Infiltrative Diseases of the Heart

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Infiltrative diseases targeting the cardiovascular system are a subgroup of restrictive cardiomyopathies. An early diagnosis is critical in initiating therapy to mitigate the deleterious effects of the pathologic process underlying these forms of cardiomyopathies. Infiltrative cardiac disease is rare and therefore often underdiagnosed. This review outlines the prevalence of 3 of the most common forms of restrictive cardiomyopathy: sarcoidosis, hemochromatosis, and amyloidosis. Infiltrative cardiomyopathy can have a variable prognosis depending on its etiology. It is a progressive disorder that, if left untreated, can lead to early mortality. A summary of the pathology, diagnosis, disease course, and therapy is provided, along with the utility of noninvasive testing as a means of diagnosis.
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Infiltrative diseases of the heart are classified as a subgroup in a spectrum of restrictive cardiomyopathies. These cardiomyopathies are defined as heart muscle disease in which there is impaired ventricular filling with decreased or normal diastolic volume of the ventricles. This form of cardiomyopathy, though relatively uncommon in developed countries, is a cause of significant morbidity and mortality in underdeveloped areas of the world. Cardiac dysfunction results from increased stiffness of the myocardium. This increased stiffness causes intracardiac pressure to increase abruptly with only minimal increases in volume. Abnormal diastolic properties result from myocardial fibrosis, infiltration, and scarring of the endocardium.[1] These cardiomyopathies

can cause biventricular dysfunction. Thus, patients may present with a myriad of symptoms, including signs of heart failure (eg, peripheral edema, conversational dyspnea, increased jugular venous pressure, ascites, or pulmonary edema on chest radiograph). The cardiac silhouette is often normal on the chest radiograph. It is important to consider infiltrative cardiomyopathy in the differential diagnosis of a patient with heart failure who does not exhibit cardiomegaly and has preserved left ventricular (LV) systolic function.

Infiltrative cardiomyopathy can have a variable prognosis depending on its etiology. It is a progressive disorder and, if left untreated, leads to early mortality. It is therefore important to make an accurate diagnosis; that is, differentiate restrictive cardiomyopathies from constrictive pericarditis. Both present with similar signs and symptoms. History of prior pericarditis often alludes to constrictive pericarditis as a likely diagnosis. In developing countries, tuberculosis is a classic etiology for constriction rather than restriction.

New diagnostic modalities, including genetic testing and advanced cardiovascular imaging (cardiac magnetic resonance imaging [MRI] and computed axial tomography), can assist the clinician in developing a treatment plan early in the course of the disease. This article outlines the 3 most common forms of restrictive cardiomyopathy: sarcoidosis, hemochromatosis, and amyloidosis.

Sarcoidosis

Prevalence and Epidemiology

The challenge of diagnosing cardiac sarcoid is arduous. Clinical manifestations vary from benign manifestations to life-threatening arrhythmias and cardiomyopathy. First described in 1929, cardiac sarcoidosis was not clinically recognized until the 1970s.[2] Most of our estimates on the incidence of this disease are based on ante mortem studies in patients with sarcoidosis who have symptomatic cardiac involvement. These estimates range from 5% to 10% in the adult population.[3,4] The Johns Hopkins University (Baltimore, MD) followed 181 chronic sarcoid patients over a 5-year period. Cardiac involvement was seen in 7% of these patients.[5] There are several necropsy series documenting higher rates of incidence.[4,6] In a retrospective autopsy review from Los Angeles County University of Southern California Medical Center (Los Angeles, CA), cardiac involvement was found in 19.5% (24 of 123), of sarcoidosis patients.[4]

Sarcoidosis can affect racially heterogeneous populations in a cohort of patients who are relatively young; most people develop the disease before age 50 years. The incidence peaks between age 30 and 39 years. African American women in the same age cohort had a 20% higher risk of sarcoidosis compared with African American men of the same age. In addition, African Americans had a higher frequency of extrathoracic and symptomatic disease and were diagnosed at a slightly earlier age.[7] There is a sex predilection for women that is seen across different ethnic and racial groups.

Although 25% of patients with sarcoidosis have cardiac granulomas at autopsy, only 5% have signs or symptoms of cardiac involvement.[4,6] Patients with cardiac sarcoid can present with sudden cardiac death as their first manifestation. It can be difficult to prove the diagnosis histologically. There is poor yield on myocardial biopsies because, unlike diffuse myocardial infiltration seen with amyloidosis or Fabry disease, sarcoid granulomas demonstrate a localized pattern of occurrence due to the patchy distribution of the noncaseating granulomas. Biopsy provides a dismal definitive diagnosis yield close to only 10%.[8] Further, the biopsy is done on the right ventricular free wall, whereas the sarcoid is usually found in the basal and left lateral wall segments.[9] Cardiac MRI with delayed enhancement is becoming an alternative to diagnosis when the endomyocardial biopsy result is inconclusive. Therefore, treatment may be necessary in select patients with suspected cardiac involvement, even in the absence of histologic confirmation.

