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Infiltrative Cardiovascular Diseases

Cardiomyopathies That Look Alike

James B. Seward, MD,* Grace Casaclang-Verzosa, MD†

Rochester, Minnesota

Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances that cause the ventricular walls to become progressively rigid, thereby impeding ventricular filling. Some infiltrative cardiac diseases increase ventricular wall thickness, while others cause chamber enlargement with secondary wall thinning. Increased wall thickness, small ventricular volume, and occasional dynamic left ventricular outflow obstruction (e.g., amyloidosis) can outwardly appear similar to conditions with true myocyte hypertrophy (e.g., hypertrophic cardiomyopathy, hypertensive heart disease). Likewise, infiltrative disease that presents with a dilated left ventricle with global or regional wall motion abnormalities and aneurysm formation (e.g., sarcoidosis) may mimic ischemic cardiomyopathy. Low-voltage QRS complex was the sine qua non of infiltrative cardiomyopathy (i.e., cardiac amyloid). However, low-voltage QRS complex is not a uniform finding with the infiltrative cardiomyopathies. The clinical presentation, along with functional and morphologic features, often provides enough insight to establish a working diagnosis. In most circumstances, however, tissue or serologic evaluation is needed to validate or clarify the cardiac diagnosis and institute appropriate therapy.   (J Am Coll Cardiol 2010;55:1769–79) © 2010 by the American College of Cardiology Foundation

Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances that cause the ventricular walls to become progressively rigid, thereby impeding ventricular filling. Some infiltrative cardiac diseases increase ventricular wall thickness (Table 1), while others cause chamber enlargement with secondary wall thinning (Table 2). The clinical presentation, along with functional and morphologic features, often provides enough insight to establish a working diagnosis. However, in most circumstances, tissue or serologic evaluation is needed to validate or clarify the cardiac diagnosis and institute appropriate therapy. This report highlights the unique features of the various infiltrative cardiac diseases, which may have similar features.

Infiltrative Heart Disease

General considerations. CARDIAC FUNCTION ASSESSMENT. Infiltrative diseases of the heart are generally characterized by progressive diastolic dysfunction, which typically precedes the development of overt systolic dysfunction. Although increased myocardial mass is characteristic of most infiltrative diseases, the quantification of mass is usually not a major determinant of survival. Doppler echocardiography has simplified the assessment of diastolic physiology and

atrial remodeling, which are hallmarks of the restrictive disease process. The chronicity of diastolic dysfunction is best characterized by depressed Doppler myocardial relaxation velocity (mitral annular E tissue velocity) and increased left atrial volume index (1). Systolic dysfunction is commonly measured as a decrease in the ejection fraction or systolic tissue Doppler velocity (2).

The role of computed tomography and cardiac magnetic resonance (CMR) imaging and late gadolinium enhancement (LGE) in providing incremental information for risk assessment in infiltrative cardiomyopathies has not been adequately established. However, cardiac structure, function, and tissue characteristics can be obtained by CMR LGE. Gadolinium causes magnetic hyperenhancement in conditions in which extracellular space is expanded (i.e., myocyte necrosis, myocardial edema, scar formation, and protein infiltration) (3,4). CMR has been used to characterize the type of infiltrative disease by the location and distribution of LGE and enable the evaluation of disease activity and response to therapy. The sensitivity of CMR in patients with early disease who do not have abnormal findings on echocardiography is unknown. However, screening of subclinical early cardiac involvement may become possible should CMR LGE prove to have adequate sensitivity in detecting amyloid infiltration. The abnormalities in myocardial and blood pool kinetics hold the promise of serial quantification of cardiac amyloid load and treatment follow-up.

Electrophysiologic considerations. It is important to emphasize that wall thickness is not necessarily a reliable

indicator of hypertrophy. Infiltrative disorders, with accumulation of abnormal substances within myocytes or the myocardial interstitium, may cause increased wall thickness without actual myocyte hypertrophy. Consequently, increased wall thickness does not consistently correlate with an increase in QRS complex amplitude. In fact, QRS complex amplitude can become decreased (low voltage), a phenomenon more commonly observed with accumulations within the interstitium than within myocytes. The absence of increased voltage on the electrocardiogram (ECG) despite the appearance of "hypertrophy" can be the first clue to certain infiltrative diseases (e.g., cardiac amyloid, Friedreich ataxia). However, low-voltage QRS complex is not a uniform finding with the infiltrative cardiomyopathies. Some infiltrative myopathies have increased voltage (e.g., Danon and Fabry diseases), which will be seen when there is an increase in the size of cardiac myocytes, normal intraventricular conduction, and synchronous activation occurring globally in the myocardium (Table 1).

Genetic testing. The role of genetic testing in differentiating phenocopies of left ventricular (LV) hypertrophy is evident when clinical or imaging data are inconclusive. Genetic testing is now available on a clinical basis for several of the genes responsible for cardiomyopathies. However, it has its limitations and challenges. Testing sensitivity is low, and there may be more than 1 genetic variant in an affected patient or within a single family. Other challenges of genetic evaluation, especially in children, include age-dependent penetrance, the management of asymptomatic children, the psychological effects of testing asymptomatic minors, and expense (5,6).

