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# Restrictive Cardiomyopathy

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**Key Points**

- Restrictive cardiomyopathy (RCM) is characterized by reductions in the rate and extent of ventricular relaxation and resultant diastolic dysfunction.
- The RCMs are endomyocardial fibroelastosis, amyloidosis, hypertrophic cardiomyopathy (HCM), hemochromatosis, and injury to the heart from ionizing radiation.
- The major differential diagnosis for RCM is constrictive pericarditis.

## Definition

*Restrictive cardiomyopathy* (RCM) is the term used to describe the third and least common of the cardiomyopathies that are defined as *heart muscle diseases of unknown cause* (also see Chapters 55 and 56).

*Restrictive cardiomyopathy* is defined as "organic interference with filling of the ventricles as the result of endocardial or myocardial disease or a combination of both with rapid early but slow late ventricular filling."[1–23] It is a component of the syndrome known as *diastolic heart disease*, which includes hypertrophy, amyloidosis, hemochromatosis, radiation-induced fibrosis, and constrictive pericarditis. Diastolic heart disease is defined as "heart disease initially and predominantly involving diastolic rather than systolic function." It does not refer to the most common causes of diastolic impairment, including impairment of systolic function due to systemic arterial hypertension, coronary artery disease, and valvular heart disease.[21]

## Pathophysiology

The most common cause of RCM is endomyocardial fibrosis (EMF), now known as *eosinophilic endomyocardial disease*. Other causes include cryptogenic EMF without eosinophilia, hemochromatosis, amyloid heart disease, and radiation-induced heart muscle disease.

Constrictive pericarditis represents diastolic heart disease in its purest form. The impairment of ventricular filling is the result of the tight compression of the ventricles by the restricting pericardium, with the myocardium remaining normal in all except severe and prolonged cases. The tight pericardium permits rapid early filling without restriction, but as the ventricles expand against the rigid pericardium, middle and late filling is suddenly slowed and then halted. Systolic function remains normal until the late stages. In other restrictive diseases, thickening and rigidity of the endocardium and myocardium have much the same pathophysiologic effect whether the resistance to inflow and stiffening of the myocardium is due to infiltration with amyloid tissue or excessive iron deposits or fibrosis.[22,23] It is characteristic of hypertrophic cardiomyopathy (HCM) that the massive hypertrophy, together with the fibrosis and myofibrillar disarray, produces similar functional defects. There are many differences between HCM and EMF, but increased myocardial stiffness associated with disturbed relaxation and prolongation of ventricular filling is common to both (see later).

There are important differences between constrictive pericarditis and RCM, which are dependent on the differing effects of generalized constriction in constrictive pericarditis and regional areas of endomyocardial disease that affect one or both ventricles in a patchy manner in RCM. These differences are discussed later.

## The Eosinophil in Heart Disease

The disorder involving EMF described by Loeffler as *endocarditis parietalis fibroplastica* is associated with hypereosinophilia and occurs in temperate climates. A similar condition, *tropical endomyocardial fibrosis*, occurs in

†Posthumously, Dr. Goodwin remains an author of this chapter. Dr. Goodwin died in June 2001.

**TABLE 57.1. Stages of eosinophilic endomyocardial disease**

| *Pathologic stage* | *Clinical stage* |
|---|---|
| Acute inflammatory | Recurrent fever<br>Paroxysmal atrial fibrillation<br>Episodic heart failure (embolism rare) |
| Organizing fibrotic (pericardial effusion mainly in tropical EMF) | Heart failure<br>Tricuspid and mitral regurgitation<br>Embolism |
| Thrombotic ↓↑ | Heart failure<br>Embolism<br>Tricuspid and mitral regurgitation |

EMF, endomyocardial fibrosis.

hot, humid climates but without an obvious association with hypereosinophilia. At present, tropical EMF and Loeffler's eosinophilic endomyocardial disease are considered to represent the same process.[24] The Churg-Strauss syndrome also combines hypereosinophilia with heart disease, but instead of EMF, there is a dilated form of heart muscle disease, frequently with pericardial effusion and often with bronchial asthma. The eosinophilia-myalgia syndrome associated with the ingestion of L-tryptophan tablets produces lesions in the coronary arteries and conduction system.[25]

The pathologic findings in EMF and Loeffler's disease are essentially identical, although there are physical differences due to geography, climate, culture, associated illnesses, and genetic influences.[26,27] *Hypereosinophilic syndrome*[28] is a term used to describe multiple organ involvement in association with hypereosinophilia and with cardiac involvement in 95% of cases. Hypereosinophilic disease may be present with cardiac features that may later be associated with involvement of other systems; it may present with extracardiac features and then involve the heart; or it may involve the heart only.[29,30]

Available evidence strongly suggests that hypereosinophilic endomyocardial disease is caused by the abnormal behavior of eosinophils.[26,31,32] Qualitatively abnormal eosinophils actively damage the endocardium and myocardium. Counts of such cells are usually around 1.510/mm,[31] and they show degranulation and vacuolation. They exude a cationic protein, which is thrombogenic and damages the endocardium. An increase in Fc receptors causes more effective

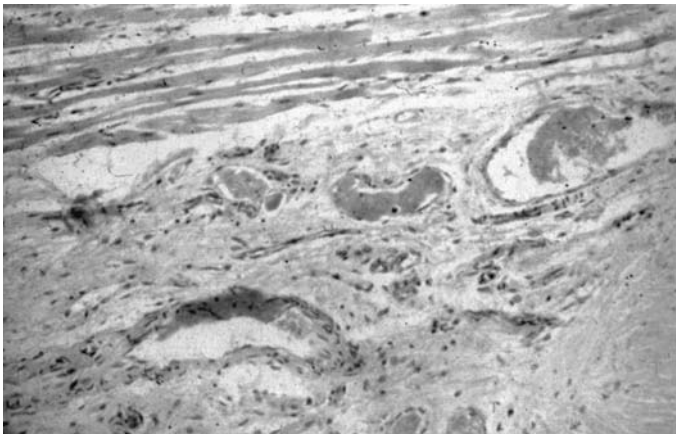


**FIGURE 57.1.** Photomicrograph of ventricular myocardium in stage 2 endomyocardial fibrosis shows extensive fibrosis but no eosinophilic infiltration.

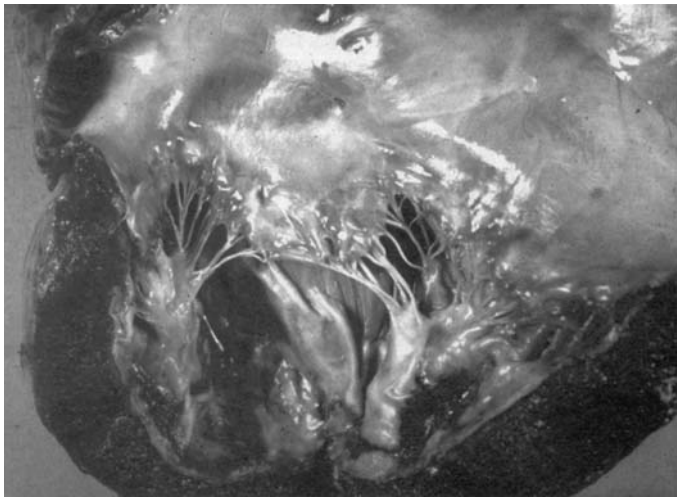


**FIGURE 57.2.** Heart with left ventricular endomyocardial fibrosis. There is extensive fibrosis involving the endocardium and the anterior, but not the posterior, mitral valve apparatus. Widespread antemortem thrombus overlies the endocardial fibrosis.

binding to immunoglobulin (Ig)- and C3B-coated particles to produced a cytotoxic response. In addition to damaging the endocardium, the abnormal eosinophils infiltrate the myocardium and may degranulate, causing myocardial lesions.[31] Eosinophil granular protein can be detected in acute thrombotic and necrotic myocardial lesions in acute necrotizing eosinophilic myocarditis.

There are three principal stages in eosinophilic endomyocardial disease. The first is an acute inflammatory action in the endomyocardium, with intense infiltration of eosinophils. The second is one of organization with endocardial and myocardial fibrosis and endarteritis obliterans of myocardial arterioles; eosinophils progressively disappear from the lesions. The third stage is one of thrombosis. The three stages are not always clear cut, and they may overlap (Table 57.1 and Figs. 57.1 to 57.3).

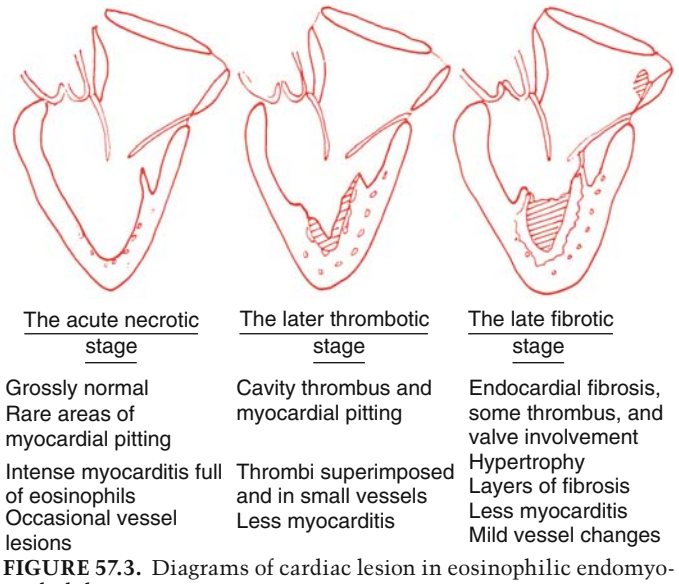



**FIGURE 57.3.** Diagrams of cardiac lesion in eosinophilic endomyocardial disease.

The cause of the abnormality in the eosinophil is not known. A viral infection might be responsible, but there is no direct evidence for this, and no virus has been isolated. There seems to be little doubt that the cationic protein is responsible for the inflammatory reaction in the endomyocardium, so the heart disease may be regarded, in a sense, as the result of a hematologic disorder. Because the eosinophilic disorder is cryptogenic, it is logical to consider EMF as a cardiomyopathy, although when other organs are involved, as in the hypereosinophilic syndrome, it could be regarded as a form of specific heart muscle disease.[21]

The abnormal eosinophils are not usually associated with bone marrow precursors that would suggest a leukemic process; however, eosinophilic leukemia can produce deposits in the heart, although it does not usually cause endomyocardial disease. Endomyocardial fibrosis in Africa and in other tropical areas has not been found to be associated with hypereosinophilia, probably for two reasons. First, increased eosinophil counts are common in patients in Africa due to helminthic infestation independent of EMF. Second, the eosinophils have not usually been examined for degranulation or vacuolation.

