Review Article

Medical Progress

RESTRICTIVE CARDIOMYOPATHY

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RESTRICTIVE cardiomyopathy is defined as heart-muscle disease that results in impaired ventricular filling, with normal or decreased diastolic volume of either or both ventricles. Systolic function usually remains normal, at least early in the disease, and wall thickness may be normal or increased, depending on the underlying cause.[1] The condition usually results from increased stiffness of the myocardium that causes pressure within the ventricle (or ventricles) to rise precipitously with only small increases in volume. Since the condition affects either or both ventricles, it may cause symptoms and signs of right or left ventricular failure. Often, right-sided findings predominate, with elevated jugular venous pressure, peripheral edema, and ascites. When the left ventricle is affected, there are symptoms of breathlessness and evidence of pulmonary edema on the chest radiograph, usually with normal cardiac dimensions. The diagnosis of restrictive cardiomyopathy should therefore be considered in a patient presenting with heart failure but no evidence of cardiomegaly or systolic dysfunction. Although therapy is generally unsatisfactory, the importance of an accurate diagnosis lies in distinguishing restrictive cardiomyopathy from constrictive pericarditis, which can also present with "restrictive physiology" but which is often cured surgically.[2]

Restrictive cardiomyopathies are the least common of the cardiomyopathic disorders.[3] Outside the tropics, cardiac amyloidosis is the most frequent and most thoroughly studied. Endomyocardial fibrosis is endemic in parts of Africa, India, South and Central America, and Asia, and it occurs sporadically throughout the world. It may account for 15 to 25 percent of deaths due to cardiac disease in equatorial Africa.[4]

Restrictive myocardial disease may result from various local and systemic disorders, many of them rare and unlikely to be seen in clinical practice. Other conditions, such as amyloidosis, are more common, however, and may present with symptoms and signs of congestive heart failure (Table 1). In idiopathic restrictive cardiomyopathy, the hemodynamic abnormalities occur in the absence of specific histopathological changes.

In this article we focus on recent observations concerning restrictive cardiomyopathy, with an emphasis on idiopathic restrictive cardiomyopathy, amyloid heart disease, endomyocardial fibrosis, and infiltrative disease.

PATHOGENESIS, NATURAL HISTORY, AND SPECIFIC FINDINGS

Idiopathic Restrictive Cardiomyopathy

Idiopathic restrictive cardiomyopathy is sometimes familial. It appears to be associated with distal skeletal myopathy.[7,36,37] Autosomal dominant restrictive cardiomyopathy with atrioventricular block and skeletal myopathy has been reported in five generations of an Italian family.[7] Symptoms developed in the third to fourth decade of life, with the eventual appearance of atrioventricular block and skeletal-muscle weakness.[7] Feld and Caspi reported a cardiomyopathy with variable hypertrophic and restrictive features that affected three generations of a family with a shared HLA haplotype.[38] Restrictive cardiomyopathy without distal myopathy, the type most likely to be familial, has also been described in a father and daughter.[6] A familial, nonhypertrophic restrictive cardiomyopathy with autosomal dominant inheritance and variable penetrance has been associated with Noonan's syndrome.[39] These associations suggest that there is a genetic predisposition to idiopathic restrictive cardiomyopathy and, in some patients, that a genetic locus is associated with distal myopathic syndromes, although some cases are sporadic and possibly the result of spontaneous mutation.

In childhood, idiopathic restrictive cardiomyopathy may be more common among girls, but this is suggested only by two small studies.[40,41] The prognosis appears to be worse than in adult patients. Lewis described eight children, six of whom were girls, with a median survival of 1.4 years.[40] In a study of the Mayo Clinic data base, eight children with id-

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TABLE 1. CLASSIFICATION OF TYPES OF RESTRICTIVE CARDIOMYOPATHY ACCORDING TO CAUSE.

Myocardial
Noninfiltrative
Idiopathic cardiomyopathy*[5]
Familial cardiomyopathy[6,7]
Hypertrophic cardiomyopathy[4]
Scleroderma[8,9]
Pseudoxanthoma elasticum[10]
Diabetic cardiomyopathy[11,12]
Infiltrative
Amyloidosis*[13,14]
Sarcoidosis*[15,16]
Gaucher's disease[17]
Hurler's disease[18]
Fatty infiltration[19]
Storage diseases
Hemochromatosis[20]
Fabry's disease[21]
Glycogen storage disease[22,23]
Endomyocardial
Endomyocardial fibrosis*[24,25]
Hypereosinophilic syndrome[26]
Carcinoid heart disease[27,28]
Metastatic cancers[29,30]
Radiation*[31]
Toxic effects of anthracycline*[32,33]
Drugs causing fibrous endocarditis[34,35] (serotonin, methysergide, ergotamine, mercurial agents, busulfan)

*This condition is more likely than the others to be encountered in clinical practice.

iopathic restrictive cardiomyopathy were found between 1975 and 1993.[41] Five of these patients who had evidence of pulmonary venous congestion at presentation had a median survival of only one year.