Pathology

Nonnecrotizing granulomas are pathognomonic and are the primary abnormality in sarcoidosis. The lesion of sarcoidosis is a discrete, noncaseating, epithelioid granuloma. Cytokine stimulation causes macrophages and activated T cells to accumulate at sites of inflammation. These activated cells release chemoattractants and growth factors that result in cellular proliferation and granuloma formation.

There have been numerous hypotheses as to the causes of sarcoidosis. Most of the pathology occurs in noncardiac sites, often involving the lungs, skin, kidneys, and eyes, leading researchers to believe that there may be an environmental trigger. Numerous studies have shown associations with exposures to a variety of irritants including those in rural settings, such as wood-burning stoves, tree pollen, inorganic particles, and pesticides. Infectious organisms such as viruses, mycobacteria, *Borrelia burgdorferi,* and *Propionibacterium acnes* have been implicated as potential causes of sarcoidosis. Environmental exposure to beryllium, aluminum, and zirconium can result in a granulomatous response similar to that of sarcoidosis. Current theory suggests that disease develops in genetically predetermined hosts who

are exposed to certain environmental agents that trigger an exaggerated inflammatory immune response leading to granuloma formation.[6]

Sarcoid can occur in any area of the heart. The most common site of infiltration is the LV wall, followed by the intraventricular septum, papillary muscles, right ventricle, and atria.

Though the concept of genetic predisposition has been studied, there is no specific allelic association that has been described in sarcoidosis. Sarcoid can occur in any area of the heart. The most common site of infiltration is the LV wall, followed by the intraventricular septum, papillary muscles, right ventricle, and atria.[10] Obliteration of the conduction system with involvement of the sinoatrial node, atrioventricular (AV) node, and the bundles may occur.[11] In some cases, a right bundle branch block may be the only abnormality on electrocardiograph (ECG), suggesting myocardial involvement in sarcoidosis. The first clinical manifestation of cardiac sarcoid is usually arrhythmia, such as ventricular tachycardia or complete heart block. In a series of 100 consecutive patients presenting with high-degree AV block requiring pacemaker implantation, cardiac sarcoidosis was found in 11.2% of the 89 patients that were retrospectively followed. None of these patients had a prior diagnosis of sarcoid and all were thought to have idiopathic AV block.[12] First-degree AVB occurs secondary to inflammation around the AV node or bundle of His. Patients who present with syncope should be evaluated by ECG and Holter monitoring. Even with optimized antiarrhythmic therapy, some patients have recurrent ventricular arrhythmias. Therefore, the guidelines support implantation of a cardiac defibrillator (ICD) in sarcoid patients who present with ventricular tachycardia and who are at risk for sudden death (Figures 1 and 2).

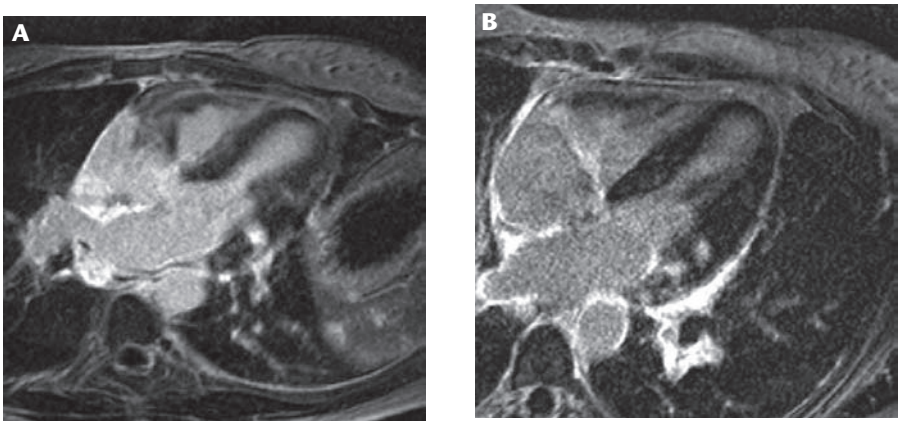

Figure 1. *Magnetic resonance images of the left ventricular outflow tract **(A)** and the 4-chamber projections **(B)** show patchy infiltration of the left ventricular lateral wall. Reprinted with permission from Nemeth MA et al.[47]*