The distribution of eosinophilic endomyocardial disease is characteristic, essentially involving the inflow tracts of the ventricles. Either or both ventricles can be involved, with the endocardial fibrosis gradually obliterating the cavity from the apex and leaving only a small area of outflow tract beneath the pulmonary valve (Figs. 57.2 and 57.3). There usually is a plaque of fibrous tissue on the left atrial (LA) endocardium; otherwise, the atria are not involved directly but become enlarged as a result of the ventricular disease and of atrioventricular (AV) valvular regurgitation.

In the tropics, EMF can account for 10% of pediatric patients with cardiologic disease.[33] A study[34,35] compared the incidence of EMF in the tropics with EMF in temperate climates and found that patients in the United Kingdom tended to be older, were mainly males, and often had a systemic illness.[28,29] Tropical patients tended to be younger, had an equal male/female ratio, and often came from poor, undernourished families with heavy parasitic infestation, especially with filariasis. Abnormal eosinophil morphology has not thus far been seen. In the tropics, the involvement of both ventricles occurs in only 51% of patients, whereas biventricular disease is more common in temperate climates. However, endomyocardial biopsy abnormalities are identical, although half of the patients in the United Kingdom present in the acute early necrotic (stage 1) phase, whereas most patients in the tropics present in the late fibrotic state.

## Clinical Recognition

### History and Physical Examination

The inflammatory first stage of the illness is marked by episodes of palpitations and dyspnea due to atrial fibrillation, periods of fever, progressive lassitude, and general malaise. The fibrotic second stage is notable for symptoms of heart failure and of AV valvular regurgitation, with progressive fatigue, increasing dyspnea, and swelling of the ankles and abdomen (Table 57.1). When left-sided disease is dominant, dyspnea, which may be paroxysmal, is notable, whereas with right-sided involvement, the emphasis is on fatigue, swelling of the ankles and abdomen, and tightness of the throat due to the high jugular venous pressure. Despite reduced effort tolerance because of the low cardiac output, patients may remain reasonably ambulant until the very late stages. At any stage, however, embolism to the lungs may occur, producing hemoptysis.

The physical signs depend on the site and extent of the disease. In right-sided disease, there is peripheral edema, hepatomegaly, and ascites. The jugular venous pressure is raised, often to the angle of the jaw up to 20 cm above the sternal angle. Tricuspid regurgitation is common, especially when there is atrial fibrillation, producing a dominant systolic (CV) wave in the jugular venous pulse with a normal *y* descent. The external jugular vein may exhibit palpable systolic pulsation. The very high venous pressure may produce a "moon face" and even proptosis. In early cases, the jugular venous pulse shows the characteristic dip-and-plateau configuration, with prominent A and V waves and *x* and *y* descents typical of RCM. The jugular venous pressure may rise on inspiration, giving a positive Kussmaul sign. The arterial pulse is small in volume and thready because when the right ventricle is extensively obliterated, the entire cardiac output depends on right atrial function. Pulsus alternans may be present. When there is a large pericardial effusion, the cardiac impulse is quiet and cardiac pulsation is obscured, but otherwise, the large right atrium may produce pulsation to the right of the sternum. The heart sounds are faint, and gallop rhythm is common (Fig. 57.4). A systolic murmur that increases on inspiration may be heard in the tricuspid area as a result of tricuspid regurgitation. The abdomen is distended with ascites, and the liver is enlarged and pulsating. In addition, there often is generalized muscular wasting due to tissue hypoxia resulting from the low cardiac output.

In left-sided disease, the emphasis is often but not always on mitral regurgitation. The arterial pulse is small in volume and poorly sustained. The cardiac impulse may be displaced outside the midclavicular line. The jugular venous pressure

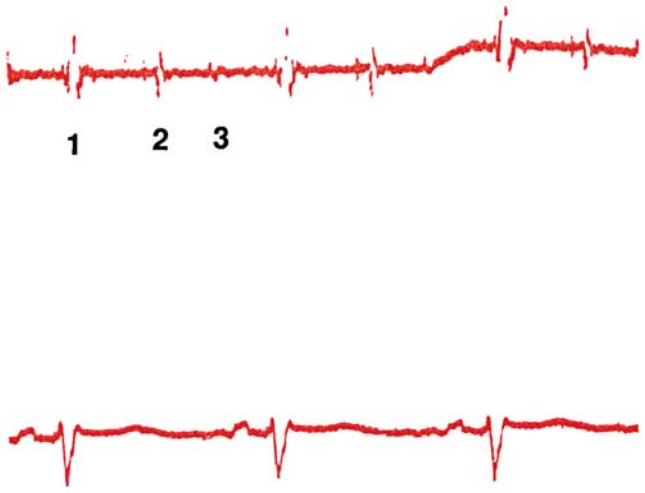



**FIGURE 57.4.** Phonocardiogram shows third heart sound (3) in eosinophilic endomyocardial disease.

may be unremarkable or show a dominant A wave (if there is sinus rhythm) due to pulmonary hypertension. Auscultation also may be unremarkable, apart from a third heart sound and (in sinus rhythm) a fourth sound. Tachycardia is common, and summation gallop of third and fourth heart sounds is usual. When mitral regurgitation is present, there is a holosystolic murmur at the cardiac apex, radiating usually to the axilla. The murmur tends to diminish in intensity toward the end of systole as the anterior chordae of the mitral valve that are relatively free of disease (Fig. 57.2) render the valve competent. Pulmonary valve closure is accentuated when there is pulmonary hypertension due to the high LA pressure. Eventually, signs of right heart failure develop. Systemic embolism may occur at any time and is encouraged by the presence of paroxysmal or established atrial fibrillation.

In both right- and left-sided types, systemic blood pressure and pulse tend to be low, and tachycardia is invariable in well-advanced cases because an increase in heart rate is the only way the patient can maintain cardiac output.

## Laboratory Examination

A moderate degree of anemia is common, but the striking feature in eosinophilic endomyocardial disease is the elevated eosinophil count. This alone, however, does not cause EMF, as demonstrated in the case of a patient with progressive renal failure and hypertensive heart failure with uremic pericarditis and with 84% eosinophils of a total white blood cell count of 38,000 but without any evidence of endomyocardial disease.[36] Therefore, although the total eosinophil count is raised for one reason or another, it appears that the eosinophil must first become activated to discharge the granules and cationic protein to cause the endomyocardial damage.[36] If more than 20% of eosinophils contain vacuoles and more than 15% are degranulated, endomyocardial damage is almost invariably confirmed by biopsy.[31] Therefore, EMF depends on the number of degranulated eosinophils rather than on the total count.

There are no specific biochemical blood changes. Liver function tests can be abnormal as the result of heart failure, with very high jugular venous pressure. Hypokalemia may result from the use of diuretics.

### Radiology

In right-sided EMF, prominence of the right atrium is the main feature. When there is a pericardial effusion, the cardiac silhouette may be enormous, with marked enlargement to the right of the sternum. The lung fields tend to be clear unless pulmonary embolism has reduced the vascular markings or produced pulmonary infarction. The pulmonary arteries are not usually prominent. In left-sided disease, the left ventricle is enlarged, especially when there is mitral regurgitation, as is the left atrium. There is often a linear strip of calcification along the left border of the heart, which is characteristic of calcification in endocardial thrombus (Fig. 57.5A). The lung fields may show evidence of raised LA pressure, with reduction in caliber of lower lobe vessels and interstitial costophrenic lines. In advanced cases, there may be frank pulmonary edema (Fig. 57.5B).