In adults the clinical course is more variable. In a national survey from Japan, there were 26 patients with idiopathic restrictive cardiomyopathy, among whom 2 died early from the illness, 2 others died after the illness had lasted 5 to 10 years, and 6 died after it had lasted 10 years. The remaining patients were still alive at the completion of the survey, with a mean follow-up of 57 months.[42] Most small series suggest a protracted clinical course in adults.[5,43]

Idiopathic restrictive cardiomyopathy is characterized by a mild-to-moderate increase in cardiac weight. Biatrial enlargement is common, and thrombi are often present in the atrial appendages. The cavity size and wall thickness of the ventricles tend to be normal, with normal or reduced global systolic function. The right ventricle may eventually become enlarged, depending on the presence and degree of pulmonary hypertension. Patchy endocardial fibrosis is present. On microscopical examination, the pericardium is normal; interstitial fibrosis may range in extent from nonexistent to severe and is usually patchy[43] (Fig. 1). There may be fibrosis of the sinoatrial and atrioventricular nodes[7] resulting in complete heart block that requires permanent pacing.[36]

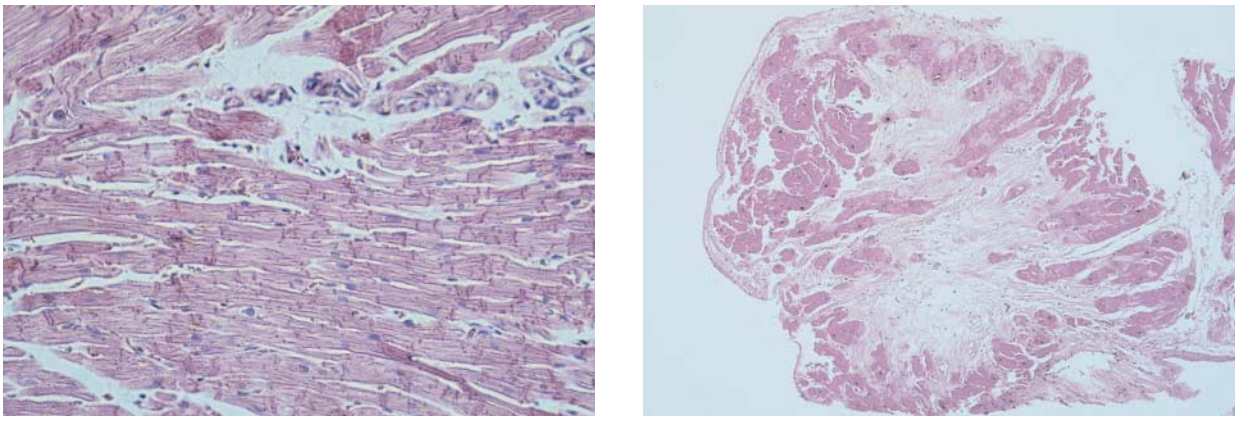
Amyloidosis

There are many types of amyloidosis in humans,[44] but cardiac involvement is more common in primary amyloidosis, which is caused by the production of immunoglobulin light chains by plasma cells, often due to multiple myeloma. Secondary amyloidosis is caused by the deposition of protein other than immunoglobulin and is familial, senile, or due to a chronic inflammatory process. Restrictive cardiomyopathy is thought to result from injury to tissue due to the replacement of normal myocardial contractile elements by infiltrative interstitial deposits.[45]

Genetic variants of the plasma protein transthyretin (prealbumin) may cause inherited forms of amyloidosis associated with cardiomyopathy. More than 40 different mutations of transthyretin are associated with amyloid deposition.[46] The majority are autosomal dominant and are associated with peripheral ascending neuropathy and cardiac amyloidosis. Abnormalities of diastolic filling can occur even in the absence of clinical evidence of restrictive cardiomyopathy.[47,48] Most transthyretin-related amyloidosis results from a change of a single nucleotide in the gene for transthyretin that results in amino acid substitutions in the mature protein; therefore, the cases are clustered in kindreds.[49-51] A mutation of transthyretin has also been identified that is associated with familial amyloidosis in which cardiomyopathy is the prominent feature and there is no peripheral neuropathy.[52] Recently, seven patients were described, among whom angina pectoris was a primary reason for presentation and only two of whom had neuropathy. The mutation was found to be in the transthyretin gene, with a substitution of lysine for the wild-type threonine at position 59 in the mature protein.[53] In a study of 52 patients with familial amyloidosis, 27 percent had cardiomyopathy,[54] and there was a high incidence of peripheral neuropathy and autonomic neuropathy. The presence of cardiomyopathy was strongly predictive of a poor prognosis, with 55 percent of the patients dying of arrhythmia or cardiac failure. Transthyretin was identified by immunohistochemical analysis in 31 of the 34 tissue specimens in this study,[54] and transthyretin mutations were identified in 24 of the 31. Antigenic mapping studies have suggested that in such cases the configuration of transthyretin within the amyloid fibrils is altered.[55]