General management. Most infiltrative diseases have until recently been considered irreversible, and supportive measures were the only available means of management. General management consists of improving diastolic function with angiotensin receptor blockers and angiotensin-converting enzyme inhibitors. Beta-blockers and statins, which are known to be useful for heart failure management, may be of benefit. Systolic hypertension and overt fluid overload can justify the cautious use of thiazide diuretics. Excessive or protracted diuresis (i.e., using loop diuretics) should be avoided in the presence of hypovolemia and small, noncompliant ventricular cavities. Novel treatment modalities will be briefly discussed when applicable.

Infiltrative Cardiomyopathies That Look Like Hypertrophic or Hypertensive Heart Disease

Cardiac amyloid. Cardiac amyloid is the prototype of infiltrative heart disease with increased wall thickness (Fig. 1). Cardiac involvement is common in all forms of amyloidosis

and is the most frequent cause of morbidity and mortality (7). Symptoms include heart failure (i.e., breathlessness and exercise intolerance), arrhythmias, conduction block, dynamic ventricular outflow obstruction, and hypotension.

Characteristic echocardiographic appearance of cardiac amyloid includes increased thickness of both LV and right ventricular walls, normal or small LV cavity size, and a nonspecific granular appearance of the myocardium (Fig. 2). Atrial enlargement, thickened papillary muscles, and valve leaflets and small to moderate pericardial effusion are also commonly present. LV compliance gradually decreases as myocardial deposition of amyloid fibrils progresses (8). Progressive diastolic dysfunction is a universal finding (8). Systolic dysfunction is typically evident only in advanced stages (9). Doppler echocardiography is used to establish and serially monitor the magnitude of diastolic and systolic dysfunction. CMR will show diffuse LGE throughout both ventricles, particularly the subendocardium (3).

Despite increased ventricular wall thickness, 30% to 50% of patients with demonstrable amyloid disease will have normal-voltage QRS complexes, and the remainder show low-voltage complexes. A pseudoinfarction pattern, particularly in the inferoseptal wall, may be observed in the precordial leads (10). A decrease in QRS complex amplitude occurs because of myocyte atrophy along with decreased conduction velocity and dyssynchronous activation resulting from amyloid deposition (11,12).

Cardiac amyloidosis is diagnosed either directly by endomyocardial biopsy or indirectly using noninvasive diagnostic tools (2-dimensional echocardiography, magnetic resonance imaging, and ECG) and histologic confirmation of amyloid on a noncardiac tissue specimen. Upon unequivocal establishment of the diagnosis and tissue confirmation of amyloid type, prompt therapy is warranted for primary amyloidosis to arrest or reverse cardiac dysfunction (Fig. 3). Poor cardiac reserve severely narrows the management strategies in the late stages (7,13). Untreated patients have a median survival of <6 months after the onset of heart failure (13). Melphalan, steroids, immunomodulating agents, and stem cell transplantation after chemotherapy yield promising results (14–17). However, the mortality rate of transplantation ranges from 11% to 40% (18,19). In some patients with advanced cardiac involvement, cardiac transplantation may be performed before stem cell transplantation (20,21).

Fabry disease. Fabry disease is an X-linked autosomal recessive disease due to a lack of lysosomal enzyme, α-galactosidase A, which breaks down neutral glycosphingolipids (22). This causes intracellular lysosomal accumulation of ceramide trihexoside (globotriaosylceramide), primarily in the skin, kidneys, and heart (22). Men are commonly affected, with the condition diagnosed early in childhood, but cardiac involvement is not manifested until the third or fourth decade of life (23). Cardiac involvement in Fabry disease can mimic the morphologic and clinical features of hypertrophic cardiomyopathy (HCM; very thick walls, systolic anterior motion of the anterior mitral valve