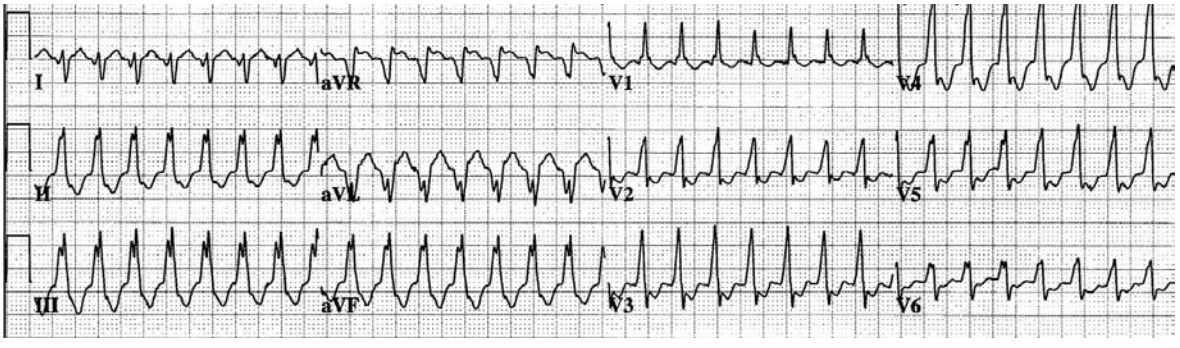

Figure 2. *An electrocardiogram illustrates ventricular tachycardia that originates from the basal lateral wall of the left ventricle in a patient with myocardial sarcoidosis. Reprinted with permission from Nemeth MA et al.[47]*

Deposition of the papillary muscles can cause mitral or tricuspid regurgitation. Aortic regurgitation can occur with direct involvement of the cusp. Mitral valve dysfunction in severe cases can cause pulmonary hypertension and hemodynamic instability requiring replacement of the valve.

Infiltration of the myocardium by nonnecrotizing granulomas may present as heart failure. Congestive heart failure (CHF) is the second most common cause of mortality in patients with cardiac sarcoidosis and can be categorized as either systolic or diastolic dysfunction. The clinician has to have a high index of suspicion for cardiac sarcoidosis in a young patient with CHF, advanced AV block, and regional wall motion abnormalities affecting the anteroseptal and apical regions that improve with stress testing.[13]

Infiltration of the pericardium may present as pericardial effusion. The coronary vessels may become infiltrated and cause fibrotic changes imitating ischemia. If left untreated, long-term fibrosis from myocardial scarring can become a nidus for forming aneurysm. This presentation is often termed pseudoinfarction because there are clinical symptoms and ECG changes suggesting acute injury pattern but without corresponding wall motion abnormalities on echocardiography. The workup may include ^{201}Thallium (^{201}Tl) scanning. Single-photon emission computed tomography (SPECT) imaging shows perfusion abnormalities during rest that improve during stress (reverse redistribution pattern). Segmental areas of decreased ^{201}Tl uptake are thought to represent areas of fibrosis or granulomatous infiltration. The pattern of abnormality on perfusion does not correlate to coronary artery distribution. In the presence of normal coronary angiography, defects in SPECT imaging may represent myocardial sarcoidosis.[4]

The risks of sudden death and progressive CHF are the most feared complications of cardiac sarcoidosis and underscore why this disease must be diagnosed early and followed with extreme vigilance. The timeliness of diagnosis in these patients proves to be not only challenging but also life preserving.

The cornerstone of medical management of cardiac sarcoidosis is corticosteroid therapy, which can result in improvement of myocardial contractility, reduction of LV dimension, and reversal of AV block. An initial treatment regimen with corticosteroids may delay the progression of the disease. A high dose is not necessary. It is more important to start the dose before the occurrence of severe systolic dysfunction.[14] Refractory sarcoidosis unresponsive to escalating steroid and immunosuppression therapies might respond to antibodies directed against tumor necrosis factor α.[15]

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Hemochromatosis

Hereditary hemochromatosis is an autosomal recessive disorder, characterized by abnormal iron overload. Tyrosine replaces cysteine at position 282 of the *HFE* gene on chromosome 6. The protein altered in this change is C282Y. Homozygous carriers of *C282Y* mutation are genetically predisposed to abnormal iron metabolism that affects the liver, pancreas, heart, and other organs. The disorder has a genetic predilection for people of Northern European ancestry.[16,17] Overall, its prevalence in the white population is approximately 1 in 300, with a higher prevalence in the Anglo-Celtic-Nordic population.[18]

In the average American diet, approximately 15 to 20 mg of iron is ingested daily. Of this, only 1 to 2 mg is absorbed by the gut. People who carry the *C282Y* mutation absorb 3 to 4 mg of iron daily. The net positive iron is stored in the liver. Over time the capacity of the liver to absorb the excess iron is overwhelmed. The ferrous iron accumulating in the liver parenchyma results in lipid peroxidation, cellular death, and fibrosis. Ongoing hepatic fibrosis can lead to cirrhosis and hepatocellular carcinoma in 30% of cases and is responsible for one-third of deaths in hemochromatosis.[19,20]