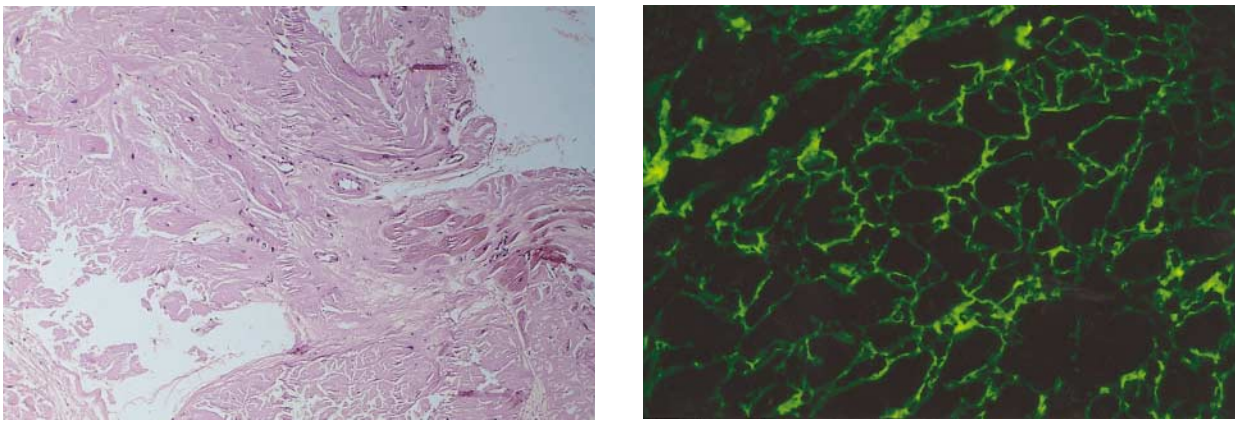
Amyloid infiltration of the heart is common in the elderly. Atrial deposition of amyloid, containing atrial natriuretic peptide and amyloid P components, has been found in 91 percent of 100 aged hearts.[56] Isolated atrial amyloid was significantly more prevalent in the hearts of patients over 80 years old and was located in the subendocardial layer. Such amyloid is also more common in patients with chronic heart diseases, such as rheumatic or congenital diseases.[57]

The myocardium of patients with cardiac amyloi-



A B

Figure 1. Endomyocardial-Biopsy Specimens from Patients with Idiopathic Restrictive Cardiomyopathy.
The specimen in Panel A (hematoxylin and eosin, ×250) has myocytes with slight hypertrophy but is otherwise normal; that in Panel B (hematoxylin and eosin, ×40), from another patient, shows marked interstitial fibrosis, which may also occur in idiopathic restrictive cardiomyopathy.



A B

Figure 2. Endomyocardial-Biopsy Specimens from Patients with Cardiac Amyloidosis.
Panel A (hematoxylin and eosin, ×250) shows interstitial deposition of amyloid fibrils in a specimen from the right ventricle. Panel B (immunofluorescent stain, ×400) shows lambda light chains.

dosis is firm, rubbery, and noncompliant. The ventricular cavities are often normal, small, or moderately dilated, with thrombi in the atrial appendages. On histologic examination, there is interstitial deposition of insoluble amyloid fibrils in all four cardiac chambers (Fig. 2). This can result in increased wall thickness without cavity dilatation. The pericardium, cardiac valves, and coronary arteries may also be involved.[50] The left-ventricular-wall thickness is one of the prognostic variables, with survival ranging from 2.4 years in patients with normal ventricular-wall thickness to 0.4 year in those with markedly increased wall thickness.[36,58] The granular, sparkling appearance seen on two-dimensional echocardiography, said to be characteristic of cardiac amyloidosis, but not diagnostic of it, is also correlated with increased wall thickness.[58] In the absence of overt echocardiographic evidence of cardiac amyloidosis, abnormalities of diastolic filling can occur[47] and are also predictive of decreased survival. Klein et al. showed that a shortened deceleration time and an increased ratio of the early diastolic filling velocity to the atrial filling velocity as measured by Doppler echocardiography were stronger predictors of early death from cardiac causes than were the mean left-ventricular-wall thickness or fractional shortening.[59] Radionuclide imaging, showing increased diffuse uptake of technetium-99m pyrophosphate[60] and indium-111 antimyosin,[61] can also be used to diagnose cardiac amyloidosis.

