to hemorrhagic. Although most patients present with pleuritic chest pain and fever, others may remain asymptomatic and afebrile. Clinically, the hemodynamic response to cardiac compression may be blunted (i.e., absence of tachycardia) in patients with renal failure, due to accompanying autonomic dysfunction [42]. Pericardial rubs are common but

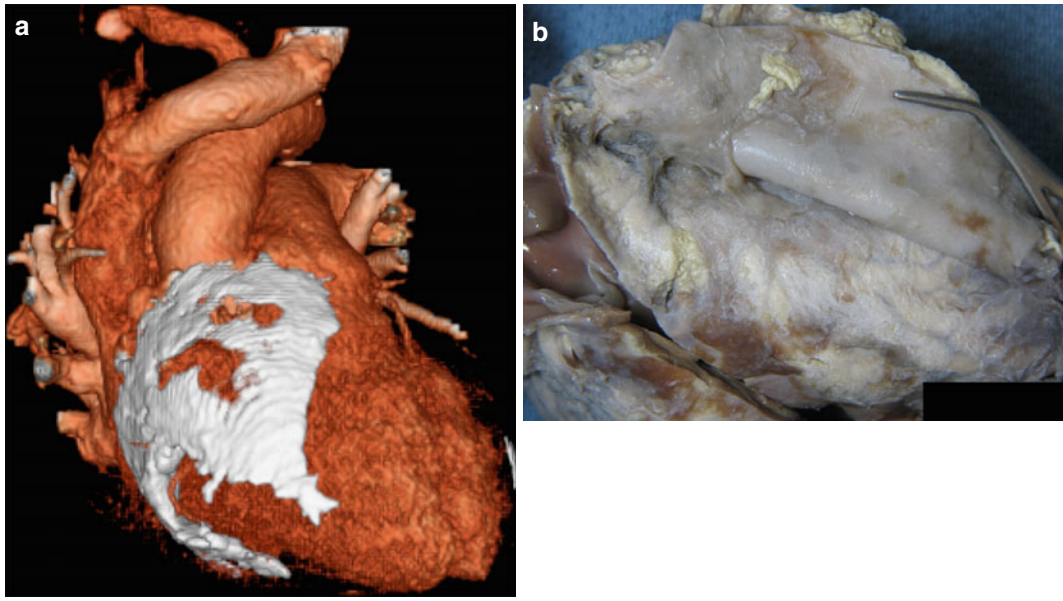

Fig. 2.3 Radiation pericarditis. (**a**) CT 3D volume rendering of substantial calcification of the pericardium in a patient with radiation induced constrictive pericarditis. (**b**) Radiation induced constrictive pericarditis in a patient with Hodgkin's disease. The thickened and calcified parietal pericardium is artificially folded outward to demonstrate an elaborate network of adhesions and thickening between the parietal and visceral pericardium (Image **a**: Courtesy of Dr. Michael L. Steigner, Brigham and Women's Hospital, Harvard Medical School, Boston, MA. Image **b**: Courtesy of Dr. Stephen Sanders, Boston Children's Hospital, Harvard Medical School, Boston, MA)

are often transient. Pericardial effusions are found by imaging in the majority of patients and may be accompanied by pleural effusions. Typical ECG findings of pericarditis are often absent. Treatment requires intensive dialysis, which typically results in rapid improvement of symptoms and size of the effusion. However, vigorous dialysis should not be initiated until cardiac compression has been ruled out, as a rapid decrease in intravascular volume could result in tamponade physiology in that setting. Furthermore, it is preferable to consider non-heparinized hemodialysis, or peritoneal dialysis, in the setting of a significant pericardial effusion to avoid the possibility of intrapericardial hemorrhage. NSAIDS and systemic corticosteroids have been used in cases of dialysis failure with limited efficacy.

Subxiphoid pericardiotomy is reserved for non-resolving effusions, and at some centers is accompanied by instillation of a nonabsorbable steroid. Full pericardiectomy is rarely needed for refractory cases.