In the absence of other causes of iron overload such as β thalassemia, sideroblastic anemia, or iatrogenic disease, the fasting transferrin saturation is the most useful screening and diagnostic test for hemochromatosis. A fasting transferrin saturation of 45% or greater suggests hemochromatosis. The serum ferritin level should be measured concomitantly with fasting transferrin. A normal serum ferritin level in a patient with elevated fasting transferrin saturation may be associated with latent hemochromatosis. Patients with hemochromatosis need to repeat testing in 2 years to identify any progression of the disease. Serum ferritin levels are elevated if $>$ 200 mg/L in premenopausal women and $>$ 300 mg/L in men or postmenopausal women. Patients may also manifest with hepatomegaly and elevated liver enzymes. However, ferritin is an acute phase reactant and

levels may be increased in inflammatory conditions, acute liver failure, and malignancy. Because of diurnal variation, serum iron concentration is an unreliable test to diagnose hemochromatosis. Genetic testing can help identify the 3 mutations (*C282Y*, *H63D*, and *S65C*) in the *HFE* gene that are responsible for 90% of the cases of hereditary hemochromatosis. Genetic testing provides the advantage of early diagnosis of a treatable disease in those individuals presenting with abnormal laboratory studies prior to the development of cirrhosis.[21,22]

The clinical presentation of iron overload includes liver disease, skin pigmentation, diabetes mellitus, arthropathy, impotence in men, and cardiac enlargement with or without conduction defects; 30% of all hemochromatosis patients have diabetes. Men manifest symptoms 10 to 15 years earlier than women because women, during their reproductive years, lose iron during pregnancy and menstruation.[23] Most patients experience symptoms between the ages of 30 and 50 years, and men are 10 times more likely to have symptoms than women.

Cardiac Hemochromatosis

Manifestations of cardiac involvement are related to iron deposition in the myocardium. Iron overload over time leads to dilated cardiomyopathy, conduction abnormalities presenting as arrhythmias, and heart failure. Compared with other infiltrative diseases such as amyloidosis, which deposit abnormal proteins outside the myocytes, hemochromatosis causes deposition within the myocytes. Iron can deposit in critical areas of the heart, involving the left ventricle, the AV node, and the conduction system. ECG abnormalities are present in up to 35% of symptomatic patients.[24] Ventricular ectopy is the most common finding. Supraventricular and ventricular tachycardias and varying degrees of heart block can also occur.[25]

The association of coronary artery disease with hemochromatosis is controversial. It has been hypothesized that patients with hemochromatosis develop endothelial dysfunction. Iron catalyzes oxygen radical formation. Lipid peroxidation with the reactive oxygen may be involved in the process of atherogenesis. Increased levels of ferritin and transferrin saturation reduce endothelium-dependent dilation, which is a marker of endothelial dysfunction. It is postulated that iron depletion therapy normalizes endothelial function and thus reduces the risk of cardiovascular events.[26]

Echocardiographic findings have been well defined in hemochromatosis. LV diastolic failure occurs before the development of systolic dysfunction. The utility of Doppler mitral inflow and pulmonary venous flow patterns have been established for the assessment of diastolic function. Prolonged atrial reversal duration of 100 ms or longer, along with the presence of a negative difference between the mitral A-wave and atrial reversal duration in the pulmonary venous flow, predicts hemochromatosis with reasonable accuracy.[27] In a small retrospective study evaluating pediatric patients with iron overload, it was shown that keeping serum ferritin levels low helped to preserve normal LV systolic and diastolic function.[28] If left untreated the disease can progress into dilated cardiomyopathy that can show a restrictive pattern on echocardiography. Treatment with phlebotomy can improve cardiac function before irreversible damage occurs in the advanced stages of the disease.

Diagnosis

Aside from echocardiography and serum markers, genetic testing can also be performed. Currently, there are tests available to identify the *C282Y* mutation responsible for hemochromatosis. It must be emphasized that not all patients with hemochromatosis carry the *C282Y* gene mutation. Currently, there are no easily accessible tests available for the other genetic mutations found in this disease.

Advanced imaging using computed tomography can identify increased density of the heart caused by iron deposition (Figure 3). MRI is a noninvasive alternative to biopsy for quantifying iron overload. Subsequent MRIs can be used to quantify the efficacy of iron depletion therapy.[29]

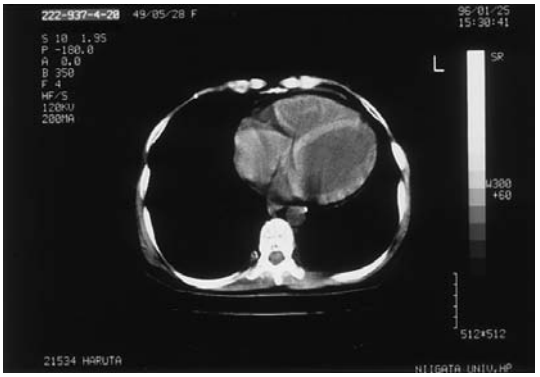

Figure 3. *Standard-plane computed tomography image showing high-density areas in the right and left ventricles as a result of iron deposition in the myocardium. Reprinted with permission from Niwano S et al. Iron deposition in myocardium documented on standard computed tomography in cardiac hemochromatosis.* Circulation. *1998;97:2371.*[48]