Amyloid deposits may also be found in the sinoatrial and atrioventricular nodes and the bundle branches. A variety of cardiac arrhythmias can occur, including complex ventricular arrhythmias. These appear to be correlated with the severity of heart failure and abnormalities seen on echocardiography.[62]

Bradyarrhythmias are less common. Depending on the stage of the disease, the patient can present with some combination of asymmetric septal thickening, angina, heart failure, abnormal diastolic function, and a reduced ejection fraction.[63]

Cardiac amyloid can be characterized by analyzing endomyocardial-biopsy tissue,[50,64,65] and immunohistochemical staining may help in distinguishing the various types.[65,66] Serum amyloid P component and apolipoprotein E are found in amyloid fibrils and may have a role in fibrillogenesis.[67,68]

Endomyocardial Fibrosis and Eosinophilic Cardiomyopathy

Endomyocardial fibrosis and Löffler's endocarditis (eosinophilic cardiomyopathy) are thought to be different manifestations of restrictive obliterative cardiomyopathy, both associated with eosinophilia.[69] Morphologic abnormalities of eosinophils have been noted in patients with Löffler's endocarditis, suggesting that these eosinophils were mature or stimulated. It is thought that the intracytoplasmic granular content of activated eosinophils is responsible for the toxic damage to the heart.[70] Animal models of hypereosinophilia due to parasitic infection have shown cardiac dysfunction and accumulation of eosinophils in the myocardium, in addition to histologic alterations leading to decreased myocardial compliance.[71] On occasion, the fibrosis in the hypereosinophilic syndrome is localized and produces valvular regurgitation or stenosis of the atrioventricular valves, which can be ameliorated by valve replacement.[72] The eosinophilia–myalgia syndrome associated with the use of tryptophan containing a contaminant[73] resulted in restrictive cardiomyopathy,[74] suggesting that eosinophilia may have been responsible for the cardiac damage.

The overall prognosis of patients with endomyocardial fibrosis is poor and depends on the degree and location of involvement in the heart. Typically, the disease has an insidious onset, with the development of increasing severe right- or left-sided heart failure. Sudden death and syncopal episodes are not common in endomyocardial fibrosis, as compared with the other causes of restrictive cardiomyopathy. However, atrial fibrillation does occur and is more frequent in patients with right ventricular disease.[25] Other electrocardiographic abnormalities include low QRS voltage, first-degree atrioventricular block, and left atrial enlargement.[25] Typical echocardiographic features include thickening of the inferior basal left ventricular wall and endocardial deposition of thrombus, with apical obliteration and mitral regurgitation.[75] Major systemic or pulmonary embolism is uncommon. Roberts et al. reported that 95 percent of a group of patients were dead at two years,[76] and in one series from Uganda 44 percent of patients died less than one year after the onset of symptoms and an additional 40 percent died from one to three years after onset.[77]

In endomyocardial fibrosis, the heart is usually normal in size. The ventricular cavities vary in size but are often markedly obliterated by extensive endocardial thickening. The thickening may also involve the papillary muscles and the associated atrioventricular-valve apparatus, and the valve may become deformed. Patchy fibrosis may be visible, particularly in the subendocardium.[78] Pathologic changes consistent with chronic valve regurgitation are often present.

Other Infiltrative and Storage Diseases

A number of infiltrative conditions can result in restrictive cardiomyopathy. Gaucher's disease is due to a deficiency of the enzyme beta-glucocerebrosidase, which results in the accumulation of cerebroside in a number of organs, including the heart.[17] Related syndromes cause similar defects.[79] Hurler's syndrome leads to a restrictive cardiomyopathy due to the deposition of mucopolysaccharide in the myocardial interstitium as well as the cardiac valves and coronary arteries.[18] Fabry's disease is an X-linked disorder of glycosphingolipid metabolism that is due to a deficiency of lysosomal ceramide trihexosidase, which results in the intracellular accumulation of a glycolipid in a number of organs, including the heart. Patients with Fabry's disease can present with restrictive cardiomyopathy.[21] There is full expression in male patients and incomplete expression in female patients.