| Table 1	Conditions Presenting With Increased LV Mass and Thick Ventricular Walls						
Condition	**Age at Presentation**	**History and Clinical Presentation**	**Echocardiography**	**ECG Profile**	**CMR LGE**	**Biopsy**	**Ref. #**
Cardiac amyloid	>30 yrs	Heart failure symptoms, nephrotic syndrome, idiopathic peripheral neuropathy, unexplained hepatomegaly	Symmetrical increase in LV and RV wall thickness, dilated LA and RA, granular appearance of myocardium, pericardial effusion, decreased EF in advanced cases	Decreased or normal QRS complex voltage, pseudoinfarction in inferolateral leads	Global, diffuse, pronounced in subendocardium; RV and LV walls	Myocyte atrophy, amyloid replaces normal cardiac tissue	(3,7,10)
Fabry disease	Male: 11 ± 7 yrs; female: 23 ± 16 yrs	Neuropathic pain, impaired sweating, skin rashes	Symmetrical increase in LV and RV wall thickness, normal EF	Increased or normal QRS complex voltage, short or prolonged PR interval	Focal, midwall, inferolateral wall	Enlarged myocytes with clusters of concentric glycolipid (myelinoid bodies) within lysosomes	(3,22,28,29)
Danon disease	<20 yrs	Heart failure, skeletal myopathy, mental retardation	Very thick LV (20–60 mm), RV may or may not be thick, decreased EF	Increased or normal QRS complex voltage, short PR interval (delta wave)	Subendocardial, does not correspond to perfusion territory	Sarcoplasmic vacuolization, focal storage of PAS-positive material, myofibrillar disarray	(32,34,36)
Friedreich ataxia	25 yrs (range 2–51 yrs)	Gait abnormality	Increase in LV septal and posterior wall thickness, normal EF	Normal QRS complex voltage, ventricular tachycardia		Nonspecific	(41,42,44,47)
Cardiac oxalosis	>20 yrs	Juvenile urolithiasis and nephrocalcinosis	Symmetrical increase in LV and RV wall thickness; patchy, echodense speckled reflection; normal EF	Increased or normal QRS complex voltage, complete heart block	Increased myocardium attenuation on CT	Intra- and extracellular deposition of oxalate crystals without concomitant inflammation and necrosis	(49,50,51)
Mucopolysaccharidoses	1–24 yrs (median, 10 yrs)	Variable depending on subtype, coarse facial features, delayed mental development, skeletal deformities, corneal clouding, hepatosplenomegaly	Asymmetrical septal hypertrophy, mitral and/or aortic valve stenosis or insufficiency, normal EF	Increased or decreased QRS complex voltage, malignant arrhythmia		Swollen myocytes with clear cytoplasm due to accumulation of mucopolysaccharides within lysosomes	(12,53,55,56)
Differential diagnosis							
Hypertrophic cardiomyopathy	17–18 yrs	Maybe asymptomatic, dyspnea, angina, syncope, sudden death	Asymmetrical hypertrophy, small LV cavity, LVOT obstruction, normal EF	Increased QRS complex voltage, pseudo–delta wave, giant T-wave inversion	Patchy, midwall, junctions of the ventricular septum and RV	Myocyte hypertrophy, myofibrillar disarray, and interstitial fibrosis	(4)
Hypertensive heart disease	Adults	History of hypertension	Symmetrical increase in LV wall thickness, mild LV dilation, normal EF	Increased QRS complex, nonspecific ST-T-wave changes	No pattern, predominantly subendocardial	Enlarged myocytes with enlarged or replicated nuclei	(4)

CMR = cardiac magnetic resonance; CT = computed tomography; ECG = electrocardiogram; EF = ejection fraction; LA = left atrium; LGE = late gadolinium enhancement; LV = left ventricle; LVOT = left ventricular outflow tract; RA = right atrium; RV = right ventricle.

Table 2	Conditions With Dilated LV and Infarct Pattern						
Condition	Age at Presentation	History	Echocardiography	ECG	CMR LGE	Cardiac Biopsy	Ref. #
Sarcoidosis	Young adults	Congestive heart failure	Variable wall thickness, focal or global hypokinesis, LV aneurysm	Infrahisian block, atypical infarction pattern	Patchy, basal and lateral LV walls	Noncaseating, multinucleated giant cell granuloma surrounded by band of dense collagen fibers	(62,63,65,70)
Wegener disease	Young adults	Chronic upper and lower respiratory tract infections	Regional hypokinesis, pericardial effusion, mild MR, LV systolic dysfunction	Atrial fibrillation, atrioventricular block, atypical infarction pattern	Diffuse, midwall	Vasculitis with necrotizing granulomatous inflammation	(74,75)
Hemochromatosis	Hereditary hemochromatosis: >30 yrs in men, older in women; secondary hemochromatosis: any age	Hereditary hemochromatosis: liver function abnormalities, weakness and lethargy, skin hyperpigmentation, diabetes mellitus, arthralgia, impotence in men; secondary hemochromatosis: hemolytic anemia, multiple blood transfusions	Dilated LV with global systolic dysfunction	Supraventricular arrhythmia, ventricular conduction abnormality is rare		Iron deposits within the myocyte	(4,77–79)
Differential diagnoses							
Ischemic cardiomyopathy	Adult	Coronary artery disease, congestive heart failure	Dilated LV, regional hypokinesis corresponding to perfusion territory, decreased systolic function	Multiform premature ventricular complexes, nonsustained ventricular tachycardia	Subendocardial, different degrees of transmural extension, corresponds to perfusion territory		(3,78)
Idiopathic dilated cardiomyopathy	Adult	Congestive heart failure, no known cardiovascular disease	Dilated LV with global systolic dysfunction	Atrial fibrillation	No LGE, or if present, midwall and patchy		(3,78)