Therapy

Therapeutic phlebotomy was the first successful treatment of hemochromatosis-induced iron overload. Normal ferritin levels for men and women range between 250 and 400 ng/mL. When the serum ferritin levels reach 1000 ng/mL the risk of hepatic fibrosis is increased. Weekly phlebotomy of 1 to 2 units of blood is performed to attain a serum ferritin level of 50 ng/mL and a transferrin saturation level below 30%. Each unit drawn results in 200 to 250 mg of iron lost. Once this level is reached, less aggressive maintenance therapy can be continued to keep serum ferritin below 100 ng/mL and transferrin saturation below 50%.[30] Dietary recommendations should be explained to the patient to limit the amount of iron consumed. Red meats and fortified cereals should be used in moderation. Iron supplements should obviously be avoided. Vitamin C can also potentiate the absorption of iron from the intestine and should be limited. Alcoholic beverages should be avoided by patients with evidence of liver injury (as seen by elevated enzymes). Although alcohol sometimes increases iron absorption, the tannin in red wine actually can inhibit its absorption. Patients with hereditary hemochromatosis are susceptible to septicemia from *Vibrio vulnificus* infection, and thus are advised to avoid consumption of uncooked seafood.[31]

Amyloidosis

Amyloidosis is a systemic disease with varying presenting features, therapies, and prognosis. On a molecular level there is alteration in the process of physiologic protein folding that generates toxic, insoluble protein aggregates that become incorporated in the β-sheet fibrillar protein.[32] There have been 20 proteins identified in the pathogenesis of amyloidosis.[33] The pathology results from abnormal aggregation and deposition of these insoluble protein fibrils in the extracellular matrix of various tissues and organs. The mechanisms of tissue and organ damage include free radical injury, interruption of the architectural integrity of the tissue causing organ dysfunction, local cytotoxicity, and formation of pathologic ion channels that induce apoptotic cell destruction. Large deposits of amyloid replace the normal tissue and affect the function of the organ mechanically.

Amyloid fibrils can deposit in myocardial vessels and cause local ischemia. Amyloid deposition is associated with fibrosis of conduction tissue, resulting in conduction abnormalities and arrhythmias. Valvular dysfunction from amyloid deposition may also occur.[34]

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There are 4 subtypes of amyloidosis with different structural units of the amyloid proteins. These structural units of the protein are monoclonal immunoglobulin light chain fragments, breakdown products of serum amyloid A, and transthyretin (a prealbumin) protein.[35] The subtypes are classified as systemic AA amyloidosis, systemic AL amyloidosis, hereditary systemic amyloidosis, and senile systemic amyloidosis.[36]

Systemic AL Amyloidosis

This is the most common form of amyloidosis, often associated with a plasma cell dyscrasia. The AL fibrils are produced from monoclonal immunoglobulin light chains. Multiple myeloma is most often associated with AL amyloidosis, along with lymphoma and macroglobinemia. However, up to 80% of the cases are correlated with benign forms of monoclonal gammopathies. The heart is affected in nearly all cases, portending a very poor prognosis. CHF is the usual presenting feature in half of these patients. Once CHF occurs, the median survival is less than 6 months in patients without treatment.[37] Early recognition and initiation of appropriate therapy is extremely important.

Fewer than 5% of patients with cardiac AL amyloidosis have disease isolated to the heart. It is vital to screen for noncardiac complaints that include syncope, dizziness, postural hypotension, easy bruising, painful sensory neuropathy, and carpal tunnel syndrome.

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The amyloid patient presenting with heart failure usually has progressive dyspnea with high right-sided filling pressure. In advanced stages of the disease, profound peripheral edema as well as ascites can be seen.[38] Cardiac cachexia can cause weight loss. Hypoalbuminemia from nephrotic syndrome caused by renal amyloidosis can cause anasarca and edema. Factor X deficiency, along with poor connective tissue integrity and poor endothelial function from amyloid infiltration, can cause

mucosal bleeding and ecchymoses. Raccoon eyes ecchymoses is very specific to this disease.[39]

Dynamic LV outflow tract obstruction is seen in patients with hypertrophic cardiomyopathy. Cardiac amyloidosis can infrequently present with asymmetric hypertrophy that can mimic hypertrophic cardiomyopathy and cause a dynamic outflow obstruction. Patients with amyloidosis presenting with orthostatic hypotension or syncope usually have other causes such as arrhythmias and vasovagal effects from neuropathy.[40]

Systemic AA Amyloidosis

This disorder occurs from a chronic inflammatory state in which a sustained acute phase response results in increased production of serum amyloid A protein (SAA). Renal involvement is almost always observed with proteinuria and renal failure.[41] Cardiac involvement is not usual in this subtype. Reversal of organ dysfunction can be achieved with suppression of SAA production.