Cardiac sarcoidosis may cause interstitial inflammation (Fig. 3), which initially impairs diastolic function, whereas systolic function remains normal or nearly normal.[80] Subsequent injury and fibrosis result in impaired systolic function. Diffuse hypokinesia can occur, as well as focal abnormalities of regional wall motion that especially affect the basal septum but spare the apex.[81] It is likely that the myocardium is often involved in patients with systemic sarcoidosis,[16] which may result in subclinical cardiac dysfunction.[82] The course of the disease is variable; in some patients it progresses rapidly to death with no preexisting symptoms.[83,84] The most dramatic presentation of cardiac sarcoidosis is sudden death or high-degree heart block, usually due to direct involvement of the cardiac conduction system.[85] Fatal myocardial sarcoidosis appears to be more common in Japanese patients than in whites or blacks.[86] Myocardial imaging with thallium-201 or gallium-67 has been helpful in demonstrating abnormal segmental uptake, which may indicate areas of myocardial involvement.[87-89] In particular, abnormal uptake of gallium-67 may predict the response to corticosteroids when thallium imaging is positive.[88] Although endomyocardial biopsy is useful in the diagnosis of cardiac sarcoidosis,[16,90] a negative biopsy does not rule out the diagnosis.[91]

Other Restrictive Conditions

Carcinoid heart disease occurs as a late complication of the carcinoid syndrome in up to half of cases, with tricuspid regurgitation as the predominant lesion.[28] The development of cardiac lesions is correlated with circulating levels of serotonin and its principal metabolite, 5-hydroxyindoleacetic acid.[92] The pathological lesion consists of fibrous plaques involving the tricuspid and pulmonary valves and the right ventricular endocardium. The plaques are composed of smooth-muscle cells embedded in a stroma rich in acid mucopolysaccharides and collagen but devoid of elastic components.[93] Immunohistochemical observations suggest that the proliferation of fibroblasts, as evidenced by the increased expression of transforming growth factors $\beta 1$ and $\beta 3$, is involved in the development of the carcinoid fibrotic plaque.[94]

Besides causing dilated cardiomyopathy, anthracyclines can also cause endomyocardial fibrosis.[32] The risk of restrictive cardiac failure is greatly increased when there is a history of irradiation.[33] Therefore, substantial abnormalities of diastolic function occur after treatment with anthracyclines, even administered many years previously, and the abnormalities appear not to be correlated with the dose.[33] The diagnosis of fibrosis of the endocardium, whether due to anthracyclines or other agents, such as methysergide, may require endomyocardial biopsy.[35]

Radiation-induced myocardial and endocardial fibrosis can also result in restrictive cardiomyopathy. There is increased interstitial fibrosis, particularly in the right ventricle.[95] In patients who have undergone radiotherapy for Hodgkin's disease, the transverse cardiac diameter and cardiothoracic ratio are decreased, and many patients have subclinical cardiomyopathy.[96] In irradiated rats the biosynthesis of catecholamines is considerably reduced and the density of cardiac beta-adrenergic receptors is increased as compared with those of controls, with a delay between structural injury to the myocardium and hemodynamic deterioration.[97] Loss of endothelial alkaline phosphatase has also been demonstrated and may cause heart failure after cardiac irradiation.[98]

PRESENTATION

The underlying cause of restrictive cardiomyopathy may not be obvious on presentation. Symptoms include dyspnea, paroxysmal nocturnal dyspnea, orthopnea, peripheral edema, and ascites, as well as general fatigue and weakness. Angina does not occur except in amyloidosis, in which it may be the presenting symptom.[50] In advanced cases, all the signs of heart failure are present except cardiomegaly. The findings are similar to those in severe constrictive pericarditis.[4,99] Up to one third of patients with idiopathic restrictive cardiomyopathy may present with thromboembolic complications.[42] Cardiac conduction disturbances are particularly common in amyloidosis[100,101] and sarcoidosis.[102] Atrial fibrillation is common in idiopathic restrictive cardiomyopathy and cardiac amyloidosis.[103] In the elderly, restrictive cardiomyopathy remains a diagnosis of exclusion, but it should be differentiated from age-related changes in diastolic compliance.[104]

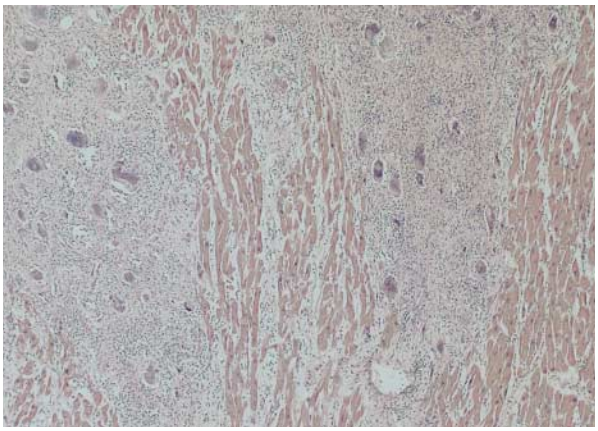


Figure 3. Endomyocardial-Biopsy Specimen from a Patient with Cardiac Sarcoidosis (Hematoxylin and Eosin, ×125).
There is extensive interstitial fibrosis, and granulomas can be seen in which giant cells are visible.