MR = mitral regurgitation; other abbreviations as in Table 1.
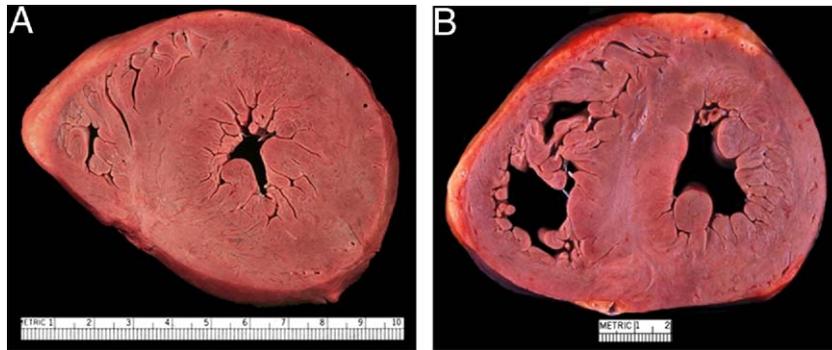
Figure 1   **Two Hearts From Autopsy (Short-Axis Views) Showing Markedly Thickened Left Ventricular Walls**

(A) Amyloidosis; **(B)** hypertrophic cardiomyopathy. Clinically, both hearts were characterized by diastolic dysfunction.
Without additional information (such as electrocardiographic or endomyocardial biopsy findings), these 2 conditions can closely mimic each other.

leaflet) and accounts for 3% of cases initially diagnosed as HCM (24,25). However, asymmetrical hypertrophy causing severe LV outflow tract obstruction and significant mitral insufficiency are typically absent in Fabry disease (26). LV wall thickness and LV mass increase as age and the severity of disease advance (22). Ejection fraction and fractional shortening are usually preserved (22). Progressive diastolic dysfunction is evident, but restrictive filling pattern is an infrequent finding (22). On 2-dimensional echocardiography, nonspecific binary appearance of the endocardial border corresponding to endomyocardial sphingolipid compartmentalization, creating a 2-layered appearance of the myocardium, has been observed (24,27). CMR will typically show focal inferolateral midwall LGE sparing the subendocardium (3,28). Progressive diastolic dysfunction best characterizes the prognosis.

Fabry disease is not associated with decreased QRS complex amplitude but rather shows ECG features of LV hypertrophy commensurate with the wall thickness (29). A pattern of pre-excitation can be seen (29). However, in some cases, when deposition occurs within the atrioventricular node, the PR interval may be prolonged (30).

Enzyme replacement therapy has been shown to reduce LV wall thickness and improve regional myocardial function, but its effect on survival has yet to be adequately determined (31).

Danon disease. Like Fabry disease, Danon disease is a rare X-linked disorder due to primary deficiency of lysosome-associated membrane protein 2 (32,33). It affects men at an early age (in the teens) and women in later years (in the 20s). Affected men typically present with a triad of heart failure, skeletal myopathy, and mental retardation (34). In female carriers, the disease predominantly affects the cardiac myocytes (35).

Cardiac symptoms begin during adolescence, and patients die of heart failure in their third decade (34). Echocardiographic characteristics include a marked symmetrical increase in LV wall thickness (range 20 to 60 mm), significantly greater than that typically found in patients with HCM (32). LV systolic dysfunction is often severely impaired (32,34). LV outlet obstruction is uncommon (34). A prominent increase in right ventricular wall thickness (≥10 mm) in the absence of pulmonary disease may also be observed (32). Unlike HCM, in which LGE is midepicardial and patchy, Danon disease has subendocardial LGE (36).

Unlike amyloidosis, Danon disease is a myocyte disorder, not an interstitial one, and thus is associated with normal or increased QRS complex amplitude. In addition, conduction velocity (pre-excitation) may be enhanced (37,38). Unlike HCM, Danon disease and associated glycogen storage disorders (lysosome-associated membrane protein 2 or protein kinase, adenosine monophosphate-activated, gamma 2 noncatalytic subunit mutations) are associated with true pre-excitation and the presence of single or multiple accessory pathways (37,38). Short PR interval and delta waves (Wolff-Parkinson-White syndrome) is a common finding causing syncope in most patients (34). Palpitations or documented arrhythmias in patients with this disorder may be related to the ventricular myopathic process (ventricular tachycardia) or the accessory pathway (orthodromic or antidromic precipitating tachycardia).

Genetic testing for lysosome-associated membrane protein 2 gene mutation is definitive and is the major diagnostic criterion in women (in whom the protein may be present because of 1 normal X chromosome) (34). There is no specific treatment for Danon disease (34). Potentially life-threatening pre-excitation atrial fibrillation or atrial flutter with conduction through the accessory pathways should be treated by ablation or sodium-channel blockers. The value of cardiac transplantation has not been established, because very few patients live long enough (they die at very young ages) to undergo transplantation (35,39). The most common cause of death is severe heart failure (32,34).