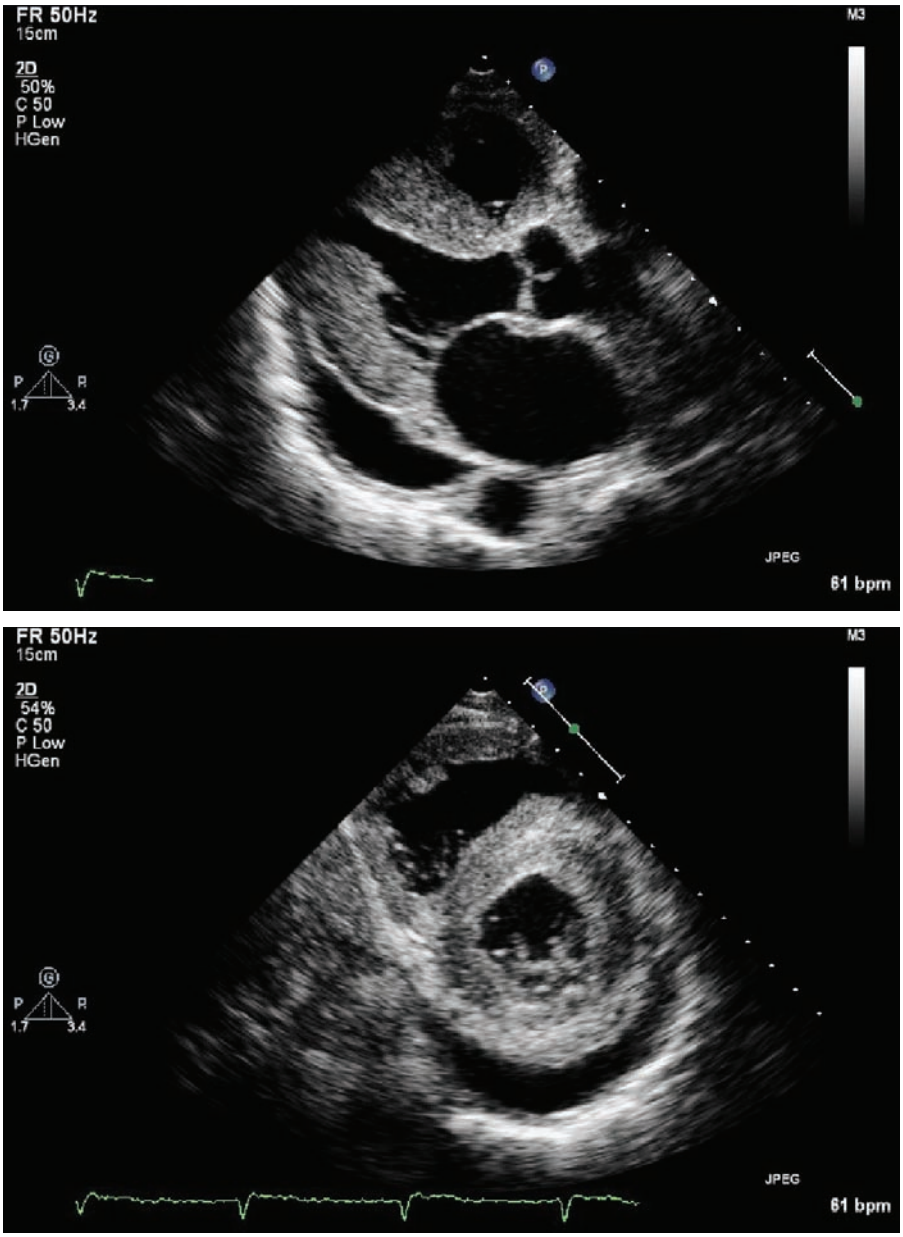
Hereditary Systemic Amyloidosis

Hereditary amyloidosis is due to the production of amyloids from a mutant transthyretin protein. The most common form of the mutation occurs in the *TTR* gene at the 122 codon, which causes a substitution of the isoleucine for the valine during translation.[38] This mutation is found among 23% of African Americans who have cardiac amyloidosis.[36] It usually presents with renal failure, peripheral neuropathy, and intracranial hemorrhage from cerebral angiopathy. Cardiac forms can occur with valvular infiltration, severe heart failure, and arrhythmias.[33] The age of onset is usually about age 40 years. Compared with AL amyloidosis, the survival in transthyretin amyloidosis is better because of the absence of the toxic light chain deposition in the myocardium. Transthyretin is produced by the liver with little effect on liver function. Definitive treatment is liver transplant, which removes the precursor of amyloid deposition. There is some evidence that certain nonsteroidal drugs may stay the progression of amyloidosis. These agents have limited use in amyloid cardiomyopathy cases due to the potential for fluid retention.[38]

Senile Systemic Amyloidosis

The heart is usually the main target in this disorder that is derived from a wild type (nonmutant) transthyretin.[42] It is an indolent, progressive infiltrative process leading to cardiomyopathy. It is often seen in elderly men, usually occurring without systemic manifestations such as macroglossia and heavy proteinuria, as are seen in other forms

Figure 4. *An echocardiogram of a patient with amyloidosis, showing left atrial enlargement, left ventricular hypertrophy, the granular sparkling pattern, and thickened mitral valve leaflets suggesting infiltration.*



of amyloidosis. Patients can develop a restrictive cardiomyopathy but have a better prognosis than the aggressive AL form because the rate of fibrillar deposition is slower. Accurate diagnosis in these cases can allow the patient a certain degree of reassurance and clinicians need not prescribe a course of potentially harmful chemotherapy.[43]

