

*Medical Progress***RESTRICTIVE CARDIOMYOPATHY**

SUDHIR S. KUSHWAHA, M.B., B.S., M.D.,

JOHN T. FALLON, M.D., PH.D.,

AND VALENTIN FUSTER, M.D., PH.D.

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-

From the Cardiovascular Institute, Box 1030, Mount Sinai Medical Center, 1 Gustave Levy Pl., New York, NY 10029, where reprint requests should be addressed to Dr. Kushwaha.

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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.

idiopathic 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 patchy⁴³ (Fig. 1). There may be fibrosis of the sinoatrial and atrioventricular nodes⁷ 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-

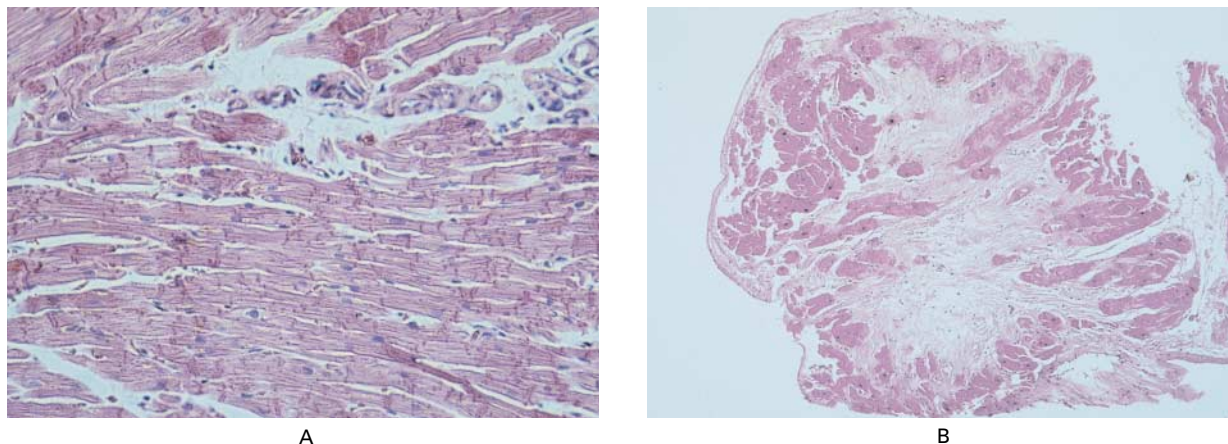


Figure 1. Endomyocardial-Biopsy Specimens from Patients with Idiopathic Restrictive Cardiomyopathy.

The specimen in Panel A (hematoxylin and eosin, $\times 250$) has myocytes with slight hypertrophy but is otherwise normal; that in Panel B (hematoxylin and eosin, $\times 40$), from another patient, shows marked interstitial fibrosis, which may also occur in idiopathic restrictive cardiomyopathy.

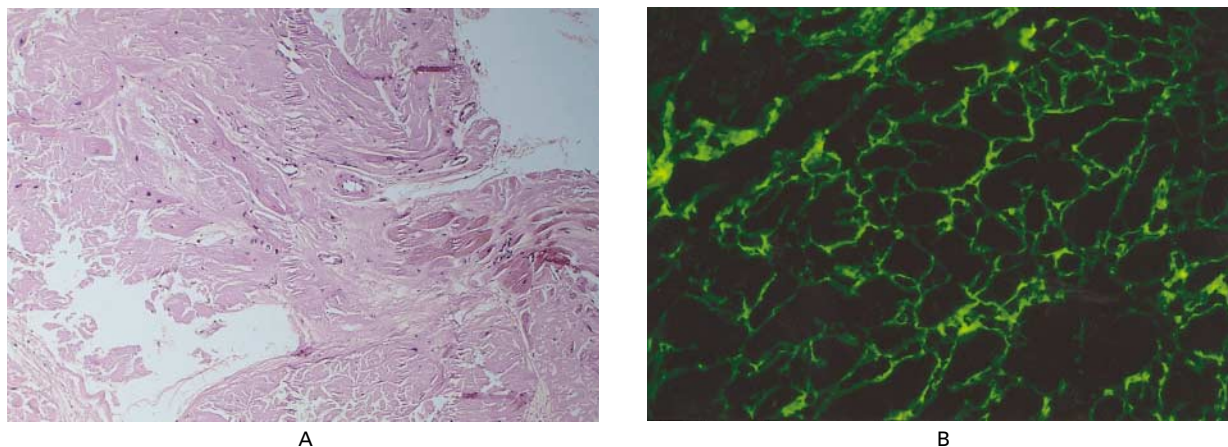


Figure 2. Endomyocardial-Biopsy Specimens from Patients with Cardiac Amyloidosis.