DIAGNOSTIC EVALUATION

The initial diagnostic approach should attempt to rule out constrictive pericarditis, which results in clinical signs and symptoms similar to those of restrictive cardiomyopathy,[105,106] as described in the next section.

The jugular venous pulse wave and the degree of elevation of the jugular venous pressure indicate the severity of the hemodynamic impairment.[5] Rapid x and y descents may be present in sinus rhythm, but the most prominent wave is the y descent. The jugular venous pulse fails to fall during inspiration and may actually rise (Kussmaul's sign). Peripheral edema and ascites are present in advanced cases, and the liver is enlarged and pulsatile. The left ventricular systolic impulse is usually normal. The first heart sound is usually normal, and the second heart sound is split normally. Splitting widens in the normal way during inspiration, and the pulmonary component is not accentuated. There is usually a third heart sound that is right or left ventricular in origin, and less commonly a fourth heart sound. In advanced cases the carotid and peripheral pulses may show evidence of a low output state, with sinus tachycardia and low pulse volume.

The chest film shows that the cardiac size is usually normal. Atrial enlargement is present if there is atrioventricular valvular regurgitation. Pulmonary congestion is often seen, as well as interstitial edema, with Kerley B lines in the more severe cases. Pleural effu-

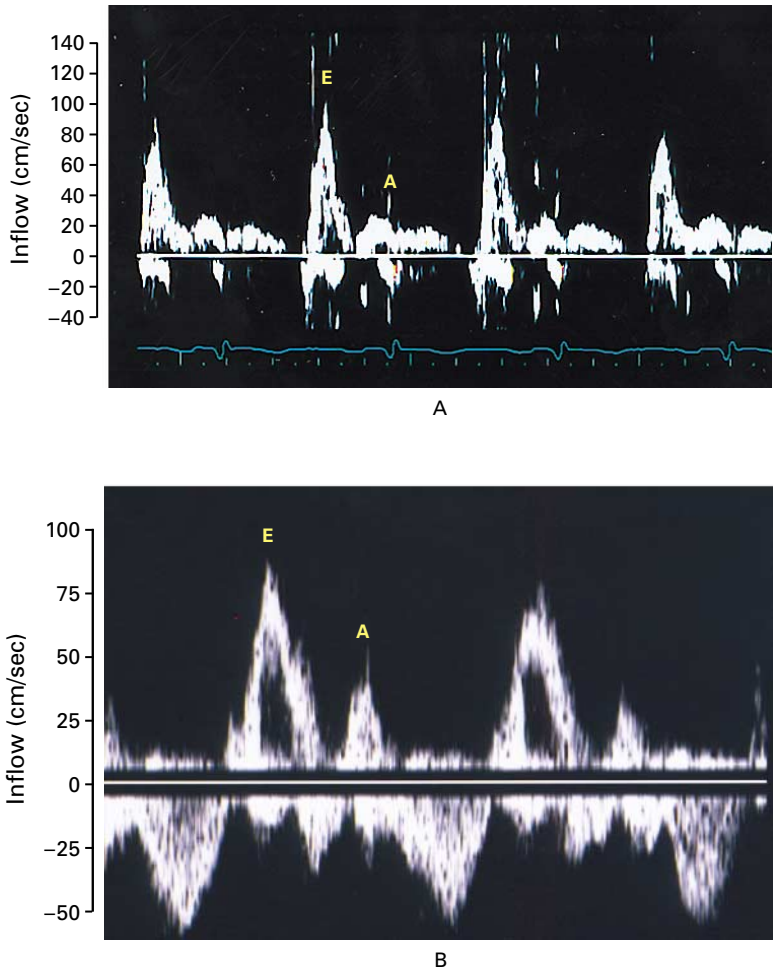


Figure 4. Doppler Patterns of Left Ventricular Inflow in a Patient with Restrictive Cardiomyopathy Due to Cardiac Amyloidosis (Panel A) and a Normal Subject without Cardiac Disease (Panel B).