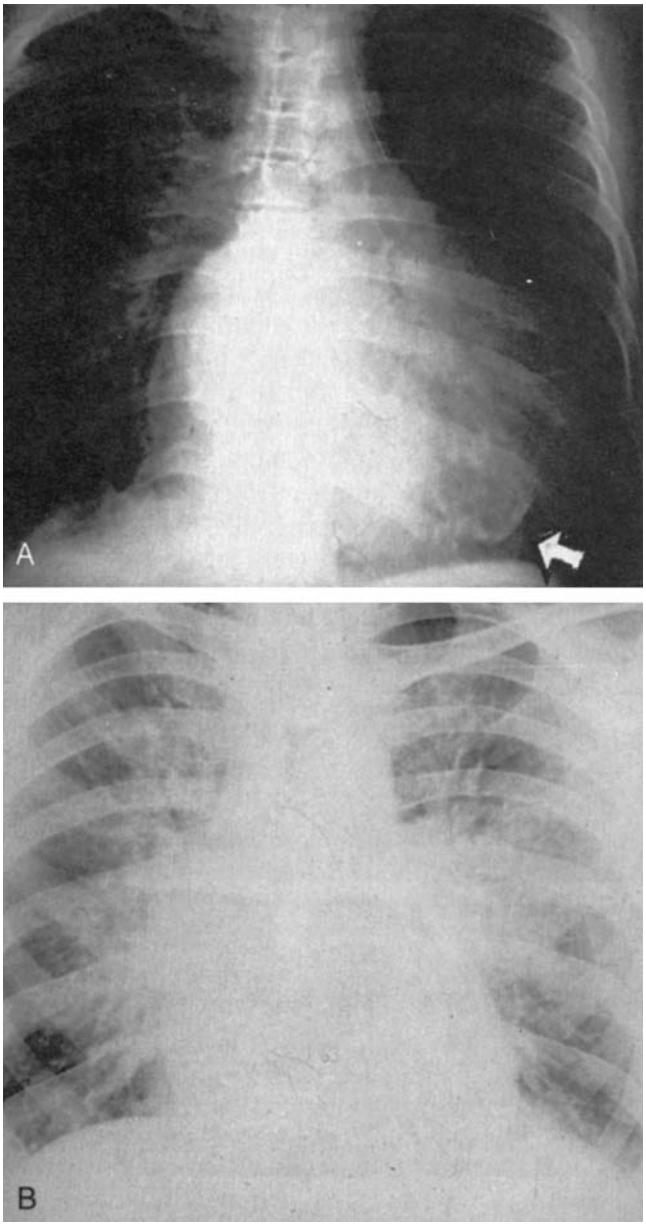



**FIGURE 57.5.** (A) Six-foot posteroanterior chest radiograph in endomyocardial fibrosis shows linear calcification (arrow) in the region of the left ventricle. (B) Acute massive pulmonary edema in left ventricular endomyocardial fibrosis.

### Electrocardiography

The electrocardiogram is not specific. In right-sided disease, right-axis deviation can be expected and right atrial enlargement is shown by augmented, pointed right atrial P waves. There may be first-degree AV block or right bundle-branch block.

Low-voltage QRS complexes and flat T waves are seen when there is a significant pericardial effusion. In left-sided disease, increased QRS voltage and T-wave inversion signal LV hypertrophy, and bifid P waves indicate LA enlargement. Ventricular arrhythmias tend to occur in the later stages and may be related more to heart failure than the fibrotic process.

## Echocardiography

In the inflammatory first stage, echocardiography often demonstrates thrombus at the apex of either ventricle, especially in the apical four-chamber view (Fig. 57.6).

In the fibrotic second stage, two-dimensional studies show only slightly dilated ventricles with dilated atria, and patches of fibrosis on the ventricular endocardium, apical and inflow tracts, or AV valves. Isolated valvular lesions limited to the inflow valve and not involving the intervening myocardium may be seen.[37]

Apical ventricular contraction is usually preserved even in the presence of thrombus. Bright, sparkling echoes are often seen from the endocardial surfaces and myocardium but are not diagnostic, being representative only of high reflective echoes due to fibrosis (Fig. 57.6).

Transesophageal echocardiography provides a useful posterior window on the left atrium and is helpful in demonstrating mitral and tricuspid regurgitation. Assessment of the extent and severity of the disease is facilitated by the use of color-coded and amplitude-processed echo imaging.

Doppler studies in diastolic heart disease do not necessarily reveal any specific features of eosinophilic endomyocardial disease except for the characteristic patchy endocardial fibrosis and apical ventricular obliteration. The restrictive process leads to impairment of ventricular compliance, with a large increment of early diastolic filling pressure for a small increase in volume as ventricular filling is halted in the first half of diastole. Pulsed Doppler records at the tip of the mitral or tricuspid valves show normal or increased peak E wave velocity and shortened deceleration time of the early filling E wave (Fig. 57.7).

Rapid filling is shortened and left ventricle (LV) isovolumetric relaxation time is diminished.[37] These Doppler findings are not specific to EMF or RCM. They are similar in other forms of diastolic heart disease and also in other forms of LV disease characterized by increased stiffness, including HCM and coronary artery disease.[36] Occasionally, advanced cases of dilated cardiomyopathy with marked myocardial fibrosis and endocardial thickening resulting from prolonged heart failure may show similar but less severe findings.

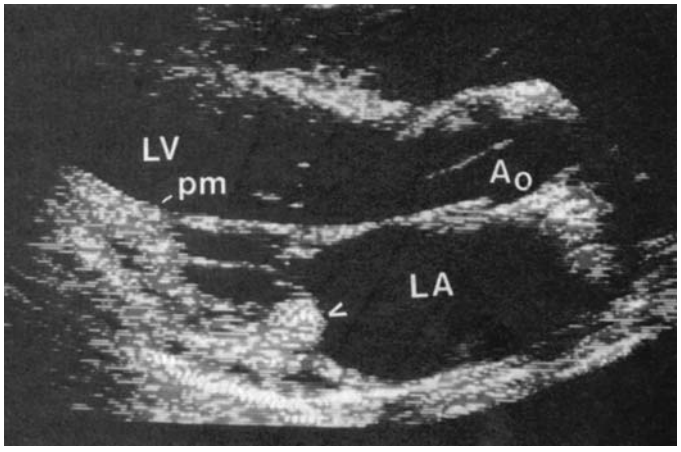



**FIGURE 57.6.** Color-coded two-dimensional echocardiogram in eosinophilic endomyocardial disease shows bright echoes (see text). Arrowhead indicates probable thrombus. $A_o$, aorta; LA, left atrium; LV, left ventricle; pm, papillary muscle.

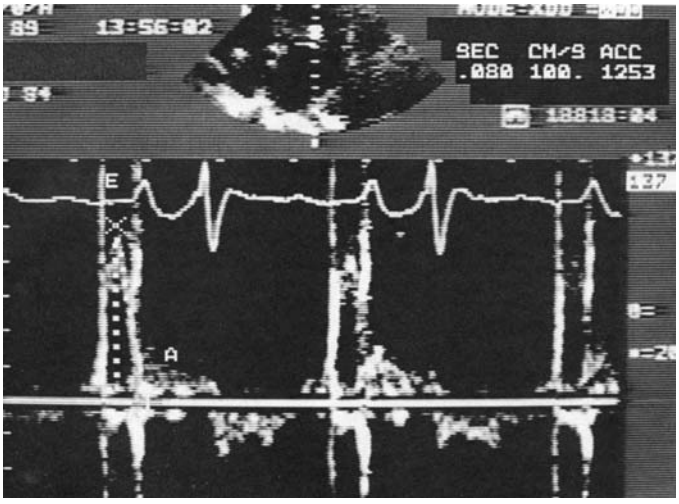



**FIGURE 57.7.** Pulsed Doppler record of mitral valve inflow velocity shows a restrictive pattern in endomyocardial fibrosis. High-peak early E inflow velocity (100 mm/s), short deceleration time (80 mm/s), and small peak atrial (A) inflow velocity (25 mm/s) are shown. E/A ratio is increased to 4.

The most useful application of echocardiography in the diagnosis and assessment of eosinophilic endomyocardial disease is the demonstration of endocardial patches of thickening and obliteration of the apical ventricular cavities, supported by Doppler evidence of AV valve regurgitation. These techniques are also valuable in differentiation of EMF from other forms of RCM.

## Cardiac Catheterization and Angiocardiography

In all types of RCM, the characteristic rapid early ventricular filling and slow or absent late ventricular filling produce a significant hemodynamic pattern and ventricular and atrial pressure curves. The rapid inflow produces an early low ventricular diastolic pressure, with a dip followed by rapid leveling off to a high end-diastolic level. The LV systolic pressure is often low due to the ventricular damage and heart failure. Right ventricular systolic pressure tends to be elevated because of LV disease. Because the disease is patchy and may involve left and right ventricles to different degrees, the early diastolic pressures in both ventricles differ (Fig. 57.8), in contrast to constrictive pericarditis in which, because the constrictive effect is generalized and equally affects both ventricles, the early and late diastolic pressures are identical (Fig. 57.8).

Atrial pressure pulses best noted in the jugular venous pressure waveform show dominant A and V waves, with rapid *x* and *y* descents. The *x* descent represents the rapid inflow. The V wave summit marks the end of ventricular systole and is prominent because of the elevated ventricular filling pressure.