Panel A (hematoxylin and eosin, $\times 250$) shows interstitial deposition of amyloid fibrils in a specimen from the right ventricle. Panel B (immunofluorescent stain, $\times 400$) 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, ab-

normalities of diastolic filling can occur⁴⁷ 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 pyrophosphate⁶⁰ 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 hyper eosinophilia 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 hyper eosinophilic 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 contaminant⁷³ 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 conduc-

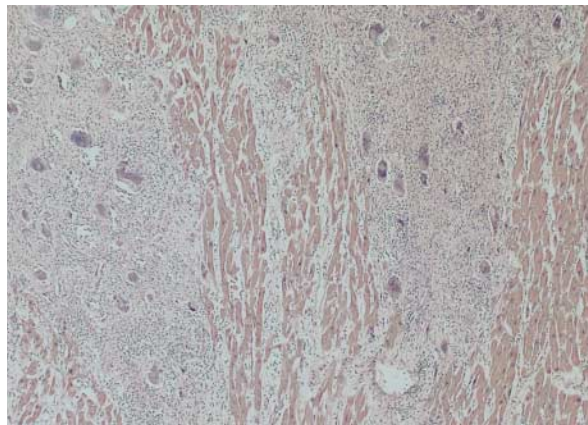


Figure 3. Endomyocardial-Biopsy Specimen from a Patient with Cardiac Sarcoidosis (Hematoxylin and Eosin, $\times 125$). There is extensive interstitial fibrosis, and granulomas can be seen in which giant cells are visible.

tion 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

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-

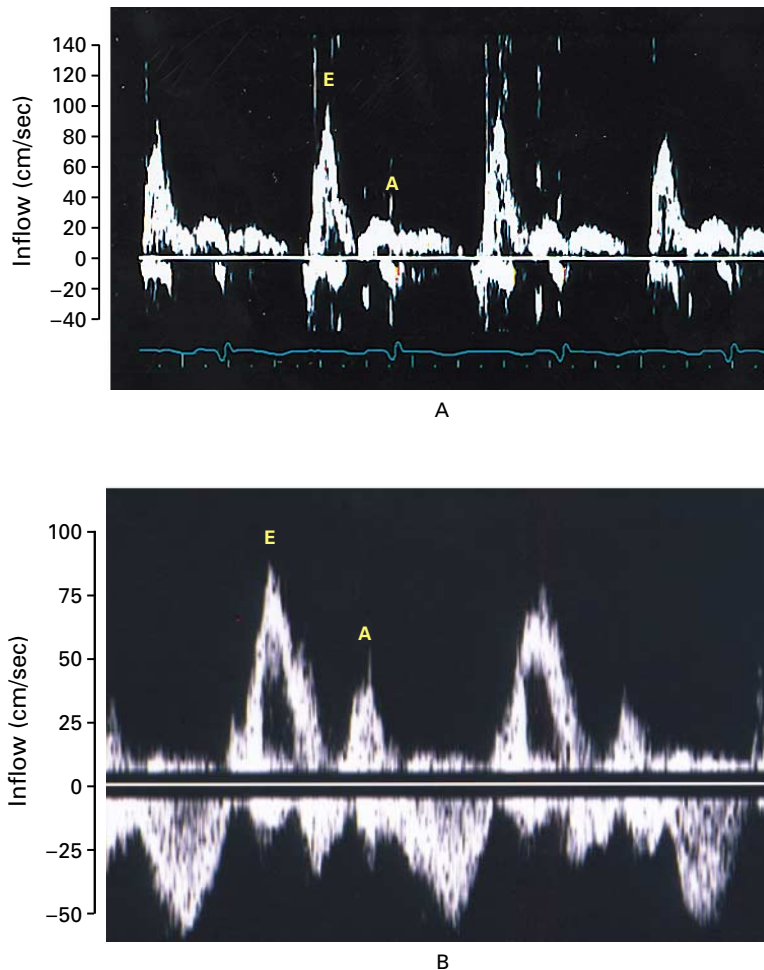


Figure 4. Doppler Patterns of Left Ventricular Inflow in a Patient with Restrictive Cardiomyopathy Due to Cardiac Amyloidosis (Panel A) and a Normal Subject without Cardiac Disease (Panel B). The ratio of early-diastolic filling (E) to atrial filling (A) is higher in the patient with restrictive cardiomyopathy. (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 (≥ 1.0 m per second), decreased atrial filling velocity (≤ 0.5 m per second), an increased ratio of early diastolic filling to atrial filling (≥ 2), a decreased deceleration time (≤ 150 msec), and a decreased isovolumic relaxation time (≤ 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 contrac-

tion 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 sarcoidosis¹¹³ 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 cases¹²¹ 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 therapy¹³³ 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.