The ratio of early-diastolic filling (E) to atrial filling (A) is higher in the patient with restrictive cardiomyopathy. (Figure courtesy of Dr. Martin Goldman.)

sions may also occur. The electrocardiogram shows nonspecific ST- and T-wave abnormalities. There may be depolarization abnormalities, such as bundle-branch or ventricular hypertrophy, or abnormalities of conduction, including atrioventricular block.[50,107]

On Doppler echocardiography, the pattern of mitral-inflow velocity in restrictive cardiomyopathy is typically one of increased early diastolic filling velocity ($\geq$1.0 m per second), decreased atrial filling velocity ($\leq$0.5 m per second), an increased ratio of early diastolic filling to atrial filling ($\geq$2), a decreased deceleration time ($\leq$150 msec), and a decreased isovolumic relaxation time ($\leq$70 msec) (Fig. 4). Pulmonary-vein or hepatic-vein flow testing in patients with restrictive cardiomyopathy shows that systolic forward flow is less than diastolic forward flow and that there is increased reversal of diastolic flow after atrial contraction with inspiration in the hepatic and pulmonary veins. There is also a shortened deceleration time across the mitral and tricuspid valves, indicating an abrupt cessation of ventricular filling.[108]

During cardiac catheterization, the characteristic hemodynamic feature is a deep and rapid early decline in ventricular pressure at the onset of diastole, with a rapid rise to a plateau in early diastole. This is the so-called dip and plateau or square-root sign and is manifested in the atrial-pressure tracing as a prominent y descent followed by a rapid rise to a plateau. The right atrial pressure is elevated, and the wave form is M- or W-shaped, as in constrictive pericarditis; usually respiratory variation of venous pressure is absent, but the y descent may become deeper during inspiration. The right ventricular systolic pressure may be elevated to around 40 mm Hg, but di-

TABLE 2. THE DIFFERENTIAL DIAGNOSIS OF RESTRICTIVE CARDIOMYOPATHY AND CONSTRICTIVE PERICARDITIS.*

TYPE OF EVALUATION	RESTRICTIVE CARDIOMYOPATHY	CONSTRICTIVE PERICARDITIS
Physical examination	Kussmaul's sign may be present Apical impulse may be prominent S3 may be present, rarely S4 Regurgitant murmurs common	Kussmaul's sign usually present Apical impulse usually not palpable Pericardial knock may be present Regurgitant murmurs uncommon
Electrocardiography	Low voltage (especially in amyloidosis), pseudoinfarction, left-axis deviation, atrial fibrillation, conduction disturbances common	Low voltage (<50 percent)
Echocardiography	Increased wall thickness (especially thickened interatrial septum in amyloidosis) Thickened cardiac valves (amyloidosis) Granular sparkling texture (amyloid)	Normal wall thickness Pericardial thickening may be seen Prominent early diastolic filling with abrupt displacement of interventricular septum
Doppler studies	Decreased RV and LV velocities with inspiration Inspiratory augmentation of hepatic-vein diastolic flow reversal Mitral and tricuspid regurgitation common	Increased RV systolic velocity and decreased LV systolic velocity with inspiration Expiratory augmentation of hepatic-vein diastolic flow reversal
Cardiac catheterization	LVEDP often >5 mm Hg greater than RVEDP, but may be identical	RVEDP and LVEDP usually equal RV systolic pressure <50 mm Hg RVEDP >one third of RV systolic pressure
Endomyocardial biopsy	May reveal specific cause of restrictive cardiomyopathy	May be normal or show nonspecific myocyte hypertrophy or myocardial fibrosis
CT/MRI	Pericardium usually normal	Pericardium may be thickened

*LV denotes left ventricular, RV right ventricular, LVEDP left ventricular end-diastolic pressure, RVEDP right ventricular end-diastolic pressure, CT computed tomography, and MRI magnetic resonance imaging.

astolic hypertension is usually severe, with mean right atrial pressures of 15 to 20 mm Hg — not different from those in constrictive pericarditis. The left ventricular diastolic pressure has the same wave form as the right ventricular diastolic pressure, and although it is typically 5 mm Hg higher than the right ventricular pressure, the two often have the same value. Therefore, a finding of equal diastolic pressures in the two ventricles does not rule out restrictive cardiomyopathy. The difference between the left and right ventricular end-diastolic pressures is accentuated by exercise. Endomyocardial biopsy should be considered for patients in whom the diagnosis is not clear by other methods of evaluation.[109]