Friedreich ataxia. Friedreich ataxia is an autosomal recessive neurodegenerative disorder caused by expanded Guanine-Adenine-Adenine repeats (120 to 1,700 times, rather than the
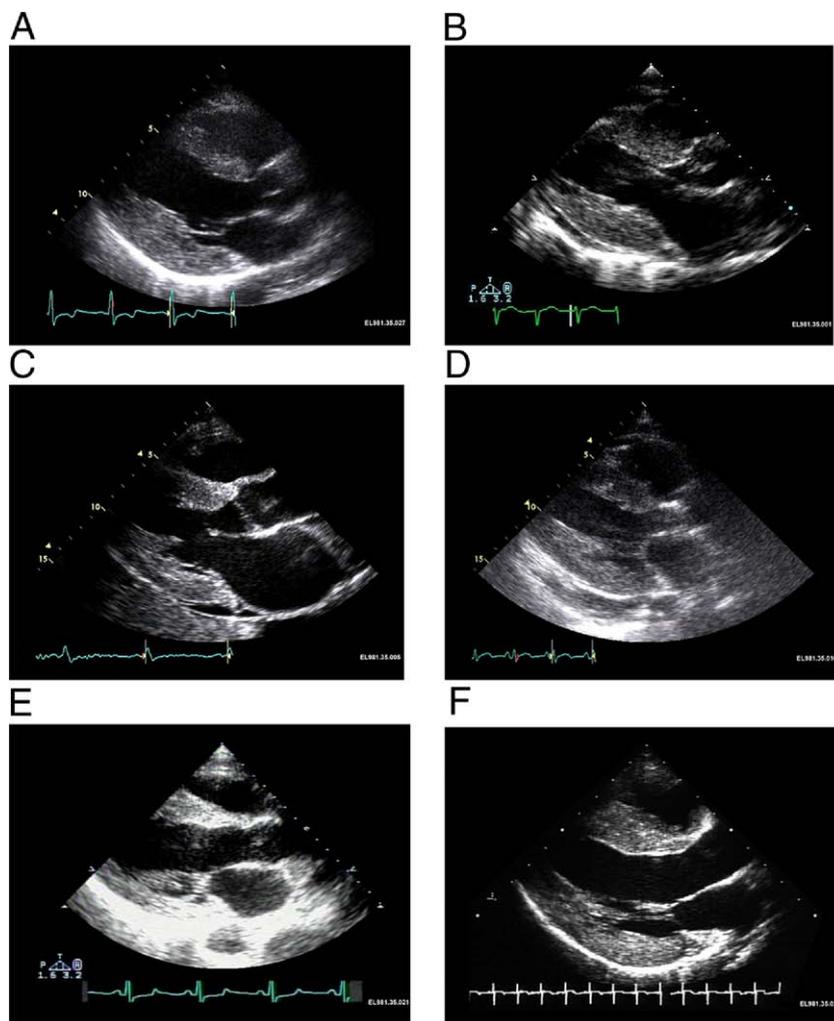
Figure 2   Conditions Presenting With Increased Left Ventricular Mass and Thick Ventricular Walls

(A) Hypertrophic nonobstructive cardiomyopathy, **(B)** hypertensive heart disease with secondary renal failure, **(C)** cardiac amyloid, **(D)** mucopolysaccharidosis, **(E)** cardiac oxalosis, and **(F)** Friedreich ataxia. See text for descriptions.

usual 8 to 22) in the frataxin gene on chromosome 9 (40). The age at onset of symptoms ranges from 2 to 51 years (40). Generally, the cardiac manifestations occur 4 to 5 years after the onset of the neurologic disorders, but occasionally heart disease occurs first (41). Cardiac disease eventually develops in 90% to 100% of patients (42).

Echocardiographic studies reveal differing patterns of increased wall thickness unrelated to the duration of the disease (43). Cardiac involvement is characterized by increased wall thickness of the interventricular septum or posterior wall (41,42,44) (Fig. 2). LV diastolic relaxation is reduced, but LV cavity size and ejection fraction are usually normal (42,44). Asymmetrical septal hypertrophy and LV outflow obstruction are rare (42,44). Severe heart failure can develop in some patients with mild LV dilation and systolic dysfunction (41). Valvular insufficiency, if present, is usually mild (42). Noncardiac dyspnea and frequent respiratory infections are due to

severe scoliosis and neuromuscular impairment of respiratory muscles (41). The 10-, 20-, and 30-year survival rates are 96%, 80%, and 61%, respectively (45). Cause of death is intercurrent pulmonary infection and cardiac dysfunction (12,41). At this time, the only known therapy is supportive. Investigational drugs include idebenone (a free radical scavenger) and deferiprone (an iron chelator) (46).

Compared with HCM, QRS complex voltage may not show the extent of LV hypertrophy (41,47). The reason for the lack of QRS complex amplification is marked connective tissue replacement and slowing of intraventricular conduction (41,47). Coronary artery disease, abnormalities of the nerve and the ganglia, and changes in the myocytes predispose these patients to regions of slow conduction and the propensity for ventricular tachyarrhythmia (41,47).