REFERENCES

- Richardson P, McKenna W, Bristow M, et al. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation* 1996;93:841-2.
- Schoenfeld MH, Supple EW, Dec GW Jr, Fallon JT, Palacios IF. Restrictive cardiomyopathy versus constrictive pericarditis: role of endomyocardial biopsy in avoiding unnecessary thoracotomy. *Circulation* 1987;75:1012-7.
- Abelmann WH. Classification and natural history of primary myocardial disease. *Prog Cardiovasc Dis* 1984;27:73-94.
- Goodwin JF. Cardiomyopathies and specific heart muscle diseases: definitions, terminology, classifications and new and old approaches. *Postgrad Med J* 1992;68:Suppl 1:S3-S6.
- Benotti JR, Grossman W, Cohn PF. Clinical profile of restrictive cardiomyopathy. *Circulation* 1980;61:1206-12.
- Aroney C, Bett N, Radford D. Familial restrictive cardiomyopathy. *Aust N Z J Med* 1988;18:877-8.
- Fitzpatrick AP, Shapiro LM, Rickards AF, Poole-Wilson PA. Familial restrictive cardiomyopathy with atrioventricular block and skeletal myopathy. *Br Heart J* 1990;63:114-8.
- Branca I, Stanciu L, Tomescu M, Berinde L, Mancas S. The value of echocardiography in the early diagnosis of myocardial impairment due to connective tissue diseases. *Med Interne* 1986;24:197-205.
- Schurle DR, Evans RW, Cohlmlia JB, Lin J. Restrictive cardiomyopathy in scleroderma. *J Kans Med Soc* 1984;85:49-50.
- Navarro-Lopez F, Llorian A, Ferrer-Roca O, Betriu A, Sanz G. Restrictive cardiomyopathy in pseudoxanthoma elasticum. *Chest* 1980;78:113-5.
- Bouchard A, Sanz N, Botvinick EH, et al. Noninvasive assessment of cardiomyopathy in normotensive diabetic patients between 20 and 50 years old. *Am J Med* 1989;87:160-6.
- Fein FS, Sonnenblick EH. Diabetic cardiomyopathy. *Cardiovasc Drugs Ther* 1994;8:65-73.
- Chew C, Ziady GM, Raphael MJ, Oakley CM. The functional defect in amyloid heart disease: the "stiff heart" syndrome. *Am J Cardiol* 1975;36:438-44.
- Cueto-Garcia L, Tajik AJ, Kyle RA, et al. Serial echocardiographic observations in patients with primary systemic amyloidosis: an introduction to the concept of early (asymptomatic) amyloid infiltration of the heart. *Mayo Clin Proc* 1984;59:589-97.
- Matsui Y, Iwai K, Tachibana T, et al. Clinicopathological study of fatal myocardial sarcoidosis. *Ann N Y Acad Sci* 1976;278:455-69.
- Perry A, Vuitch E. Causes of death in patients with sarcoidosis: a morphologic study of 38 autopsies with clinicopathologic correlations. *Arch Pathol Lab Med* 1995;119:167-72.
- Smith RL, Hutchins GM, Sack GH Jr, Ridolfi RL. Unusual cardiac, renal and pulmonary involvement in Gaucher's disease: interstitial glucocerebroside accumulation, pulmonary hypertension and fatal bone marrow embolization. *Am J Med* 1978;65:352-60.
- Renteria VG, Ferrans VJ, Roberts WC. The heart in the Hurler syndrome: gross, histologic and ultrastructural observations in five necropsy cases. *Am J Cardiol* 1976;38:487-501.
- Dervan JJ, Ilercil A, Kane PB, Anagnostopoulos C. Fatty infiltration: another restrictive cardiomyopathic pattern. *Cathet Cardiovasc Diagn* 1991;22:184-9.
- Furth PA, Futterweit W, Gorlin R. Refractory biventricular heart failure in secondary hemochromatosis. *Am J Med Sci* 1985;290:209-13.
- Hillsley RE, Hernandez E, Steenberg C, Bashore TM, Harrison JK. Inherited restrictive cardiomyopathy in a 74-year-old woman: a case of Fabry's disease. *Am Heart J* 1995;129:199-202.
- Olson LJ, Reeder GS, Noller KL, Edwards WD, Howell RR, Michels VV. Cardiac involvement in glycogen storage disease III: morphologic and biochemical characterization with endomyocardial biopsy. *Am J Cardiol* 1984;53:980-1.