In renal transplant patients [43], CMV pericarditis should be excluded as a cause of pericardial effusion. An effusion may also appear as a rare side effect of sirolimus immunosuppressant therapy in this population (≤2 % of patients).

Congenital Anomalies of the Pericardium

Total and Partial Absence of the Pericardium

Congenital defects of the pericardium are rare (1/10,000 of autopsies), and are divided into total absence of the pericardium (heart and lung in the same cavity) and partial absence (Fig. 2.4). The defects are the result of failure of the pleuropericardial membranes to fuse in utero. The pericardium develops during the third to seventh weeks of embryonic life from the lateral mesodermal plate that lines the pleural, pericardial

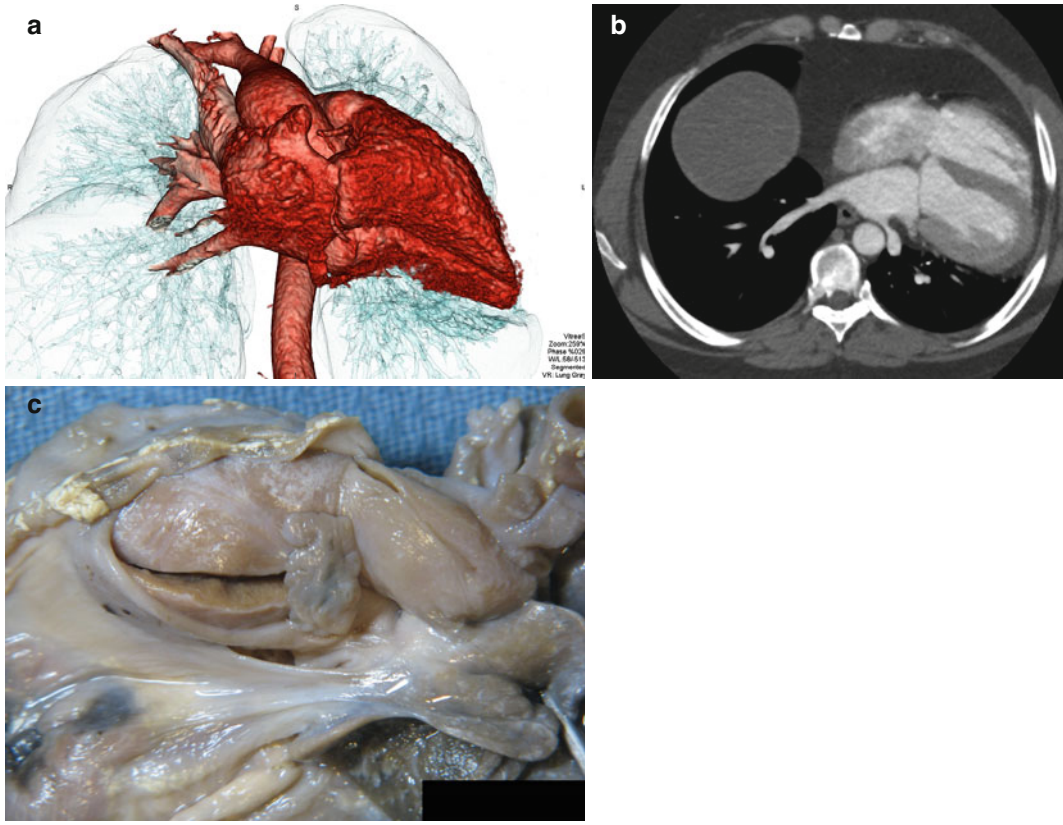

Fig. 2.4 Partial absence of the pericardium. (**a**) CT 3D volume rendered image depicting the lateral displacement of the heart to the left. The exposed great vessels cause the lung to abnormally occupy the space between the aorta and pulmonary artery (*arrow*). (**b**) Axial CT image depicting the extreme lateral rotation of the heart with its apex pointing posteriorly. (**c**) Pathological specimen – the pericardium is missing over the lateral left border of the heart and the proximal great vessels. The existing pericardium has a thickened and smooth edge (Images **a**, **b**: Courtesy of Dr. Michael L. Steigner, Brigham and Women's Hospital, Harvard Medical School, Boston, MA. Image **c**: Courtesy of Dr. Stephen Sanders, Boston Children's Hospital, Harvard Medical School, Boston, MA)