Myocardial oxalosis. Primary hyperoxaluria is a rare autosomal recessive disorder characterized by an enhanced
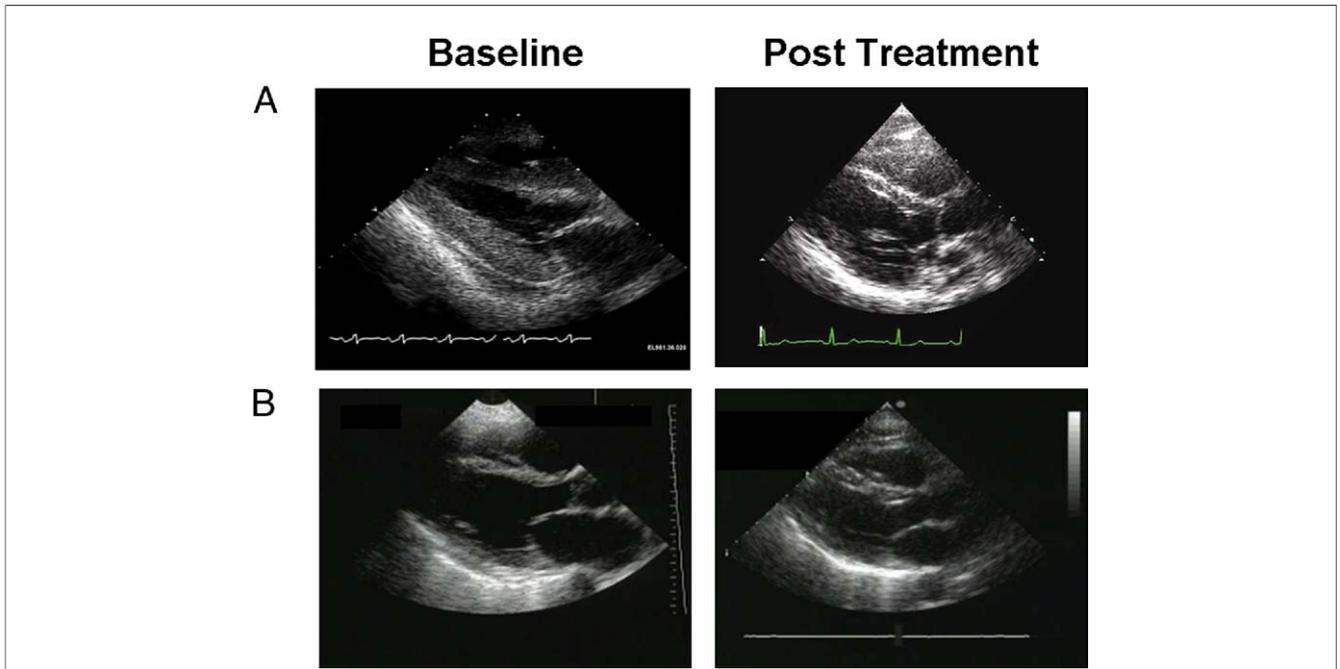
Figure 3   Dramatic Treatment Response

(A) Cardiac amyloid. Echocardiogram of a 37-year-old woman in New York Heart Association functional class IV. Left ventricular (LV) and right ventricular walls are thick with mild pericardial effusion and grade 3 diastolic dysfunction. Five years after stem cell transplantation, the LV and right ventricular walls are normal, there is no pericardial effusion, and diastolic function is normal. The patient is now in New York Heart Association functional class I. (B) Hemochromatosis. Echocardiogram of a 55-year-old woman who presented with dyspnea and fatigue. The left ventricle is dilated, with marked systolic dysfunction (ejection fraction = 16%). Six years after repeated therapeutic phlebotomy, LV cavity decreased in size, and systolic function improved (ejection fraction = 69%).

production of oxalic acid, leading to the deposition of oxalate crystals in different organs, particularly the heart and the kidneys (48,49). Echocardiography demonstrates biventricular symmetrically thickened walls (49,50) (Fig. 2). Ejection fraction may be normal in the early stage of this disease (50). In advanced cases, mild biventricular dilation has been observed (50). In contrast to LV hypertrophy found in long-term dialysis patients, the myocardium in hyperoxaluria is characterized by patchy, echodense speckled reflection most prominent in the papillary muscles (50,51). In the very late stages, computed tomography can demonstrate oxalate deposits as increased attenuation of the myocardium (Fig. 4). Diastolic function is severely impaired, with elevated filling pressures and restrictive filling pattern (49,50). Patients usually present with complete atrioventricular block and ventricular conduction abnormalities correlating with diffuse extensive oxalate infiltration of the cardiac conduction system (50,51). QRS complex voltage is either increased or normal because of asymmetrical and heterogeneous involvement of the myocardium, which can inconsistently exhibit true hypertrophy (51).

There has been no consistent effect of daily hemodialysis or of combined liver-kidney transplantation to improve oxalate balance and reverse the echocardiographic abnormalities (51,52).