23. Gilbert EF. The effects of metabolic diseases on the cardiovascular system. *Am J Cardiovasc Pathol* 1987;1:189-213.
24. Chew CY, Ziady GM, Raphael MJ, Nellen M, Oakley CM. Primary restrictive cardiomyopathy: non-tropical endomyocardial fibrosis and hypereosinophilic heart disease. *Br Heart J* 1977;39:399-413.
25. Fawzy ME, Ziady G, Halim M, Guindy R, Mercer EN, Feteih N. Endomyocardial fibrosis: report of eight cases. *J Am Coll Cardiol* 1985;5:983-8.
26. Olsen EG, Spry CJ. Relation between eosinophilia and endomyocardial disease. *Prog Cardiovasc Dis* 1985;27:241-54.
27. Lundin L, Norheim I, Landelius J, Oberg K, Theodorsson-Norheim E. Carcinoid heart disease: relationship of circulating vasoactive substances to ultrasound-detectable cardiac abnormalities. *Circulation* 1988;77:264-9.
28. Pellikka PA, Tajik AJ, Khandheria BK, et al. Carcinoid heart disease: clinical and echocardiographic spectrum in 74 patients. *Circulation* 1993;87:1188-96.
29. Roberts WC, Glancy DL, DeVita VT Jr. Heart in malignant lymphoma (Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and mycosis fungoides): a study of 196 autopsy cases. *Am J Cardiol* 1968;22:85-107.
30. Stark RM, Perloff JH, Glick HJ, Hirshfeld JW Jr, Devereux RB. Clinical recognition and management of cardiac metastatic disease: observations in a unique case of alveolar soft-part sarcoma. *Am J Med* 1977;63:653-9.
31. Gottdiener JS, Katin MJ, Borer JS, Bacharach SL, Green MV. Late cardiac effects of therapeutic mediastinal irradiation: assessment by echocardiography and radionuclide angiography. *N Engl J Med* 1983;308:569-72.
32. Mortensen SA, Olsen HS, Baandrup U. Chronic anthracycline cardiotoxicity: haemodynamic and histopathological manifestations suggesting a restrictive endomyocardial disease. *Br Heart J* 1986;55:274-82.
33. Bu'Lock FA, Mott MG, Oakhill A, Martin RP. Left ventricular diastolic function after anthracycline chemotherapy in childhood: relation with systolic function, symptoms, and pathophysiology. *Br Heart J* 1995;73:340-50.
34. Mason JW, Billingham ME, Friedman JP. Methysergide-induced heart disease: a case of multivalvular and myocardial fibrosis. *Circulation* 1977;56:889-90.
35. Billingham ME. Pharmacotoxic myocardial disease: an endomyocardial study. *Heart Vessels Suppl* 1985;1:278-82.
36. Katritsis D, Wilmschurst PT, Wendon JA, Davies MJ, Webb-Peploe MM. Primary restrictive cardiomyopathy: clinical and pathologic characteristics. *J Am Coll Cardiol* 1991;18:1230-5.
37. Ishiwata S, Nishiyama S, Seki A, Kojima S. Restrictive cardiomyopathy with complete atrioventricular block and distal myopathy with rimmed vacuoles. *Jpn Circ J* 1993;57:928-33.
38. Feld S, Caspi A. Familial cardiomyopathy with variable hypertrophic and restrictive features and common HLA haplotype. *Isr J Med Sci* 1992;28:277-80.
39. Cooke RA, Chambers JB, Curry PV. Noonan's cardiomyopathy: a non-hypertrophic variant. *Br Heart J* 1994;71:561-5.
40. Lewis AB. Clinical profile and outcome of restrictive cardiomyopathy in children. *Am Heart J* 1992;123:1589-93.
41. Cetta F, O'Leary PW, Seward JB, Driscoll DJ. Idiopathic restrictive cardiomyopathy in childhood: diagnostic features and clinical course. *Mayo Clin Proc* 1995;70:634-40.