and peritoneal spaces. There is predominance of such defects of the left side (70 %) versus the right (17 %) or bilateral partial absence (13 %) [44, 45]. Two theories have been raised to explain this phenomenon. Perna et al. suggested that premature atrophy of the left duct of Cuvier that gives rise to the left superior vena cava (connecting the left innominate vein to the coronary sinus) may cause absorption of the pericardium on the left because of decreased blood supply. Alternatively, Sunderland et al. proposed that defects are the consequence of dyssynchrony between growth of the heart and the enveloping pericardium, especially on the left side where structures increase to a greater volume [46]. Associated congenital abnormalities exist in approximately 30 % of patients, including patent ductus arteriosus, bronchogenic cysts, tricuspid insufficiency, atrial septal defects, left diaphragmatic hernia and pulmonary sequestration. Although most patients with total absence of the pericardium are asymptomatic, torsion and increased stress between the base of the heart and the great vessels might explain reports of chest pain and dyspnea. This is in contrast to partial defects of the pericardium that may pose clinical risk because of displacement or herniation of heart structures (e.g., atria or partial ventricle). There is also an increased risk of traumatic aortic dissection due to increased structure mobility.

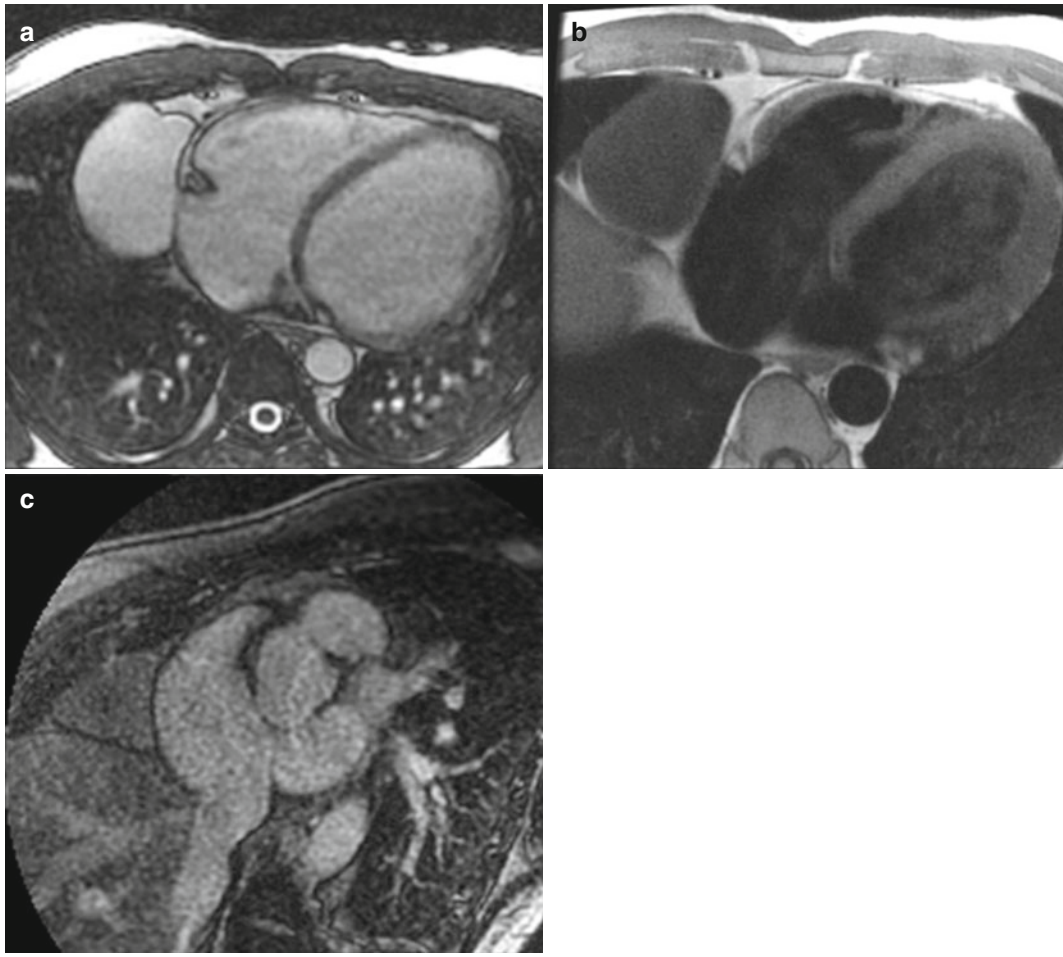

Fig. 2.5 Pericardial cyst. (**a**) Steady state free procession (SSFP) acquisition showing bright fluid filled cyst adherent to the lateral wall of the right ventricle (**b**). T1 weighted double inversion recovery sequence demonstrating hypointense fluid. (**c**) Delayed enhancement image showing no uptake of gadolinium in the cyst (Courtesy of Dr. Michael L. Steigner, Brigham and Women's Hospital, Harvard Medical School, Boston, MA)

Diagnostically, most cases are detected incidentally (during imaging or surgery).

In congenital absence of the pericardium, the heart's apex may shift to the mid-axillary line with cardiomegaly on chest X-ray and the ECG exhibits rightward axis and incomplete right bundle branch block. On echocardiography, the lateral apical shift causes right-sided predominance on the apical long-axis view (and may be incorrectly interpreted as right ventricular enlargement). MRI is the modality of choice for the detection of pericardial defects and possible herniation of heart structures [47]. Surgical pericardioplasty is indicated when there is a high risk of mechanical complication.