## Angiocardiography

In EMF, angiocardiography demonstrates restriction of filling of the ventricles and the enlargement of the atria. Late in the

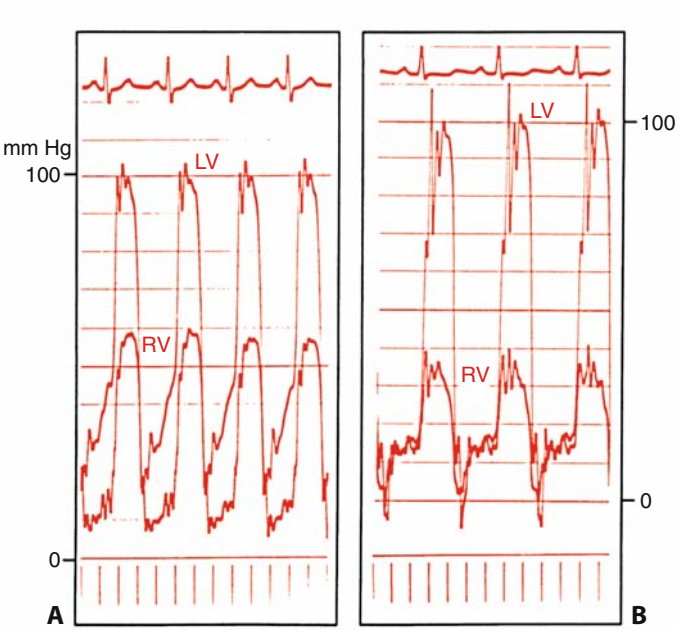



**FIGURE 57.8.** Ventricular pressure pulses in restrictive cardiomyopathy [endomyocardial fibrosis (EMF)] (A) and constrictive pericarditis (B). The left ventricular (LV) systolic pressure is low. In endomyocardial fibrosis, the early and end-diastolic pressures are raised in both ventricles, and the right ventricular (RV) systolic pressure is 48/50 mm Hg. In constrictive pericarditis, the diastolic pressures are identical in both ventricles, the early diastolic pressure falls below zero, the end-diastolic pressure is normal, and the RV systolic pressure is not elevated.

right-sided form, the right atrium is enormous and the right ventricle is reduced to a small sinus beneath the pulmonary valve (Fig. 57.9A). If a pericardial effusion is present, a clear gap will be seen between the contrast medium outlining the outer border of the right atrium and the pericardium. In left-sided EMF, the apex of the left ventricle is often blunted by a fibrothrombus (Fig. 57.9B). The appearances have been likened to a boxing glove. There may be mitral regurgitation into the enlarged left atrium. Calcification of a LV thrombus noted on a plain radiograph may be visible (Fig. 57.5A).

Angiocardiography is less valuable than echocardiography in the diagnosis and assessment of RCM. Echocardiography provides more detail, is noninvasive, is free of risk, and can be used repeatedly to judge progression.

### Endomyocardial Biopsy

Endomyocardial biopsy is useful in the detection of the typical eosinophil infiltration in the inflammatory stage and the myocardial fibrosis in the later stage, although if eosinophils are absent, the biopsy may not provide an exact diagnosis of the cause of the fibrosis, and the demonstration of characteristically abnormal eosinophils in the blood therefore may be of considerable importance. Biopsy carries a risk of embolism due to dislodgment of recent thrombus from the ventricle, and therefore should be undertaken only with strong indications. Usually, a diagnosis of eosinophilic endomyocardial disease can be made by the combination of the clinical features suggestive of RCM with the demonstration of degranulating eosinophils in the peripheral blood and the characteristic echocardiographic features supported by hemodynamic studies. Clinically, the possibility of RCM should be considered in any patient with a high jugular venous pressure and a third heart sound but little or no cardiomegaly.

### Ambulatory Electrocardiography

Ambulatory electrocardiographic monitoring can be useful in revealing arrhythmias, especially paroxysmal atrial fibrillation, ventricular tachycardia, and ectopic beats, and also in the detection of conduction defects. Therefore, the results are helpful in guiding antiarrhythmic therapy or in justifying the need for a pacemaker.

### Radionuclide Studies

Radionuclide studies do not have an important place in the diagnosis of RCM, and few data are available on EMF because

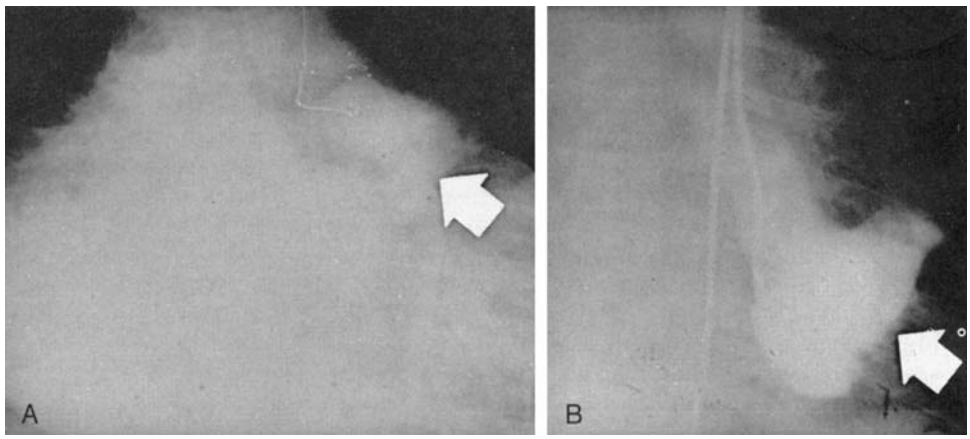



**FIGURE 57.9.** Anteroposterior angiogram in right-sided tropical endomyocardial fibrosis. (A) The right atrium is greatly enlarged, and the right ventricular volume is reduced to a small "sinus" beneath the pulmonary valve (arrow). (B) Anteroposterior left ventricular angiogram in left-sided tropical zone endomyocardial fibrosis. The left ventricular apex has been blunted by thrombus obliterating the apical cavity (arrow).

the techniques are not usually available in the tropics and the disease is rare in temperate climates. Computed tomography (CT) scanning and magnetic resonance imaging (MRI) are mainly of value in providing a definite distinction between constrictive pericarditis and RCM. The thickened pericardium can be clearly seen in constrictive pericarditis, but the pericardium is normal in RCM unless there is a pericardial effusion, in which case MRI should be used to distinguish this from fibrous pericardial thickening.

## Treatment

In the acute inflammatory stage, antiinflammatory agents, such as prednisone, may delay the onset of the fibrotic stage; hydroxyurea and vincristine have been tried. In the fibrotic stage, anticoagulants are needed, as is digitalis if there is atrial fibrillation. In the late heart-failure stage, diuretics and angiotensin-converting enzyme inhibitors will be required, but it is important not to reduce the central venous pressure greatly or slow the heart rate too much because a high-filling pressure and tachycardia are needed to maintain cardiac output. Surgical methods include endocardectomy and AV valve repair and replacement. Transplantation has been used.

**TABLE 57.2. Types of amyloid disease**

| | *Affected Area(s)* |
|---|---|
| Primary cryptogenic amyloid | Heart<br>Mucous membranes<br>Tendon sheaths<br>Tongue, connective tissue<br>Nerves<br>Kidney, rarely<br>Spleen, rarely<br>Liver, rarely |
| Non-Hodgkin's lymphoma | Heart<br>Bone marrow<br>Kidneys, skeletal muscles<br>Nerves |
| Multiple myeloma | Heart<br>Bone marrow<br>Kidneys, skeletal muscles<br>Nerves |
| Medullary thyroid carcinoma | Thyroid |
| Familial Mediterranean fever | Heart<br>Kidneys<br>Nerves |
| Reactive secondary to chronic disease | Liver<br>Spleen<br>Kidneys |
| Senile | Heart |

## Amyloid Heart Disease

Amyloid heart disease is a form of RCM and is classified as a diastolic heart disease, but it has important differences from other forms of RCM, and therefore, warrants a separate heading. In addition, it occupies a position in the classification of heart muscle disease between the cardiomyopathies and specific heart muscle disease, as defined in the section on dilated cardiomyopathy. When amyloid disease is confined to the heart, it is included in the restrictive group of cardiomyopathies, but when it is more widespread and involves organs other than the heart, it warrants being classified as a specific heart muscle disease.

Amyloidosis is a disorder of protein metabolism in which the abnormal fibrillar amyloid protein is laid down intercellularly. Some amyloid AL fibrils are derived from monoclonal macroglobulin light chains. Amyloid disease may be primary (cryptogenic), in which the cause cannot be identified, or it may be associated with multiple myeloma and B-lymphocyte lymphoma. It also occurs in a familial form, including Mediterranean fever, in which the major protein component of amyloid is not macroglobulin. "Reactive" amyloidosis is a complication of long-standing wasting illness (e.g., malignancy, chronic infection, tuberculosis, rheumatoid arthritis). Senile amyloidosis is found accidentally at autopsy in elderly subjects, some of whom have had heart failure that may have been caused or exacerbated by the amyloid process (Tables 57.2 and 57.3).

In primary amyloidosis, the process may be confined to the heart or may also involve mucous membranes, connective tissue, tendon sheaths, the tongue, and peripheral nerves. The amyloid deposits may be massive, leading to organ dysfunction and failure, including postural hypotension and severe and relentless cardiac, renal, or hepatic failure. The tongue may be so large as to prevent the patient from being able to speak normally or swallow easily. Small capillaries may also be infiltrated, leading to the classic "scratch petechiae" or purpura induced by gentle stroking of the eyelids, cheeks, or anterior chest. In macroglobulinemia, non-Hodgkin's lymphoma, and myeloma, amyloid may involve the heart, bone marrow, kidney, and peripheral nerves or skeletal muscles. Often, these amyloid deposits are scattered and small in amount. In the familial type, amyloid involves the nervous system and kidneys. In the senile type, only the heart is attacked, and the protein involved is different from that in macroglobulinemia.[38]

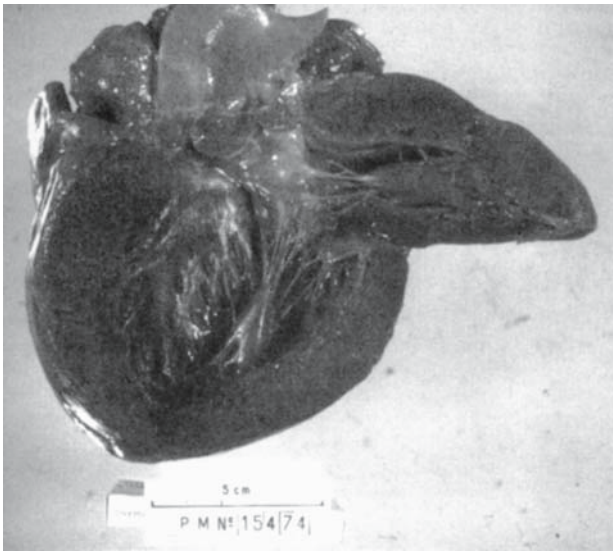
### Pathophysiology

Amyloid AL fibrils are deposited in and around the walls of capillaries, arterioles, and venules. The characteristic iodine