42. Hirota Y, Shimizu G, Kita Y, et al. Spectrum of restrictive cardiomyopathy: report of the national survey in Japan. *Am Heart J* 1990;120:188-94.
43. Siegel RJ, Shah PK, Fishbein MC. Idiopathic restrictive cardiomyopathy. *Circulation* 1984;70:165-9.
44. Buxbaum J. The amyloidoses. *Mt Sinai J Med* 1996;63:16-23.
45. Smith TJ, Kyle RA, Lie JT. Clinical significance of histopathologic patterns of cardiac amyloidosis. *Mayo Clin Proc* 1984;59:547-55.
46. Saraiva MJ. Transthyretin mutations in health and disease. *Hum Mutat* 1995;5:191-6.
47. Kinoshita O, Hongo M, Yamada H, et al. Impaired left ventricular diastolic filling in patients with familial amyloid polyneuropathy: a pulsed Doppler echocardiographic study. *Br Heart J* 1989;61:198-203.
48. Hongo M, Fujii T, Hirayama J, Kinoshita O, Tanaka M, Okubo S. Radionuclide angiographic assessment of left ventricular diastolic filling in amyloid heart disease: a study of patients with familial amyloid polyneuropathy. *J Am Coll Cardiol* 1989;13:48-53.
49. Ranløv I, Alves IL, Ranløv PJ, Husby G, Costa PP, Saraiva MJM. A Danish kindred with familial amyloid cardiomyopathy revisited: identification of a mutant transthyretin-methionine111 variant in serum from patients and carriers. *Am J Med* 1992;93:3-8.
50. Hesse A, Altland K, Linke RP, et al. Cardiac amyloidosis: a review and report of a new transthyretin (prealbumin) variant. *Br Heart J* 1993;70:111-5.
51. Fiori MG, Salvi F, Plasmati R, Tessari F, Bianchi R, Tassinari CA. Amyloid deposits inside myocardial fibers in transthyretin-Met30 familial amyloidotic polyneuropathy: a histological and biochemical study. *Cardiology* 1994;85:145-53.
52. Saraiva MJ, Almeida M do R, Sherman W, et al. A new transthyretin mutation associated with amyloid cardiomyopathy. *Am J Hum Genet* 1992;50:1027-30.
53. Booth DR, Tan SY, Hawkins PN, Pepys MB, Frustaci A. A novel variant of transthyretin, 59^{Thr→Lys}, associated with autosomal dominant cardiac amyloidosis in an Italian family. *Circulation* 1995;91:962-7.
54. Gertz MA, Kyle RA, Thibodeau SN. Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. *Mayo Clin Proc* 1992;67:428-40.
55. Gustavsson A, Engstrom U, Westermark P. Mechanisms of transthyretin amyloidogenesis: antigenic mapping of transthyretin purified from plasma and amyloid fibrils and within in situ tissue localizations. *Am J Pathol* 1994;144:1301-11.
56. Kawamura S, Takahashi M, Ishihara T, Uchino F. Incidence and distribution of isolated atrial amyloid: histologic and immunohistochemical studies of 100 aging hearts. *Pathol Int* 1995;45:335-42.
57. Looi LM. Isolated atrial amyloidosis: a clinicopathologic study indicating increased prevalence in chronic heart disease. *Hum Pathol* 1993;24:602-7.
58. Cueto-Garcia L, Reeder GS, Kyle RA, et al. Echocardiographic findings in systemic amyloidosis: spectrum of cardiac involvement and relation to survival. *J Am Coll Cardiol* 1985;6:737-43.
59. Klein AL, Hatle LK, Talierto CP, et al. Prognostic significance of Doppler measures of diastolic function in cardiac amyloidosis: a Doppler echocardiography study. *Circulation* 1991;83:808-16.
60. Falk RH, Lee VW, Rubinow A, Hood WB Jr, Cohen AS. Sensitivity of technetium-99m-pyrophosphate scintigraphy in diagnosing cardiac amyloidosis. *Am J Cardiol* 1983;51:826-30.