Diagnosis

Patients with amyloidosis can have ECG findings of low voltage and the presence of a pseudoinfarction pattern. Echocardiographic findings may consist of LV hypertrophy with granular sparkling pattern, biatrial enlargement, and restrictive filling pattern as seen on Doppler echocardiography (Figures 4 and 5).[34] Although endomyocardial biopsy is still considered the gold standard to confirm cardiac amyloidosis, advanced imaging is fast becoming the procedure of choice by clinicians. Cardiac MRI is a noninvasive way to diagnose amyloidosis when histopathological diagnosis cannot be made. Morphologic changes characteristic for amyloidosis are concentric biventricular hypertrophy with nondilated ventricles. The atria are dilated with increased interatrial septum thickness as a result of amyloid deposition (Figure 6). Table 1 shows diagnostic features of amyloidosis.

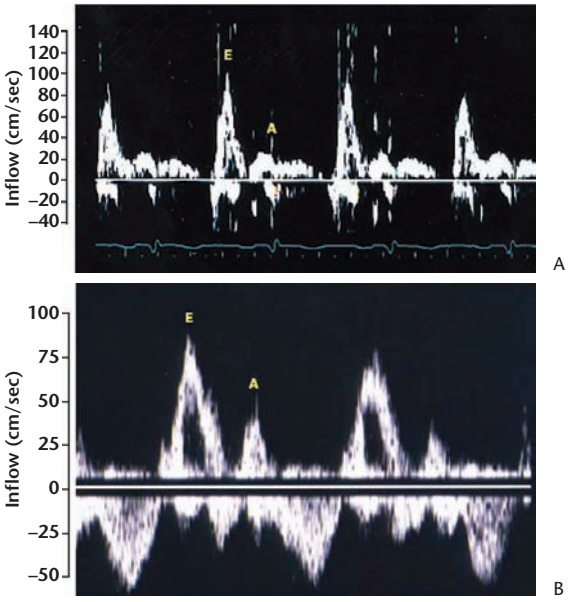


Figure 5. *Doppler echocardiography of the left ventricular inflow in a patient with restrictive cardiomyopathy secondary to amyloidosis* (A)*, and a normal Doppler signal in a patient without cardiac disease* (B)*. Reprinted with permission from Kushwaha SS et al.*[49]

Therapy for Amyloidosis

Early diagnosis and treatment is vital in this disease. There is a potential for reversing the deposition of the amyloid fibrils before irreversible organ damage has occurred. Treatment is specifically targeted at the destruction of the amyloidogenic clone. High-dose melphalan, followed by rescue with autologous stem cells or low-dose oral melphalan and corticosteroids, has been shown to improve long-term survival,[39] although this therapy also has a very high treatment-related mortality, which limits use in selected patients with multiorgan failure and cardiac involvement. Patients with advanced amyloidosis and involvement of 2 major organs are not candidates for stem cell transplantation. In these patients, use of oral melphalan and prednisone yields a response of 50% in terms of serum monoclonal protein reduction.[44]

Figure 6. *Cardiac magnetic resonance image with fast imaging with steady-state precession (FISP) in 4-chamber view. Pleural effusion (Pl eff) and pericardial effusion (Pe eff) are shown with a hypertrophied left ventricular septum (15 mm) and interatrial septum (5 mm). Reprinted with permission from Seeger A et al.*[50]

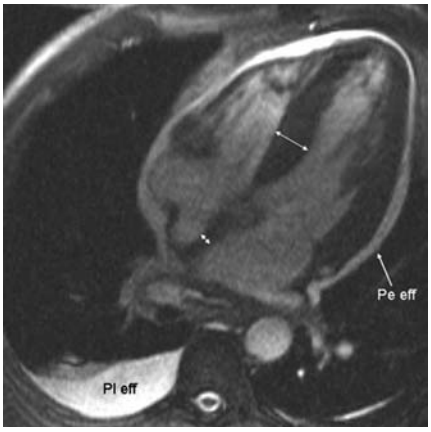


Table 1
Clinical Characteristics of Cardiac Amyloid Involvement

Dilated cardiomyopathy (cardiomegaly, predominant systolic dysfunction)
Restrictive cardiomyopathy (slight cardiomegaly, predominant diastolic dysfunction, stiff heart syndrome)
Congestive heart failure
Electrocardiographic disorders (rhythm abnormalities, low-voltage QRS, sick sinus syndrome, pseudoinfarct pattern, atrioventricular and ventricular conduction abnormalities)
Coronary insufficiency (myocardial infarction, angina)
Valvular dysfunction
Pericardial tamponade
Enhanced sensitivity to digitalis glycosides
Atrial thrombosis-embolization

Adapted with permission from Kholová and Niessen.[33]