**TABLE 57.3. Classification of amyloidosis**

| |
|---|
| Primary amyloidosis (AL type) with no evidence of preexisting or coexisting disease |
| Amyloidosis associated with multiple myeloma (also AL type) |
| Reactive amyloidosis associated with chronic infectious diseases such as osteomyelitis, tuberculosis, ulcerative colitis, or other chronic inflammatory disease (AA type) |
| Heredofamilial amyloidosis, neuropathic (AF transthyretin or prealbumin type), and the amyloidosis associated with familial Mediterranean fever (AA type) |
| Local amyloidosis with focal, tumor-like deposits that occur in isolated organs without evidence of systemic involvement |
| Amyloidosis associated with aging, especially in the heart and the brain |
| Amyloidosis associated with long-term hemodialysis |
| Amyloidosis of endocrine tissues (e.g., precalcitonin in medullary carcinoma of the thyroid gland) |

AL, amyloid-light chain type; AA, protein A; AF, amyloid fibril.

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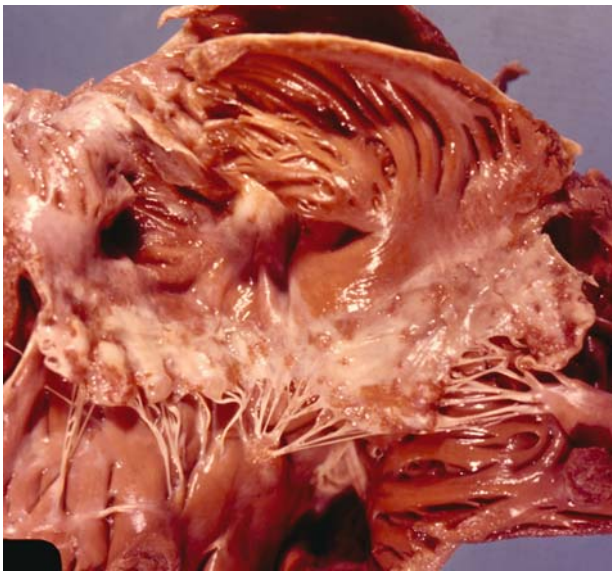

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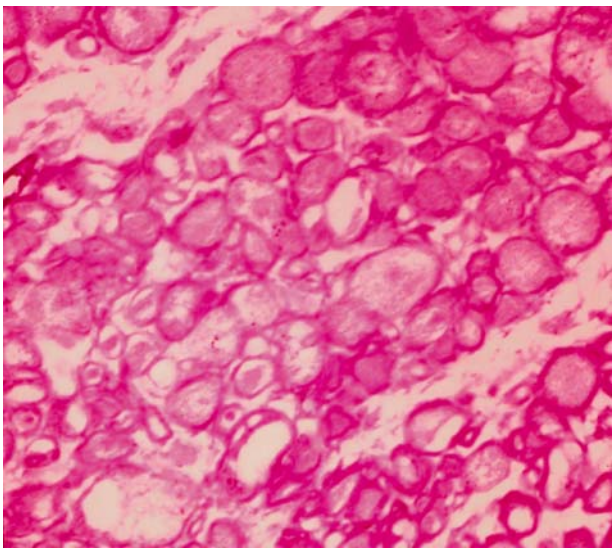

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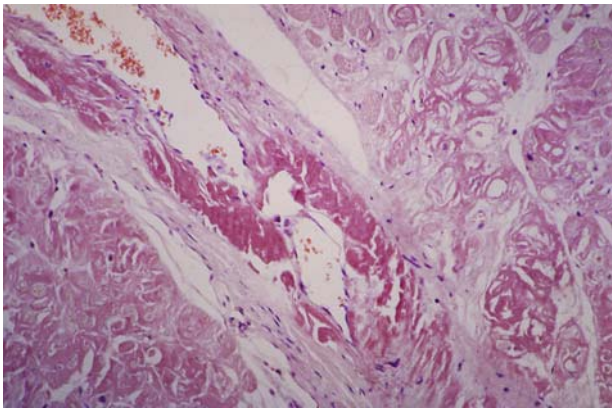

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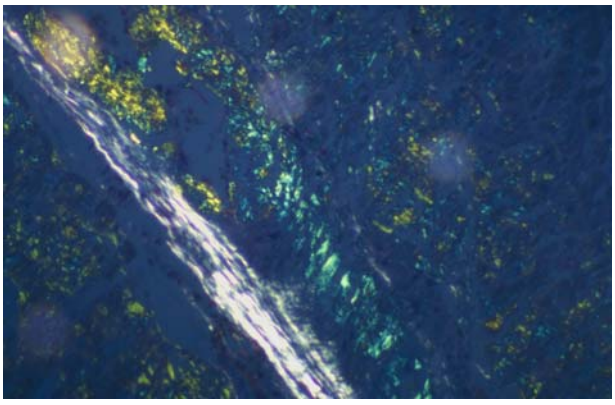

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**FIGURE 57.10.** (A) The heart in amyloid disease. There is usually ventricular hypertrophy without obvious dilatation. (B) Cardiac amyloidosis. Gross photograph of opened right heart showing tan and white deposits of amyloid in the mural and valvular endocardium. (C) Photomicrograph (high magnification) of myocardium stained with crystal violet showing rings of amyloid deposited around cardiac muscle cells (cut in cross-section). The amyloid deposits impair oxygenation of the myocytes and produce stiffness to the myocardium. (D) Photomicrograph (high magnification) of myocardium stained with Congo red showing extensive amyloid deposition in an intramural coronary artery and replacing cardiac muscle cells. (E) Photomicrograph (high magnification) of myocardium stained with Congo red and photographed under polarized light showing the typical apple green birefringence of the amyloid deposits.

reaction may be negative, but amyloid stains apple green with Congo red under polarized light and gives a metachromatic reaction to methyl violet. Staining techniques and light microscopy may occasionally be negative in tissue from endomyocardial biopsy samples, but the use of electron microscopy will show the characteristic irregularly arranged deposition of protein.

The gross pathology of the heart shows thickened, firm, rubbery ventricular muscle (Fig. 57.10), with atrial enlargement and sometimes thrombi in the appendages. The ven-

tricular septum can be disproportionately hypertrophied and the papillary muscles exaggerated, resembling HCM. Amyloid deposits are found between the myocardial fibers and papillary muscles, as well as in surrounding blood vessels, which may be compressed. Endocardial and atrial involvement can occur. The valves may be thickened, and focal pericardial deposits of amyloid tissue can also be found. Amyloid deposits are not infrequently detected in the conducting tissue. The pathologic processes account for the common triad of angina, heart failure, and arrhythmia.

When present, the stiff, poorly compliant ventricular muscle and the endocardial involvement account for the restrictive features of the disease. These are discussed later.

## Clinical Recognition

Amyloid heart disease is more common in men than women and is rare before the age of 30 years.[38] Symptoms include cardiac pain, dyspnea, and swelling of the legs and abdomen due to heart failure, with palpitations or syncope due to tachyarrhythmias or bradyarrhythmias. Heart failure is often due to impairment of both systolic and diastolic function, although it may also be caused by selective systolic or diastolic dysfunction.[39] Orthostatic hypotension is common as a result of autonomic, adrenal, or cardiac infiltration.

## Physical Examination

On examination, the patient usually looks ill and tired and may have lost weight. A trace of icterus may be present. When heart failure is severe, the jugular venous pressure is increased, showing the characteristic tall A and V waves and sharp *x* and *y* descents unless there is tricuspid regurgitation or atrial fibrillation. The heart may not appear to be obviously enlarged. There often is a systolic murmur caused by tricuspid or mitral regurgitation or a systolic murmur of aortic valve sclerosis secondary to amyloid infiltration of the aortic valve. A LV third sound is usually absent[38,40] because of a lack of sufficiently rapid LV filling, but a right ventricular third sound may be heard that increases in intensity with inspiration. Ascites, hepatomegaly, and edema of the legs is common.

Extracardiac involvement includes lymph gland enlargement, mononeuritis, and gastrointestinal symptoms. Occasionally, the patient presents with a rash due to infiltration of the skin. Periorbital hematomas are well recognized although rare. In the primary form of amyloidosis, the tongue is thickened and rubbery, and the mucous membranes may be erythematous and thickened, especially the conjunctiva (Fig. 57.11). Carpal tunnel syndrome may occur due to involvement of the palmar fascia.

### Chest Radiography

There usually is little or no cardiac enlargement, but changes of pulmonary venous congestion due to the high filling pressure in the left ventricle are marked. Pericardial effusion may increase apparent cardiomegaly. Occasional patients, however, present with a dilated and hypertrophied heart and a clinical picture with features of both dilated and restrictive cardiomyopathy.