DISTINCTION BETWEEN RESTRICTIVE CARDIOMYOPATHY AND CONSTRICTIVE PERICARDITIS

A clinical history suggestive of pericarditis makes a diagnosis of constrictive pericarditis more likely. In nonindustrialized nations, a history of tuberculosis is more suggestive of constrictive pericarditis than of restrictive cardiomyopathy. Constrictive pericarditis may also follow trauma,[110] including cardiac surgical procedures.[111] Radiation therapy can also cause pericardial disease, including acute pericarditis, with clinical evidence of constrictive pericarditis appearing years later.[112] Although they rarely do so, some causes of restrictive cardiomyopathy may also lead to constrictive pericarditis, including sarcoidosis[113] and amyloidosis.[114]

A number of studies, using different techniques, have attempted to distinguish the two conditions, including studies of left ventricular filling characteristics,[115] radionuclide angiography,[116] digitized echocardiography,[117] Doppler echocardiography,[118,119] endomyocardial biopsy,[2] and computed tomography and magnetic resonance imaging.[105,120] Table 2 summarizes the important differences between the two conditions. No technique is totally reliable, and in some patients the only way of making the differential diagnosis is to perform pericardiectomy.

TREATMENT

Symptomatic Therapy

Diuretics are used to treat venous congestion in the pulmonary and systemic circulation. Their excessive use in patients with restrictive diseases may reduce ventricular filling pressures, leading to decreased cardiac output and symptoms of fatigue and lightheadedness, with signs of hypotension and hypoperfusion. Digoxin should be used with caution, since it is potentially arrhythmogenic, particularly in patients with amyloidosis. The development of atrial fibrillation with the removal of the atrial contribution to ventricular filling may worsen existing diastolic dysfunction, and a rapid ventricular response may further compromise the pumping function. It is therefore important to maintain sinus rhythm, and medications such as amiodarone are often needed for this purpose. If cardioversion is attempted to treat atrial fibrillation, particularly in a patient with amyloidosis, the abnormal sinus node may fail as an effective pacemaker. Advanced conduction-system disease needs to be treated

by the implantation of a pacemaker.[83] Because stroke volume tends to be fixed in restrictive cardiomyopathy, the onset of bradyarrhythmias may precipitate cardiac failure, and the heart rate will need to be supported. In cardiac sarcoidosis, malignant ventricular arrhythmias are a frequent mode of presentation and may require treatment with an automatic implantable defibrillator or an antitachycardia device.[102]

Anticoagulation with warfarin is recommended because of the propensity for thrombus to form in the atrial appendage and the subsequent risk of embolic complications.[75] Patients with atrial fibrillation, valvular regurgitation, and low cardiac output are at particular risk.

Specific Therapy

Cardiac Amyloidosis

The prognosis of patients with primary systemic amyloidosis remains poor, with a median survival of about two years despite intervention with alkylating-agent–based chemotherapy in selected cases[121] and specific treatments directed to the underlying cause of the amyloidosis. In a recent trial, interferon therapy did not prove to be beneficial in primary systemic amyloidosis.[122] In specific cases, chemotherapy has dramatic benefits, with improvement in systemic as well as cardiac manifestations.[123,124] A recent trial in 100 patients with systemic amyloidosis showed that a combination of melphalan, prednisone, and colchicine was advantageous for patients whose major manifestations of amyloid disease were other than cardiac or renal.[125] When transplantation has been performed to treat cardiac amyloidosis, recurrence in the transplanted heart can occur.[126,127] The long-term survival of these patients appears to be limited, although some may have a reasonable intermediate outcome.[128]

Endomyocardial Fibrosis and Eosinophilic Cardiomyopathy

Medical therapy with corticosteroids and cytotoxic drugs is appropriate during the early phase of Löffler's endocarditis and improves symptoms and survival.[69,129] Surgical therapy, with excision of the fibrotic endocardium and replacement of the mitral or tricuspid valves, is palliative in the fibrotic stage of the disease but may provide symptomatic improvement.[130,131] The operative mortality is in the range of 15 to 25 percent.[130]

Other Conditions

The prognosis and complications of hemochromatosis depend on the amount and duration of iron excess.[132] Early diagnosis and treatment with venesection or iron-chelation therapy[133] may prevent many of the clinical consequences and may reverse the hemodynamic abnormalities associated with heart failure in hemochromatosis.[134] Combined heart and liver transplantation in a patient with heart and liver failure due to hemochromatosis has had good results.[135]

Cardiac transplantation can be considered in patients with refractory symptoms in idiopathic or familial restrictive cardiomyopathies. Although transplantation is a treatment option for cardiac sarcoidosis, there can be recurrences of sarcoid granulomata in the transplanted heart.[136] Thus, transplantation is not usually considered a viable option in patients in whom systemic disorders are the cause of restrictive cardiomyopathy.

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