61. Lekakis J, Nanas J, Moustafellou C, et al. Cardiac amyloidosis detected by indium-111 antimyosin imaging. *Am Heart J* 1992;124:1630-1.
62. Falk RH, Rubinow A, Cohen AS. Cardiac arrhythmias in systemic amyloidosis: correlation with echocardiographic abnormalities. *J Am Coll Cardiol* 1984;3:107-13.
63. Wilmschurst PT, Katritsis D. Restrictive cardiomyopathy. *Br Heart J* 1990;63:323-4.
64. Olson LJ, Gertz MA, Edwards WD, et al. Senile cardiac amyloidosis with myocardial dysfunction: diagnosis by endomyocardial biopsy and immunohistochemistry. *N Engl J Med* 1987;317:738-42.
65. Arbustini E, Merlini G, Gavazzi A, et al. Cardiac immunocyte-derived (AL) amyloidosis: an endomyocardial biopsy study in 11 patients. *Am Heart J* 1995;130:528-36.
66. Hoshii Y, Takahashi M, Ishihara T, Uchino F. Immunohistochemical classification of 140 autopsy cases with systemic amyloidosis. *Pathol Int* 1994;44:352-8.
67. Gallo G, Wisniewski T, Choi-Miura NH, Ghiso J, Frangione B. Potential role of apolipoprotein-E in fibrillogenesis. *Am J Pathol* 1994;145:526-30.
68. Li XA, Hatanaka K, Ishibashi-Ueda H, Yutani C, Yamamoto A. Characterization of serum amyloid P component from human aortic atherosclerotic lesions. *Arterioscler Thromb Vasc Biol* 1995;15:252-7.
69. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. The idiopathic hypereosinophilic syndrome: clinical, pathophysiological, and therapeutic considerations. *Ann Intern Med* 1982;97:78-92.
70. Tai PC, Ackerman SJ, Spry CJ, Dunnette S, Olsen EG, Gleich GJ. Deposits of eosinophil granule proteins in cardiac tissues of patients with eosinophilic endomyocardial disease. *Lancet* 1987;1:643-7.
71. Schaffer SW, Dimayuga ER, Kayes SG. Development and characterization of a model of eosinophil-mediated cardiomyopathy in rats infected with *Toxocara canis*. *Am J Physiol* 1992;262:H1428-H1434.
72. Boustany CW Jr, Murphy GW, Hicks GL Jr. Mitral valve replacement in idiopathic hypereosinophilic syndrome. *Ann Thorac Surg* 1991;51:1007-9.
73. Bolster MB, Silver RM. Eosinophilia-myalgia syndrome, toxic-oil syndrome, and diffuse fasciitis with eosinophilia. *Curr Opin Rheumatol* 1994;6:642-9.
74. Berger PB, Duffy J, Reeder GS, Karon BL, Edwards WD. Restrictive cardiomyopathy associated with the eosinophilia-myalgia syndrome. *Mayo Clin Proc* 1994;69:162-5.
75. Gottdiener JS, Maron BJ, Schooley RT, Harley JB, Roberts WC, Fauci AS. Two-dimensional echocardiographic assessment of the idiopathic hypereosinophilic syndrome: anatomic basis of mitral regurgitation and peripheral embolization. *Circulation* 1983;67:572-8.
76. Roberts WC, Liegler DG, Carbone PP. Endomyocardial disease and eosinophilia: a clinical and pathologic spectrum. *Am J Med* 1969;46:28-42.
77. Shaper AG, Hutt MS, Coles RM. Necropsy study of endomyocardial fibrosis and rheumatic heart disease in Uganda 1950-1965. *Br Heart J* 1968;30:391-401.
78. Becker AE. Pathology of cardiomyopathies. *Cardiovasc Clin* 1988;19:9-31.
79. Uyama E, Takahashi K, Owada M, et al. Hydrocephalus, corneal opacities, deafness, valvular heart disease, deformed toes and leptomenigeal fibrous thickening in adult siblings: a new syndrome associated with β -glucocerebrosidase deficiency and a mosaic population of storage cells. *Acta Neurol Scand* 1992;86:407-20.