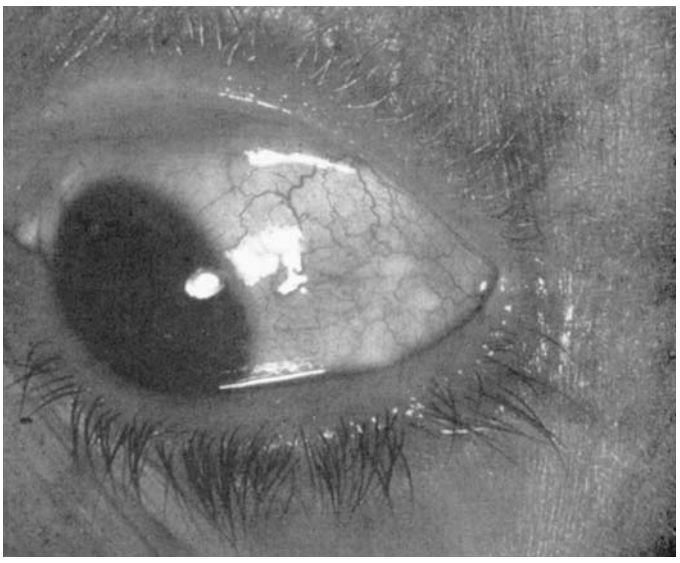

**FIGURE 57.11.** Erythematous and thickened palpebral conjunctiva in primary amyloid disease.

### Electrocardiography

There usually is a generalized low-voltage electrocardiogram resembling pericardial effusion due to the myocardial disease (Fig. 57.12). Sinus rhythm is usual, although atrial fibrillation may occur. There often are atrial and/or ventricular ectopic beats. Fascicular blocks are not uncommon. Various degrees of heart block may occur. T-wave inversion is frequent, and large Q waves may be seen; often a "pseudoinfarct" pattern may occur (Fig. 57.13).

### Echocardiography

M-mode studies reveal reduced size of the left ventricle, increased right ventricular wall thickness, and hypertrophy

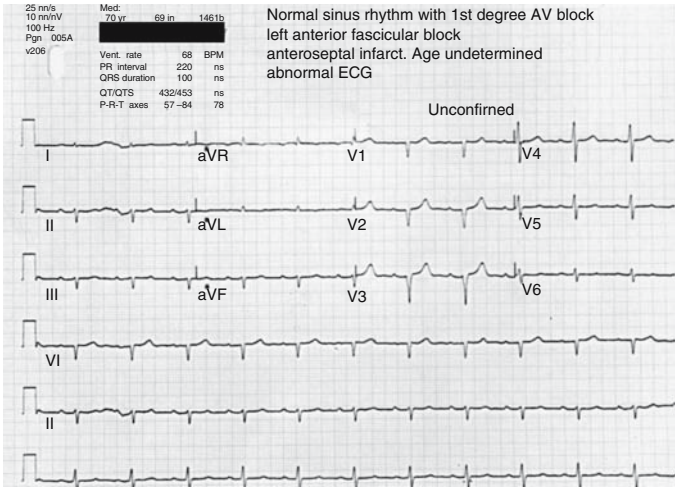


**FIGURE 57.12.** On electrocardiography, there often is low voltage due to myocardial disease, resembling pericardial effusion. Pseudoinfarct pattern, heart block, and atrial fibrillation are often present. Note the Q waves. (See the text for details.)

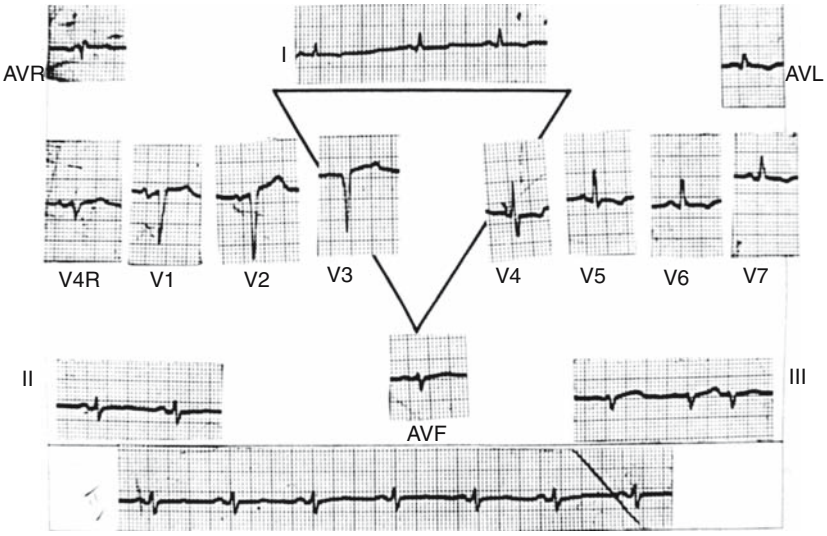


**FIGURE 57.13.** Twelve-lead electrocardiogram in cardiac amyloidosis shows precordial Q waves mimicking anterior myocardial infarction; this is referred to as a "pseudoinfarct" pattern.

of the ventricular septum and LV posterior wall. An important sign is thickening of the atrial septum.

Bright, sparkling echoes in the ventricular muscle merely reflect increased echo density and are not specific for amyloid disease. The mitral valve may be thickened.[41] In advanced disease, Doppler studies show a shortened deceleration time, normal ventricular isovolumic relaxation time, and a normal on increased peak E velocity, producing an increase in the E/A ratio.[37] Tissue Doppler echocardiography has been used to detect early impairment of systolic function even while fractional shortening remains normal.[42]

### Angiocardiography and Cardiac Catheterization

Ventriculography does not usually show dramatic abnormalities, but the end-diastolic volume is reduced and the internal aspect of the ventricles appears "shaggy." Mitral regurgitation may be seen. The major coronary arteries are normal.

The hemodynamics reflect the restrictive phenomena caused by the splinting effect of the amyloid infiltration on the heart muscle. Stroke and minute volume are reduced. The diastolic pressures in both ventricles are substantially increased but more so in the left than in the right ventricle. The characteristic dip-and-plateau pattern is modified; there is a slow rise from early diastolic pressure to end-diastolic pressure because filling is slow throughout diastole, and the normal early rapid filling phase seen in constrictive pericarditis and EMF is not present.[41] Pressure-volume curves show higher pressures at lower LV volumes than normal (i.e., a reduced compliance) (Fig. 57.14).

### Biopsy Studies

Biopsy studies of rectal and gingival tissues may reveal amyloid deposits when the disease is generalized, but cardiac biopsy is necessary to prove cardiac involvement unless a combination of clinical, hemodynamic, and echocardiographic data is sufficient for secure diagnosis. The presence of amyloid in other tissues does not guarantee its presence in the heart. Even though there is no specific treatment for amyloid disease, a tissue diagnosis is important to rule out conditions that are treatable (see later). Electron microscopic examination is helpful in the detection of amyloid deposits with certainty.

### Rapid-Speed Computed Tomography and Magnetic Resonance Imaging

Computed tomography scans suggest amyloid when diffuse ventricular thickening is associated with radiographic myocardial density lower than that when myocardial hypertrophy exists alone.[43] The main value of CT is to distinguish RCM and amyloidosis with normal pericardial structure from constrictive pericarditis. Magnetic resonance imaging provides more detail of myocardial and pericardial structure than CT, but experience is limited.

### Radionuclide Studies

Scintigraphy with technetium-99m ($^{99m}$Tc)-pyrophosphate or with an antibody directed against cardiac myosin shows

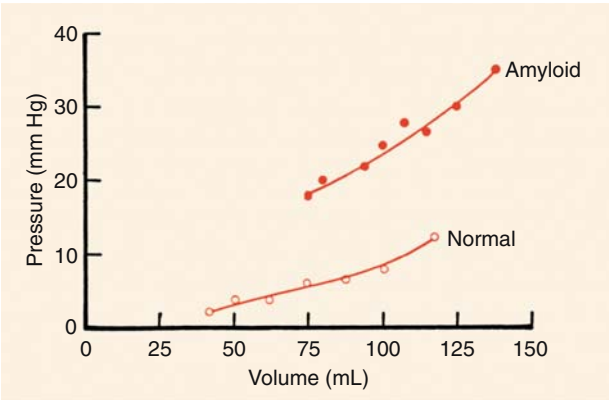


**FIGURE 57.14.** Pressure-volume curves in the left ventricle in diastole in a patient with amyloid disease and in a control subject with chest pain but normal coronary arteries. There is much greater pressure for an equivalent volume in the patient with amyloid disease than in the normal subject, reflecting the increased stiffness in the left ventricle in the former.

extensive uptake in the myocardium in severe cases, but false-negative results can occur.[44,45]

## Differential Diagnosis

The principal disorders that warrant consideration are HCM, EMF, constrictive pericarditis, and coronary artery disease. When heart failure exists, both HCM and amyloid disease may closely resemble each other, although in the absence of heart failure, there is usually no difficulty in distinguishing the two. With failure in HCM and amyloid heart disease, there is a high jugular venous pressure with LV enlargement. Systolic murmurs of AV valvular regurgitation are common, but a LV third sound is usually absent in the restrictive form of amyloid heart disease. The characteristic late onset of the systolic murmur in HCM may be lost in heart failure, and if atrial fibrillation is present, there will be no fourth heart sound.

Echocardiographic results in amyloid heart disease may closely resemble those in HCM, showing an immobile hypertrophic ventricular septum and asymmetric septal hypertrophy.[46] Bright, sparkling echoes may be seen in both HCM and amyloid disease. Definite differentiation in life may be impossible without an endomyocardial biopsy. The finding of periorbital hematomas or evidence of amyloid elsewhere in the body may clarify the situation. Hypertrophic cardiomyopathy and amyloid disease may coexist, but this combination is very unusual.