Pericardial Cysts

Pericardial cysts may be congenital or acquired; with an incidence of 1/100,000 individuals (Fig. 2.5). Congenital cysts are usually benign, asymptomatic and incidentally discovered [48, 49]. They are usually located at the right costophrenic angle (51–70 %) or left costophrenic angle (28–38 %) and rarely elsewhere in the mediastinum. Histologically they contain a single layer of mesothelial cells surrounded by connective tissue. Acquired types of cysts include inflammatory (e.g., rheumatic, post-cardiotomy or traumatic) and infectious (e.g., bacterial, echinococcal or

tuberculous). They can be divided into unilocular or multilocular types, with a diameter typically ranging from 1 to 5 cm. Symptomatology of chest pain, cough and dyspnea may arise from the mass effect of a cyst and in rare cases from hemorrhagic eruption of the cyst into the pericardial space causing tamponade. On echocardiography a cyst is imaged as a hypoechoic structure with distal acoustic enhancement because of its fluid content. Calcification of the cyst and pericardial effusion are rare. CT and MRI can distinguish cysts from other entities such as hematoma, a prominent fat pad, a large left atrial appendage or tumor [50]. Congenital cysts are usually treated conservatively unless there is evidence of structural compression. When treatment is necessary, percutaneous aspiration and ethanol sclerosis can be attempted prior to thoracotomy and surgical excision. Hydatid cysts are aspirated and the cyst is injected with ethanol or silver nitrate after pre-treatment with albendazole.

Hypothyroidism Related Pericardial Effusion

Pericardial effusion in clinical hypothyroidism is seen in up to 30 % of patients, is often large, but rarely progresses to tamponade due to its slow accumulation [51, 52]. Other cardiac manifestations of hypothyroidism include impaired ventricular contractility, bradycardia, and non-pitting edema. The ECG typically demonstrates sinus bradycardia, decreased voltage and mild prolongation of the QT interval. Therapy consists of thyroid hormone replacement therapy, and the degree of hypothyroidism determines the route of administration (i.e., intravenous versus oral). Thyroid hormone enhances the absorption of the pericardial effusion and thus unless hemodynamically compromising, there is no urgency to drain hypothyroid-induced effusions.