80. Angomachalelis N, Hourzamanis A, Vamvalis C, Gavrielides A. Doppler echocardiographic evaluation of left ventricular diastolic function in patients with systemic sarcoidosis. *Postgrad Med J* 1992;68:Suppl 1:S52-S56.
81. Valantine H, McKenna WJ, Nihoyannopoulos P, et al. Sarcoidosis: a pattern of clinical and morphological presentation. *Br Heart J* 1987;57:256-63.
82. Gibbons WJ, Levy RD, Nava S, et al. Subclinical cardiac dysfunction in sarcoidosis. *Chest* 1991;100:44-50.
83. McDougall NI, Purvis JA, Wilson CM, Adgey AA. Asystolic arrest as a presentation of sarcoidosis. *Int J Cardiol* 1994;47:165-7.
84. Kavanagh T, Huang S. Cardiac sarcoidosis: an unforeseen cause of sudden death. *Can J Cardiol* 1995;11:136-8.
85. Virmani R, Bures JC, Roberts WC. Cardiac sarcoidosis: a major cause of sudden death in young individuals. *Chest* 1980;77:423-8.
86. Iwai K, Sekiguti M, Hosoda Y, et al. Racial differences in cardiac sarcoidosis incidence observed at autopsy. *Sarcoidosis* 1994;11:26-31.
87. Tawararaha K, Kurata C, Okayama K, Kobayashi A, Yamazaki N. Thallium-201 and gallium 67 single photon emission computed tomographic imaging in cardiac sarcoidosis. *Am Heart J* 1992;124:1383-4.
88. Okayama K, Kurata C, Tawararaha K, Wakabayashi Y, Chida K, Sato A. Diagnostic and prognostic value of myocardial scintigraphy with thallium-201 and gallium-67 in cardiac sarcoidosis. *Chest* 1995;107:330-4.
89. Sacki M, Kitazawa H, Kodama M, et al. Cardiac sarcoidosis: 67Ga imaging and histology. *Circulation* 1995;91:2497-8.
90. Ratner SJ, Fenoglio JJ Jr, Ursell PC. Utility of endomyocardial biopsy in the diagnosis of cardiac sarcoidosis. *Chest* 1986;90:528-33.
91. Valantine HA, Tazelaar HD, Macoviak J, et al. Cardiac sarcoidosis: response to steroids and transplantation. *J Heart Transplant* 1987;6:244-50.
92. Robioli PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease: correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. *Circulation* 1995;92:790-5.
93. Lundin L, Funa K, Hansson HE, Wilander E, Oberg K. Histochemical and immunohistochemical morphology of carcinoid heart disease. *Pathol Res Pract* 1991;187:73-7.
94. Waltenberger J, Lundin L, Oberg K, et al. Involvement of transforming growth factor-beta in the formation of fibrotic lesions in carcinoid heart disease. *Am J Pathol* 1993;142:71-8.
95. Brosius FC III, Waller BF, Roberts WC. Radiation heart disease: analysis of 16 young (aged 15 to 33 years) necropsy patients who received over 3,500 rads to the heart. *Am J Med* 1981;70:519-30.
96. Gomez GA, Park JJ, Panahan AM, et al. Heart size and function after radiation therapy to the mediastinum in patients with Hodgkin's disease. *Cancer Treat Rep* 1983;67:1099-103.
97. Schultz-Hector S, Bohm M, Blochel A, et al. Radiation-induced heart disease: morphology, changes in catecholamine synthesis and content, beta-adrenoceptor density, and hemodynamic function in an experimental model. *Radiat Res* 1992;129:281-9.
98. Schultz-Hector S, Balz K. Radiation-induced loss of endothelial alkaline phosphatase activity and development of myocardial degeneration: an ultrastructural study. *Lab Invest* 1994;71:252-60.
99. Schoenfeld MH. The differentiation of restrictive cardiomyopathy from constrictive pericarditis. *Cardiol Clin* 1990;8:663-71.
100. Eriksson P, Boman K, Jacobsson B, Olofsson BO. Cardiac arrhythmias in familial amyloid polyneuropathy during anaesthesia. *Acta Anaesthesiol Scand* 1986;30:317-20.
101. Nakata T, Shimamoto K, Yonekura S, et al. Cardiac sympathetic denervation in transthyretin-related familial amyloidotic polyneuropathy: detection with iodine-123-MIBG. *J Nucl Med* 1995;36:1040-2.
102. Winters SL, Cohen M, Greenberg S, et al. Sustained ventricular tachycardia associated with sarcoidosis: assessment of the underlying cardiac anatomy and the prospective utility of programmed ventricular stimulation, drug therapy and an implantable antitachycardia device. *J Am Coll Cardiol* 1991;18:937-43.
103. Child JS, Perloff JK. The restrictive cardiomyopathies. *Cardiol Clin* 1988;6:289-316.
104. Backes RJ, Gersh BJ. Cardiomyopathies in the elderly. *Cardiovasc Clin* 1992;22:105-25.
105. Vaitkus PT, Kussmaul WG. Constrictive pericarditis versus restrictive cardiomyopathy: a reappraisal and update of diagnostic criteria. *Am Heart J* 1991;122:1431-41.
106. Fowler NO. Constrictive pericarditis: its history and current status. *Clin Cardiol* 1995;18:341-50.
107. Eriksson A, Eriksson P, Olofsson BO, Thornell LE. The cardiac atrioventricular conduction system in familial amyloidosis with polyneuropathy: a clinico-pathologic study of six cases from northern Sweden. *Acta Pathol Microbiol Immunol Scand [A]* 1983;91:343-9.