Clinical differentiation of amyloidosis of the heart from EMF rests mainly on the absence of the LV third sound in amyloid disease and the characteristic echocardiographic and angiographic features of EMF aided by electron microscopic endomyocardial biopsy findings. In constrictive pericarditis, the absence of evidence of systolic myocardial disorder and of significant LV hypertrophy are important differential points.

A history of angina and the presence of Q waves ("pseudoinfarct" pattern) on the electrocardiogram occur in some patients with amyloid heart disease.

Amyloidosis of the heart can be suspected on the basis of significantly elevated jugular venous pressure, with the characteristic M-shaped pattern suggesting a degree of myocardial stiffness in excess of that found in coronary artery disease. Absolute confirmation often depends on myocardial biopsy.

Cardiac amyloidosis in familial Mediterranean fever should not cause difficulty because of the association of episodes of abdominal pain, fever, pleurisy, and arthritis occurring in Levantine people on a genetic basis. This form of amyloid deposition is the only one susceptible to medical therapy; the administration of colchicine appears to delay the progression of amyloid deposition.

The most important factor in the diagnosis of amyloid heart disease is to keep the possibility in mind, particularly when the combination of a high jugular venous pressure with a restrictive pattern and unimpressive cardiomegaly is seen. Observation of this combination should result in an initial provisional diagnosis of diastolic heart disease, and steps should then be taken to narrow the field to the appropriate condition.

## Treatment

Apart from the amyloidosis associated with familial Mediterranean fever, there is no effective drug therapy. Amyloidosis associated with chronic inflammatory conditions might be stabilized with effective therapy and cure for the chronic inflammatory condition. In patients with primary amyloidosis and extensive cardiac involvement, heart failure is usually progressive, with death occurring within 14 months. Transient improvement in symptoms may be associated with the addition of a diuretic and salt restriction and, in some patients, the judicious use of cardiac glycosides. Cardiac glycosides should be used with caution in amyloidosis because some patients seem to be extremely sensitive to their effects. Furthermore, when the problem is primarily diastolic dysfunction, it is difficult to imagine that cardiac glycosides would be particularly useful. In addition, some clinicians believe the patient with cardiac amyloidosis to be extremely sensitive to cardiac glycosides.

### Chemotherapy and Stem Cell Replacement in the Treatment of Amyloidosis

Comenzo and colleagues[47] have evaluated the potential efficacy of dose-intensive melphalan with blood stem cell support in the treatment of AL amyloidosis. Their rationale for using such therapy is that autologous stem cell transplantation is effective therapy for multiple myeloma. They have treated patients with adequate cardiac, pulmonary, and renal function with stem cells mobilized with granulocyte colony-stimulating factor. In this study, blood stem cells were mobilized with granulocyte colony-stimulating factor, collected and evaluated as described previously.[48] Dose-intensive melphalan was administered intravenously over several days before the infusion of stem cells. Stem cells were infused 72 hours later. Patients received antibody prophylaxis with an oral quinolone and acyclovir beginning on day 3 after stem cell infusion. Hematopoietic activity was determined by daily blood counts and defined as days from stem cell infusion to recovery of neutrophils. Overall recovery and survival by category or organ involvement is shown in Figure 57.15. The patients were treated with dose-intensive intravenous melphalan ($200\,mg/m^2$). These authors enrolled 25 patients (median age 48 years, range 29–60 years), all of whom had biopsy-proven amyloidosis with clonal plasma cell disorders. Twenty-two patients (88%) were Southwest Oncology Group performance status 1 or 2 within a year of diagnosis and 16 (64%) had received no prior therapy. Amyloid-related organ involvement included cardiac ($n = 8$), renal ($n = 7$), hepatic ($n = 6$), neuropathic ($n = 3$), and lymphatic ($n = 1$). Fifteen patients had one or two organ systems involved, and 10 had three or more organ systems with amyloid deposition and dysfunction. With a median follow-up of 24 months and a range of 12 to 38 months, 17 of 25 patients (68%) were alive, and the median survival had not yet been reached. Thirteen of 21 patients (62%) evaluated 3 months posttransplant had complete response of their clonal plasma cell disorders. Two thirds of the surviving patients had experienced improvement in amyloid-related organ involvement in all systems, and four of 17 had stable disease. The improvement in the median performance status of the 17 survivors at follow-up was statistically significant versus baseline. Among these

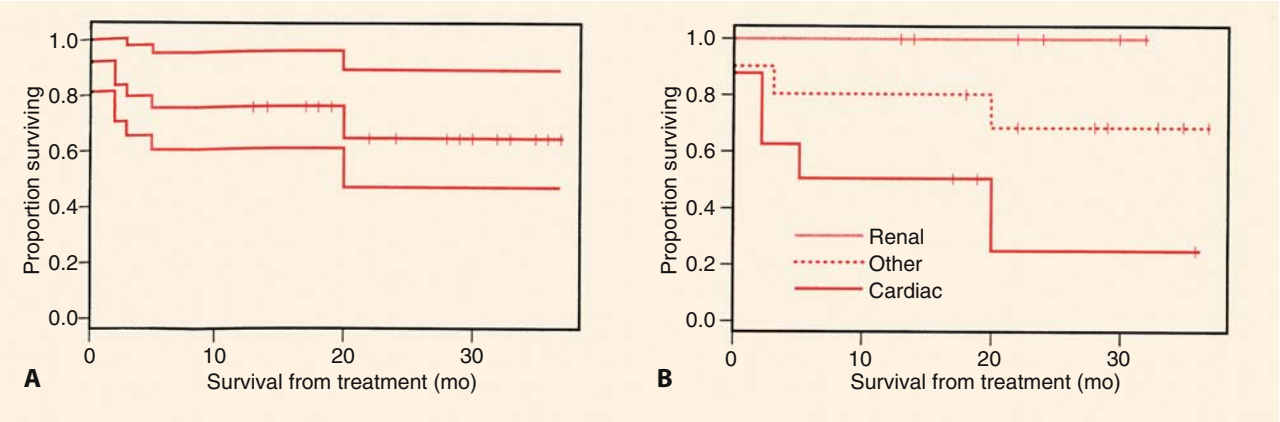


**FIGURE 57.15.** Overall survival and survival by category or organ involvement. With median follow-up of 24 months (12 to 38), 17 of 25 patients (68%) survived, and the median survival has not yet been reached. (A) A Kaplan-Meier plot shows the 95% confidence interval (CI) (proportional survival 0.65, 95% CI 0.48 to 0.88). (B) Survival by predominant organ involvement. Total and mean times of follow-up for the three cohorts are 149 and 21.3 months (renal, $n = 7$, 225 and 22.5 months (other, $n = 10$), and 101 and 12.6 months (cardiac, $n = 8$). Patients without predominant cardiac involvement had better overall survival than cardiac patients (one-tailed Fisher's exact test, $p < .05$).

patients, the negative prognostic factors for overall survival included amyloid involvement of more than two major organ systems and predominantly cardiac involvement. Three patients had relapses of the clonal plasma cell disorders at 12 and 24 months. These findings suggest that dose-intensive therapy should be considered as a treatment for patients with light chain amyloidosis who meet functional criteria for autologous transplantation of their stem cells.

## Hemochromatosis

### Pathophysiology

Hemochromatosis is associated with excessive deposition of iron in the heart and other organs, including the liver, pancreas, and skin. It occurs as either a familial or an idiopathic disorder. However, it is also found in association with defects in hemoglobin synthesis, with chronic liver disease, and with excessive oral or parenteral intake of iron over many years. The severity of myocardial dysfunction varies widely in patients with hemochromatosis, but it is associated with diastolic dysfunction and RCM, although some patients also have evidence of important systolic dysfunction.

Myocardial iron deposits are found within the sarcoplasmic reticulum and are primarily located in the subepicardial region. They are also present in the subendocardial region and are least common in the midmyocardium. The iron deposition is usually more prominent in ventricular than atrial myocardium (Figs. 57.16 and 57.17), and it may involve the cardiac conduction system. Patients with cardiac deposition of excessive iron usually have heart failure. Patients who receive more than 100 blood transfusions without associated iron loss with bleeding are at risk for the development of cardiac hemochromatosis.

### Clinical Recognition

Some patients demonstrate the classic clinical signs of "bronze diabetes," including a grayish discoloration of the skin, the development of carbohydrate intolerance, the development of liver disease with prominent liver function abnormalities progressing to cirrhosis, and heart failure. However, in individual patients, one or more of the organ dysfunctions may be more prominent, and in some patients, only heart failure is evident initially. One makes a diagnosis of hemochromatosis by finding elevated plasma iron levels in the

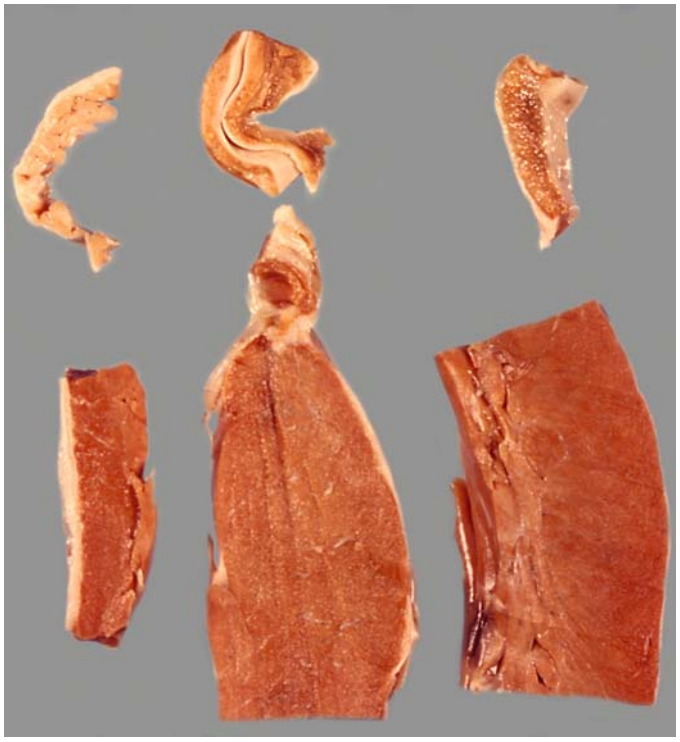

**FIGURE 57.16.** Cardiac hemochromatosis. Note the dark brown coloration of the myocardium of the right and left ventricular myocardium and interventricular septum indicating extensive myocardial iron deposition and the less severe involvement of the atrial myocardium.