Drug/Toxin Induced Pericarditis

Many drugs and toxins may precipitate pericardial inflammation and effusion [11] (Table 2.2). The mechanisms by which the pericardium is affected include drug-induced lupus reactions, hypersensitivity, "serum sickness", foreign substance reaction and immunopathy. Procainamide, hydralazine, anti-tumor necrosis factor (TNF)- α therapies, isoniazid, reserpine, methyldopa and phenytoin are examples of drugs that may induce a lupus-like response with manifestations that include pericardial effusion. Penicillin, L-tryptophan and cromolyn sodium can induce hypersensitivity reactions. Minoxidil, amiodarone, cyclosporine, and anthracyclines (e.g., doxorubicin) may result in idiosyncratic pericardial reactions. "Serum sickness" may arise after administration of blood products and foreign antisera (e.g., anti-tetanus). Venomous scorpion fish sting is an example of a toxin that has been reported to cause pericarditis. Additional foreign-substance reactions can occur from direct contact with the pericardium by talc, asbestos, silicones, tetracycline and inhalation of Teflon (polytetrafluoroethylene).

Table 2.2 Drug and toxin induced pericardial disease

1. D**rug induced lupus erythematosus (positive anti-nuclear antibody (ANA) and anti-histone antibody)** – Procainamide, hydralazine, methyldopa, isoniazid, reserpine, anti-tumor-necrosis factor (TNF)-alpha agents, phenytoin, tocainide, mesalazine
2. H**ypersensitivity reactions (eosinophilic)** – penicillin, L-tryptophan, cromolyn sodium
3. I**diosyncratic reaction** – amiodarone, minoxidil, streptokinase, cyclophosphamide, cyclosporine, thiazides, streptomycin, thiouracils, sulfa, GM-CSF, vaccines, 5-fluorouracil, bromocriptine, polymer fume inhalation, cytarabine, p-Aminosalicylic acid, mesalazine, practolol, psicofuranine, methylsergide
4. A**nthracycline derivatives** – doxorubicin, daunorubicin
5. S**erum sickness** – blood products, foreign antisera (antitetanus)
6. V**enom** – scorpion venom
7. F**oreign body reaction** – Talc (Mg silicate), tetracycline, asbestos, sclerosant, Iron
8. H**emopericardium** – anticoagulants and thrombolytic agents

Cholesterol Pericarditis

Cholesterol pericarditis is an uncommon condition manifested by elevated cholesterol levels in the pericardial effusion, with crystal formation in chronic cases. It most often results from a chronic pericardial effusion as may occur in rheumatoid arthritis, tuberculosis infection, hypothyroidism and rarely with pericardial trauma [53, 54]. Classically the associated effusion is large, has a "gold paint" hue and the cholesterol concentration is high (>500 mg/dl) with a cholesterol to triglyceride ratio >1. Crystal formation does not usually develop in myxedema. The pathophysiology of the disease is unknown, but is presumed to be related to cholesterol debris accumulation from lysed pericardial or red blood cells with thickening and scarring of the pericardial tissue. Therapy is based on treating the underlying systemic disease, and when needed for chronic scarring, pericardiectomy.

Chylopericardium

Chylopericardium is a rare condition that arises from an abnormal communication between the thoracic duct and the pericardial space [11, 55]. This may occur by direct injury to the thoracic duct from chest trauma or surgery, or indirectly by congenital malformations or tumors (lymphangiomas, aplasia of the cisterna chyli, lymphangiomatous hamartomas, lymphangiectasis and Gorham's disease) as well as acquired conditions that cause obstruction (subclavian vein thrombosis, pancreatitis, infections (e.g., TB) and mediastinal tumors). Chylous pericardial effusions appear milky-opaque on aspiration, and have a high concentration of triglycerides (>500 mg/dl), protein (>3 g/dl), a high specific gravity (1.010–1.021) and a cholesterol to triglyceride ratio <1. There is usually lymphocytic predominance and the effusion is positive for Sudan III stain for fat globules. A diet devoid of triglycerides would cause the effusion to lose its milky appearance. CT lymphangiography may identify the responsible thoracic duct abnormality. Radionuclide imaging with 99mTechnicium labeled red blood cells 24 hours after oral administration of 131-I-triolein has been shown to identify chylous effusions.