108. Appleton CP, Hatle LK, Popp RL. Demonstration of restrictive ventricular physiology by Doppler echocardiography. *J Am Coll Cardiol* 1988;11:757-68.
109. Mason JW, O'Connell JB. Clinical merit of endomyocardial biopsy. *Circulation* 1989;79:971-9.
110. Blake S, Bonar S, O'Neill H, et al. Aetiology of chronic constrictive pericarditis. *Br Heart J* 1983;50:273-6.
111. Killian DM, Furiasse JG, Scanlon PJ, Loeb HS, Sullivan HJ. Constrictive pericarditis after cardiac surgery. *Am Heart J* 1989;118:563-8.
112. Cameron J, Oesterle SN, Baldwin JC, Hancock EW. The etiologic spectrum of constrictive pericarditis. *Am Heart J* 1987;113:354-60.
113. Garrett J, O'Neill H, Blake S. Constrictive pericarditis associated with sarcoidosis. *Am Heart J* 1984;107:394.
114. Daubert JP, Gaede J, Cohen HJ. A fatal case of constrictive pericarditis due to a marked, selective pericardial accumulation of amyloid. *Am J Med* 1993;94:335-40.
115. Tyberg TI, Goodyer AV, Hurst VW III, Alexander J, Langou RA. Left ventricular filling in differentiating restrictive amyloid cardiomyopathy and constrictive pericarditis. *Am J Cardiol* 1981;47:791-6.
116. Aroney CN, Ruddy TD, Dighero H, Fifer MA, Boucher CA, Palacios IF. Differentiation of restrictive cardiomyopathy from pericardial constriction: assessment of diastolic function by radionuclide angiography. *J Am Coll Cardiol* 1989;13:1007-14.
117. Morgan JM, Raposo L, Clague JC, Chow WH, Oldershaw PJ. Restrictive cardiomyopathy and constrictive pericarditis: non-invasive distinction by digitised M mode echocardiography. *Br Heart J* 1989;61:29-37.
118. Hatle LK, Appleton CP, Popp RL. Differentiation of constrictive pericarditis and restrictive cardiomyopathy by Doppler echocardiography. *Circulation* 1989;79:357-70.
119. Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flow. *J Am Coll Cardiol* 1993;22:1935-43.
120. Masui T, Finck S, Higgins CB. Constrictive pericarditis and restrictive cardiomyopathy: evaluation with MR imaging. *Radiology* 1992;182:369-73.
121. Gertz MA, Kyle RA. Amyloidosis: prognosis and treatment. *Semin Arthritis Rheum* 1994;24:124-38.
122. *Idem*. Phase II trial of recombinant interferon alfa-2 in the treatment of primary systemic amyloidosis. *Am J Hematol* 1993;44:125-8.
123. Gertz MA, Kyle RA, Greipp PR. Response rates and survival in primary systemic amyloidosis. *Blood* 1991;77:257-62.
124. Shibuya T, Murakawa M, Tsuda Y, Harada M. Successful treatment of primary amyloidosis with dimethylsulfoxide and cytoreductive chemotherapy. *Intern Med* 1992;31:544-8.
125. Skinner M, Anderson JJ, Simms R, et al. Treatment of 100 patients with primary amyloidosis: a randomized trial of melphalan, prednisone, and colchicine versus colchicine only. *Am J Med* 1996;100:290-8.
126. Deng M, Park JW, Roy-Chowdhury R, Knieriem HJ, Reinhard U, Heinrich KW. Heart transplantation for restrictive cardiomyopathy: development of cardiac amyloidosis in preexisting monoclonal gammopathy. *J Heart Lung Transplant* 1992;11:139-41.
127. Dubrey S, Simms RW, Skinner M, Falk RH. Recurrence of primary (AL) amyloidosis in a transplanted heart with four-year survival. *Am J Cardiol* 1995;76:739-41.
128. Hosenpud JD, DeMarco T, Frazier OH, et al. Progression of systemic disease and reduced long-term survival in patients with cardiac amyloidosis undergoing heart transplantation: follow-up results of a multicenter survey. *Circulation* 1991;84:Suppl III:III-338-III-343.
129. Kim CH, Vlietstra RE, Edwards WD, Reeder GS, Gleich GJ. Steroid-responsive eosinophilic myocarditis: diagnosis by endomyocardial biopsy. *Am J Cardiol* 1984;53:1472-3.
130. Metras D, Coulibaly AO, Ouattara K. The surgical treatment of endomyocardial fibrosis: results in 55 patients. *Circulation* 1985;72:Suppl II:II274-II279.
131. Balakrishnan KG, Venkitachalam CG, Pillai VR, Subramanian R, Valiathan MS. Postoperative evaluation of endomyocardial fibrosis. *Cardiology* 1986;73:73-84.
132. Niederau C, Fischer R, Purschel A, Stremmel W, Haussinger D, Strohmeyer G. Long-term survival in patients with hereditary hemochromatosis. *Gastroenterology* 1996;110:1107-19.
133. Niederau C, Stremmel W, Strohmeyer GW. Clinical spectrum and management of haemochromatosis. *Baillieres Clin Haematol* 1994;7:881-901.
134. Politi A, Sticca M, Galli M. Reversal of haemochromatotic cardiomyopathy in beta thalassaemia by chelation therapy. *Br Heart J* 1995;73:486-7.
135. Case Records of the Massachusetts General Hospital (Case 31-1994). *N Engl J Med* 1994;331:460-6.
136. Oni AA, Hershberger RE, Norman DJ, et al. Recurrence of sarcoidosis in a cardiac allograft: control with augmented corticosteroids. *J Heart Lung Transplant* 1992;11:367-9.