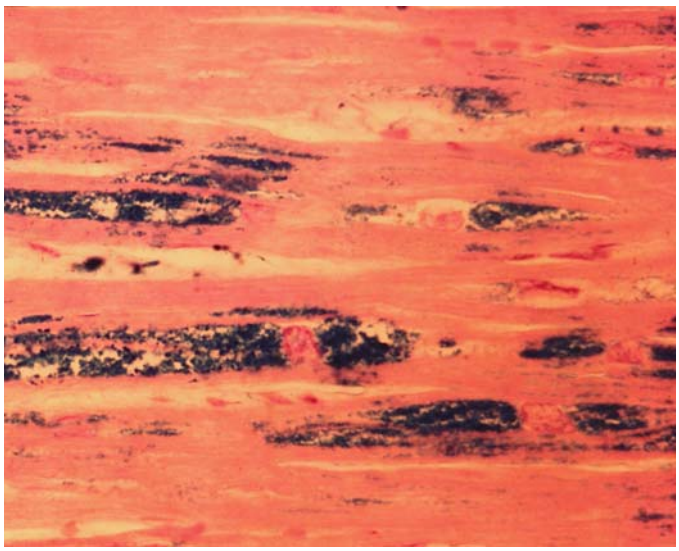

**FIGURE 57.17.** Photomicrograph (high magnification) of myocardium stained with Prussian blue showing extensive accumulation of iron deposits in cardiac muscle cells.

range of 180 to 300 mg/dL and markedly elevated values for saturation of transferrin (the iron-binding protein) to 80% to 100% (normal, 22% to 46%). Urine iron concentrations are often elevated and in the range of 9 to 23 mg/24-hour samples, with the normal values being 2 mg or less. Liver iron concentrations are also increased into the range of 600 to 1800 g/100 mg dry weight, with normal values being 30 to 140 g/100 mg dry weight.

Hemochromatosis is a disease of men and of postmenopausal women because the woman who is menstruating has an obligate source of iron loss. However, women who have ceased menstruation or who have never menstruated are also at risk for the disease.

The diagnosis is usually made through a biopsy of the skin, liver, or heart, and the demonstration of excessive iron content is made through direct measurement and the use of the Prussian blue stain, which demonstrates the massive iron overload (Fig. 57.16).

### Radiography

As is true of other forms of restrictive heart muscle disease, hemochromatosis should be suspected when there is clinical evidence of heart failure with a small or normal-sized heart in a man or in a woman who is not menstruating and who may also have carbohydrate intolerance, liver function abnormalities, or a change in skin color.

### Electrocardiography

Low voltage on the electrocardiogram is found in patients with restrictive cardiac muscle diseases based on infiltrative cardiomyopathies, including hemochromatosis. Low voltage is defined as less than 5 mm of voltage in the frontal QRS leads (i.e., leads I-aVF). There are many other causes of low voltage on the electrocardiogram, including obesity, emphysema, hypothyroidism, extensive coronary artery disease, and pericardial and pleural effusions, but RCM should always be considered.

### Echocardiography

As is true for other RCMs, one expects to find evidence of diastolic dysfunction as reflected in delayed LV filling and diastolic relaxation of the left or right ventricle, or both. The ventricles may be hypertrophied, and regional areas of hypokinesis may be found in the patient with prominent systolic dysfunction.

### Angiocardiography

Typically, one may find elevated LV and LA filling pressures in association with small or normal end-diastolic volumes. In the patient with systolic dysfunction as well, the ejection fraction will be reduced, segmental or global hypokinesis will be found, and the end-systolic volume may be elevated.

### Endomyocardial Biopsy

The findings from the endomyocardial biopsy should be diagnostic and should demonstrate evidence of excessive iron deposition in the heart both through direct measurement and with Prussian blue staining.

### Computed Tomography Scanning and Magnetic Resonance Imaging

Experience with these techniques in patients with hemochromatosis is limited to date. However, one would expect to find abnormalities similar to those found in other patients with RCMs. If tissue characterization becomes possible with either of these techniques in the future, it may be possible to identify specific abnormalities in the patient with myocardial iron overload that allow it to be distinguished. Both techniques should help in the differentiation of constrictive pericarditis from restrictive myocardial disease by demonstrating the absence of a thickened pericardium.

### Radionuclide Studies

These are not of specific use in patients with cardiac hemochromatosis.

## Treatment

When detected reasonably early, the myocardial physiologic abnormalities and some of the liver function abnormalities can be reversed with repeated phlebotomy, beginning on a once-a-week basis and progressing to once monthly after a period of several weeks to months. Clinical evidence of heart failure and severe abnormalities of liver function may disappear with the use of this therapy. The value of iron chelators, such as desferrioxamine, has also been suggested, and they represent the only alternative for the severely anemic patient who may have hemochromatosis or hemosiderosis on the basis of a very large number of blood transfusions as a therapy for chronic anemia. This compound has a high affinity for iron, it is administered parenterally, and most of the chelated iron is excreted in the urine within 4 hours of the injection. The addition of oral ascorbic acid increases iron excretion in association with the administration of an iron chelator. However, the administration of ascorbic acid not only makes

more cellular iron available for chelation but also liberates free intracellular iron, which may cause the generation of free oxygen radicals and lead to myocardial damage. Therefore, one has to worry about induction of myocardial injury by the simultaneous administration of an iron chelator and ascorbic acid. Perhaps, this can be avoided by the administration of ascorbate after the patient has been started on chelation therapy. The patient with myocardial hemochromatosis may develop heart failure, conduction disturbances, and life-threatening or fatal arrhythmias.

## Radiation-Induced Heart Disease

### Pathophysiology

Ionizing radiation as administered during radiotherapy may lead to myocardial fibrosis and restrictive myocardial disease. It may also cause pericardial injury with pericardial effusion, tamponade, or constriction. The coronary arteries and myocardial valves may also be injured by excessive radiation, leading to coronary artery fibrosis and valvular abnormalities. Patients receiving radiotherapy to the mediastinum as part of the treatment for lung cancer, lymphoma, or other mediastinal neoplasm are at particular risk, especially when more than 1800 rad is delivered in the region of the heart.

Radiation damage may also occur in small microvessels, which leads to capillary rupture and microthrombi. This may cause myocardial ischemia and lead to additional myocardial fibrosis.

Myocardial, coronary artery, and valvular heart damage occur less commonly after radiation than damage to the pericardium. With radiation therapy, some patients complain of symptoms of acute pericarditis. Transient and asymptomatic depression of LV function may be found early after radiation therapy. The development of myocardial fibrosis, injury to coronary arteries or heart valves, and the development of constrictive pericarditis may become clinically apparent months or years after the initial exposure.

### Clinical Recognition

One should be aware of the risks of pericardial, myocardial, coronary artery, and valvular heart damage in patients who receive radiotherapy or other forms of ionizing radiation in the heart region in the amounts mentioned. Every effort should be made to protect the heart when radiotherapy is used to treat a mediastinal neoplasm. Clinical recognition follows the understanding of the pathophysiology of the injury produced, and the acute or more chronic development of heart enlargement, pericardial effusion, restrictive myocardial or pericardial disease, angina, or new heart murmurs provides evidence for an injurious effect of irradiation.

#### Imaging Studies

These studies are useful in patients with radiation-induced myocardial injury to demonstrate the presence of diastolic dysfunction associated with myocardial fibrosis, valvular regurgitation or obstruction, a pericardial effusion, or constrictive pericarditis.

#### Endomyocardial Biopsy

In the months to years after the administration of ionizing radiation, a demonstration of myocardial fibrosis for patients receiving mediastinal radiation in the range of 1800 to 2000 rad or more could provide evidence of a radiation-induced myocardial abnormality.

### Differential Diagnosis

For the restrictive myocardial diseases, it is the other RCMs, including amyloidosis, hemochromatosis, endomyocardial fibroelastosis, and the heart failure associated with each of these abnormalities, that must be considered.

### Treatment

The best treatment is to do everything possible to prevent radiation-induced injury to the heart by limiting the amount of radiation the heart receives.

## Summary

The major abnormality of the heart with restrictive cardiomyopathy is diastolic dysfunction. There is a reduced rate and extent of relaxation of the heart and increased filling pressure in the LV and LA being transmitted back into the lungs, leading to dyspnea, palpitations, easy fatigability, and peripheral edema. Eosinophilic endomyocardial fibrosis, amyloidosis, hypertrophic cardiomyopathy, hemochromatosis, and injury to the heart from ionizing radiation are the usual causes. Hemochromatosis can be markedly improved by frequent phlebotomy. The major differential diagnosis is with constrictive pericarditis, and the RCMs and constrictive pericarditis can usually be distinguished by MRI or rapid speed CT measurement of pericardial thickness.

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