Restrictive cardiac physiology and the autonomic neuropathy differentiate the therapy of patients with heart failure. The mainstay of treatment in AL amyloid heart failure is the use of diuretics. There is no role for β blockers because the severe diastolic and autonomic dysfunction limits cardiac filling and may cause bradycardia. Angiotensin-converting enzyme inhibitors and angiotensin receptor blocking agents should be used very cautiously, as even a small dose can cause significant hypotension. Digoxin binds to the amyloid fibrils and can cause toxicity. Certain calcium channel blockers also have a high affinity for the fibrils and can cause hemodynamic collapse. However, anticoagulation in patients with atrial fibrillation, which is the most common arrhythmia found in amyloidosis, should not be withheld. When present, atrial fibrillation is associated with a high incidence of thromboembolism. Pacing with a dual-chamber system can help patients with restrictive cardiomyopathy and autonomic dysfunction to optimize atrial filling. The use of ICDs has not been shown to prolong survival. Death in patients with amyloidosis occurs from mechanical dissociation or congestive heart failure.[36]

Galectin-3 is a new biomarker available for the diagnosis of CHF. It is an assay for the carbohydrate-binding protein that is present in very low amounts in normal hearts, yet appears to be elevated in patients with heart failure. Galectin-3 is a marker for macrophage activity in the heart. It stimulates macrophage migration, fibroblast proliferation, and the development of fibrosis. It has been found to be an independent marker for mortality in patients with moderate to advanced CHF. This serologic test may be a promising prognostic indicator for infiltrative cardiac disease.[45]

Patients with infiltrative cardiomyopathy have variable prognoses. As shown in Figure 7, patients with cardiomyopathy due to amyloidosis and hemochromatosis have a 1-year survival of 29% and 44%, respectively. In general, patients with sarcoidosis cardiomyopathy tend to fare better, with survival rates comparable with those with other forms of idiopathic cardiomyopathy.[46] It is therefore imperative to make an accurate and early diagnosis to tailor therapy and prevent morbidity and in some cases early mortality. ■

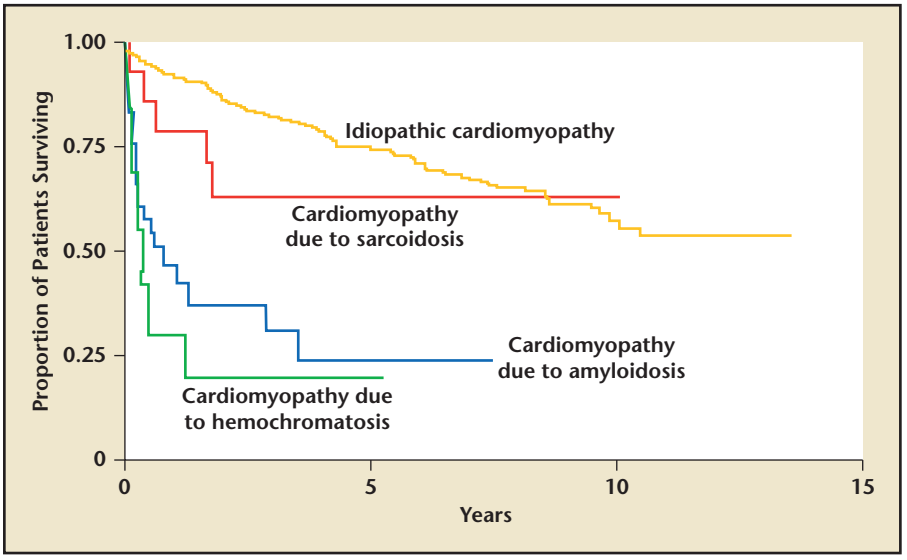


Figure 7. *Kaplan-Meier estimates of survival in patients with cardiomyopathy due to infiltrative cardiac diseases as compared with patients with idiopathic cardiomyopathy. Reprinted with permission from Felker GM et al.*[46]

Main Points

- Infiltrative diseases targeting the cardiovascular system reflect a subgroup of restrictive cardiomyopathies.
- Patients with cardiac sarcoid can present with sudden cardiac death as their first manifestation. The cornerstone of medical management of cardiac sarcoidosis is corticosteroid therapy, which can result in improvement of myocardial contractility, reduction of left ventricular dimension, and reversal of atrioventricular block.
- Hereditary hemochromatosis is an autosomal recessive disorder characterized by abnormal iron overload. Manifestations of cardiac involvement are related to iron deposition in the myocardium. Serum ferritin should be kept below 100 ng/mL and transferrin saturation should be kept below 50% in patients with hemochromatosis.
- Amyloidosis is a systemic disease with varying presenting features, therapies, and prognosis. Amyloid fibrils can deposit in myocardial vessels and cause local ischemia. Early diagnosis and treatment is vital in this disease. There is a potential for reversing the deposition of the amyloid fibrils before irreversible organ damage has occurred.
- New diagnostic modalities, including genetic testing and advanced cardiovascular imaging, can assist the clinician in developing a treatment plan early in the course of the disease.

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