Mucopolysaccharidoses. The mucopolysaccharidoses represent inborn errors of metabolism due to deficiencies in lysosomal enzymes that break down glycosaminoglycans (53). The accumulation of partially degraded mucopolysaccharides impairs proper cell function and leads to various clinical manifestations. These disorders are inherited in an autosomal recessive manner and affect men and women equally (54). Depending on the type of mucopolysaccharidosis, affected patients may have normal intellect or may be
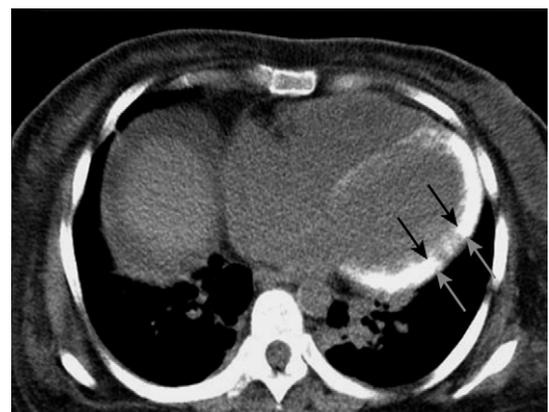
Figure 4   Unenhanced Chest Computed Tomographic Scan

Increased attenuation of myocardium is seen (arrow), compatible with advanced oxalate deposition.

profoundly retarded, experience developmental delay, or have severe behavioral problems (55). Cardiac disease occurs in almost 100% of all subtypes of mucopolysaccharidoses, but the most severe cardiac involvement is seen in type I (Hurler-Scheie syndrome) (56). Prominent valvular thickening, diffuse coronary artery narrowing, myocardial thickening, and secondary pulmonary hypertension are common findings (12,56). Asymmetrical septal hypertrophy occurs early, followed by thickening of the valves (56,57). The mitral and the aortic valves are more frequently involved, producing insufficiency and/or stenosis (56) (Fig. 2). LV systolic function is usually normal (56). ECG evidence of LV hypertrophy is uncommon (53,56). Small QRS complex voltages may be due to poor conductance of glycosaminoglycans (56). Rare intraventricular conduction delay or malignant arrhythmias have been reported (56).

Diagnosis often can be made through clinical examination and urine tests (excess mucopolysaccharides are excreted in the urine). Enzyme assays (testing a variety of cells or body fluids in culture for enzyme deficiency) are also used to provide definitive diagnosis of 1 of the mucopolysaccharidoses.

Valve replacement has been successful in patients with severe mitral valve disease (58,59). Enzyme replacement therapy and bone marrow transplantation showed improvements in cardiac structure and function in both human and animal studies (60,61). Death occurs early and is often due to cardiovascular complications (12,56).

Infiltrative Cardiomyopathies That Look Like Ischemic or Nonischemic Dilated Cardiomyopathy

Cardiac sarcoidosis. This granulomatous disease tends to affect the basal septum, atrioventricular node and atrioventricular (His) bundle, focal regions in the ventricular free walls, and the papillary muscles. Two-dimensional echocardiographic characteristics of cardiac sarcoid vary according to disease activity and include wall thickening (>13 mm) due to granulomatous expansion and wall thinning (<7 mm) due to fibrosis. With scar retraction, aneurysms may develop, especially if the patient has been treated with corticosteroids (Fig. 5). Other echocardiographic features include normal to dilated ventricular chambers, normal to reduced systolic function, global to segmental hypokinesia, and uniform thickening of left and right atrial endocardium (62,63). Segmental wall motion abnormalities characteristically do not conform to any particular coronary distribution (64). In contrast to idiopathic dilated cardiomyopathy, dyskinetic or akinetic segments are interspersed with normokinetic segments, resulting in an uneven wall motion abnormality in sarcoidosis (65). Pulmonary involvement occurs in 90% of patients with sarcoidosis, and the presence of pulmonary artery hypertension is an ominous sign and warrants referral for lung transplantation (66,67). Thus, Doppler echocardiographic examination should include the assessment of pulmonary pressures and right ventricular function to detect early signs of pulmonary hypertension.

Because of the varied echocardiographic presentations of cardiac sarcoidosis, 2-dimensional echocardiography is not sensitive or specific enough to detect early or small localized areas of myocardial involvement (68). Contrast-enhanced magnetic resonance imaging and (18F-fluoro-2-deoxyglucose positron emission tomography are more sensitive, and findings seem to correlate with disease severity (68,69). In contrast to ischemic cardiomyopathy, in which LGE always involves the subendocardium with different degrees of transmural extension, LGE in cardiac sarcoid is patchy and typically involves the basal and lateral LV walls only (70).

Atypical infarction pattern and infrahisian atrioventricular block are commonly observed on the ECG (65,68,71). Unlike idiopathic dilated cardiomyopathy, atrial flutter or fibrillation is not common in cardiac sarcoid.

There are no randomized controlled trials to provide clear guidance for the treatment of sarcoidosis with cardiac involvement. Therefore, therapy should be supportive and follow general principles for the management of sarcoidosis (62,72).