The clinical presentations of chylopericardium include acute pericarditis, a large pericardial effusion with or without tamponade physiology, or constrictive pericarditis. The first line of treatment is pericardiocentesis (which is typically required for diagnosis) and dietary modification with a medium chain enriched triglyceride diet. If the effusion reaccumulates, surgical correction or shunt placement between the pericardium and the peritoneum (where the chyle can be reabsorbed) is required [56].

Pericardial Diseases During Pregnancy

Pericardial effusions are common during pregnancy, occurring in up to 20 % of women in the first and second trimester and up to 40 % in the third trimester [57]. Such effusions are usually small in size and are almost always clinically silent. Effusions during pregnancy have been associated with increased weight (fluid retention), hypertension and nonspecific ST-T abnormalities on the ECG. The effusion usually resolves spontaneously by 2 months after delivery.

Acute pericarditis during pregnancy is similar in etiology and outcomes to the general population, but its treatment requires caution as aspirin and other NSAIDs may cause premature closure of the ductus arteriosus and can compromise fetal renal function after the 20th week of gestation. Generally, colchicine treatment is avoided during pregnancy because of demonstrated teratogenicity in animals. If needed, low-dose corticosteroids are considered safe during pregnancy (e.g., prednisone <25 mg/day, with a downward taper).

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Etiologies of Pericardial Diseases- For Patients and their Families

Pericardial diseases commonly present as pericarditis (inflammation of the pericardium) or as pericardial effusions (fluid accumulation within the pericardial space). Rarely, repeated bouts of pericarditis may result in scarring and thickening of the pericardium, a condition termed constrictive pericarditis. While there are many possible causes of pericarditis, it is often hard to identify the exact cause. On the other hand, in case of a significant pericardial effusion, a sample of fluid can be withdrawn through a needle and analyzed to aid in the diagnosis. When no definite diagnosis for pericarditis is made, it is termed idiopathic pericarditis. Most of the idiopathic cases of pericarditis are presumed to be secondary to a viral infection.

Other infections which can cause pericarditis include bacterial infections, tuberculosis, fungal, and parasitic infections. Patients with underlying AIDS frequently develop infections which can produce pericarditis as well as pericardial effusions. Pericarditis can also develop in association with underlying autoimmune diseases (diseases in which the body attacks itself), including but not restricted to rheumatoid arthritis, systemic lupus erythematosus, scleroderma, sarcoidosis and various vasculitides (e.g., Takayasu arteritis, Kawasaki disease). Some medications, like procainamide, hydralazine, phenytoin, and isoniazid, can also produce pericarditis, although this is not very common.

Also, there is a higher risk of developing pericarditis after a major heart attack. This appears in two forms, the first is early on and in conjunction with the acute infarct and a later form that involves a whole body inflammatory response (Dressler syndrome). In addition, there is a greater risk of developing pericarditis after invasive procedures of the heart and this is termed post-cardiac injury syndrome (PCIS). PCIS may be seen after heart surgery or percutaneous intervention, such as cardiac catheterization or radiofrequency ablation for rhythm disorders. Occasionally blood may accumulate in the pericardial space (hemopericardium) due to a tear in the large blood vessel leaving the heart (aortic dissection), after injury to the chest (e.g., motor vehicle accident or knife wound) or when procedures are performed on the heart, including open heart surgery, insertion of devices in the heart and other interventional procedures to the heart.

In addition, the pericardium can be involved when a disease process affects the heart muscle or the surrounding organs. Pericardial effusions are commonly seen in heart failure and lung diseases such as pneumonia or chronic disease of the lung with elevated lung pressures. Cancer may also infiltrate the pericardium and is one of the leading causes of pericardial effusion development. Occasionally pericardial effusions could be detected during pregnancy, usually without clinical significance. Additional causes of pericardial diseases include kidney disease, thyroid disease, after radiation exposure to the chest and genetic diseases such as Familial Mediterranean Fever. Rarely, a cyst (sac filled with fluid) may develop in the pericardial space, which may be present from birth (congenital) or at a later stage (acquired). Very rarely, the pericardium may either be completely or partially absent, causing the heart to shift its position inside the chest.