Sarcoid   **Hemochromatosis**   **Dilated Cardiomyopathy**
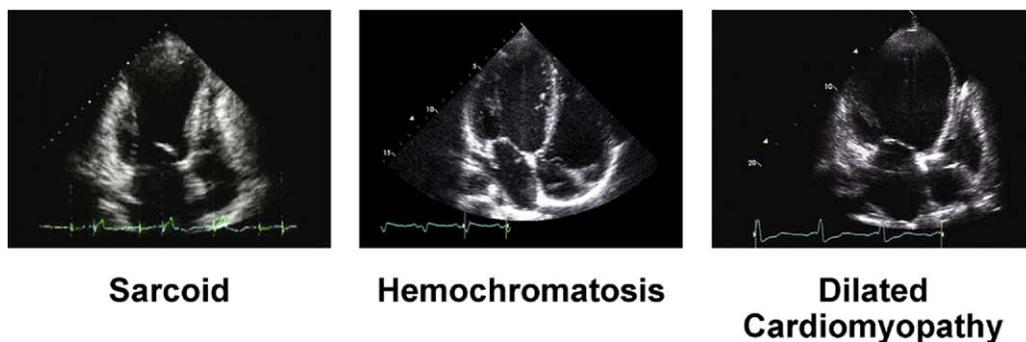
Figure 5   **Conditions With Dilated Left Ventricle and Infarct Pattern**

All 3 conditions can present with a dilated left ventricle with poor systolic function and elevated filling pressure characterized by left atrial enlargement. Cardiac sarcoid has an apical aneurysm.

Wegener granulomatosis. Wegener granulomatosis is characterized by necrotizing granulomatous inflammation, with vasculitis affecting many organ systems, particularly the upper and lower respiratory tract and the kidneys (73). In a series of 85 patients with confirmed Wegener granulomatosis who underwent echocardiography, 26 (36%) had confirmed cardiac abnormalities attributable to the disease (74). Regional wall motion abnormalities were found in 17 (65%), mild mitral regurgitation in 14 (54%), LV systolic dysfunction in 13 (50%), and pericardial effusion in 5 (19%) (74). Those with associated cardiac abnormalities had a higher mortality rate (46%) than those without (39%) (74). Cardiac sarcoidosis is suspected when regional wall motion abnormalities occur in relatively young asymptomatic patients with low cardiovascular risk profiles and are not confined to a specific coronary artery territory (74). LGE in the midwall rather than the subendocardium is consistent with fibrosis rather than infarction (75).

Management of Wegener granulomatosis requires a multidisciplinary approach. Any patient with Wegener granulomatosis and cardiac involvement is classified as having "severe" disease, defined as being life threatening or placing the affected organ at immediate risk for irreversible damage (76). Glucocorticosteroids and cyclophosphamide remain the standard of care for remission induction.

Hemochromatosis. Hemochromatosis represents an iron overload disorder or iron storage disease characterized by the accumulation of excessive iron within the cells of various internal organs. It may result from a genetic defect (hereditary hemochromatosis) or from secondary causes (secondary hemochromatosis) (12).

Cardiac hemochromatosis (iron heart) is a weak heart that is characterized by systolic dysfunction. Only rarely is diastolic dysfunction the dominant abnormality. Two-dimensional echocardiography may not be able to distinguish cardiac hemochromatosis from idiopathic dilated cardiomyopathy (Fig. 4). CMR can detect and quantify myocardial iron infiltration using T2 cardiovascular magnetic resonance imaging (77,78).

The QRS complex voltage and duration are generally preserved because of the absence of marked fibrosis with largely preserved cardiac myocytes and the nonconductive property of iron (79). With advanced disease, the ECG can have abnormal results (low QRS complex voltage) with repolarization abnormalities (79).

Liver biopsy is the definitive test for iron overload (80). With functional cardiac involvement, stainable sarcoplasmic iron is demonstrable in right ventricular endomyocardial biopsy tissues; normally, there is no stainable iron in the heart. With time, excessive sarcoplasmic iron may cause myocyte degeneration and delicate interstitial fibrosis (12).

Cessation of multiple blood transfusions, phlebotomy, and chelation therapy have been shown to reverse cardiac abnormalities due to iron overload (81–83) (Fig. 3). Some patients may require combined liver and heart transplantation (84).

Conclusions

The infiltrative cardiomyopathies are a diverse group of cardiac diseases, which are characterized by the deposition of abnormal substances within heart tissue that cause the ventricular walls to develop either diastolic dysfunction or, less commonly, systolic dysfunction. Although amyloid heart disease is commonly cited as the prototype of infiltrative heart disease, it does not exemplify the diversity of the infiltrative diseases. Because these disorders are relatively rare and their physiologic and morphologic characteristics are so variable, they tend to be misdiagnosed. Doppler echocardiographic evaluation and ECG, and CMR in some cases, in conjunction with the clinical manifestations, play a vital role in establishing an accurate diagnosis and planning the appropriate treatment.

Reprint requests and correspondence: Dr. James B. Seward, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: seward@mayo.edu.

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Key Words: infiltrative ■ cardiomyopathies ■ cardiomyopathy.

▶ **APPENDIX**

For a list of contributions, please see the online version of this article.

Infiltrative Cardiovascular Diseases: Cardiomyopathies That Look Alike

James B. Seward, and Grace Casaclang-Verzosa

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