The Cardiomyopathies

10

P. Connor Johnson
G. William Dec
Leonard S. Lilly

Chapter Outline

Cardiomyopathies are a diverse set of heart muscle disorders that cause mechanical and/or electrical dysfunction of the myocardium. Excluded from the definition of this group of diseases is heart muscle impairment resulting from other specific cardiovascular disorders such as hypertension, valvular abnormalities, or congenital heart disease. Cardiomyopathies often result in inappropriate ventricular hypertrophy or dilatation, and progressive heart failure and cardiovascular death are common end manifestations. These conditions can involve the heart alone or may be a component of a systemic syndrome.

Cardiomyopathies can be classified into three main types based on the anatomic appearance and abnormal physiology of the left ventricle (LV) (Fig. 10-1). **Dilated** cardiomyopathy (DCM) is characterized by ventricular chamber enlargement with impaired systolic contractile function; **hypertrophic** cardiomyopathy (HCM), by an abnormally thickened ventricular wall with abnormal diastolic relaxation but usually intact systolic function; and **restrictive** cardiomyopathy, by an abnormally stiffened myocardium (because of fibrosis or an infiltrative process) leading to impaired diastolic relaxation, but systolic contractile function is typically normal or near normal.

DILATED CARDIOMYOPATHY

Etiology

Myocyte damage and cardiac enlargement in DCM result from a wide spectrum of genetic, inflammatory, toxic, and metabolic causes (Table 10-1). Although many cases are currently classified as idiopathic (i.e., the cause is undetermined), examples of defined conditions associated with DCM include viral myocarditis, chronic excessive alcohol

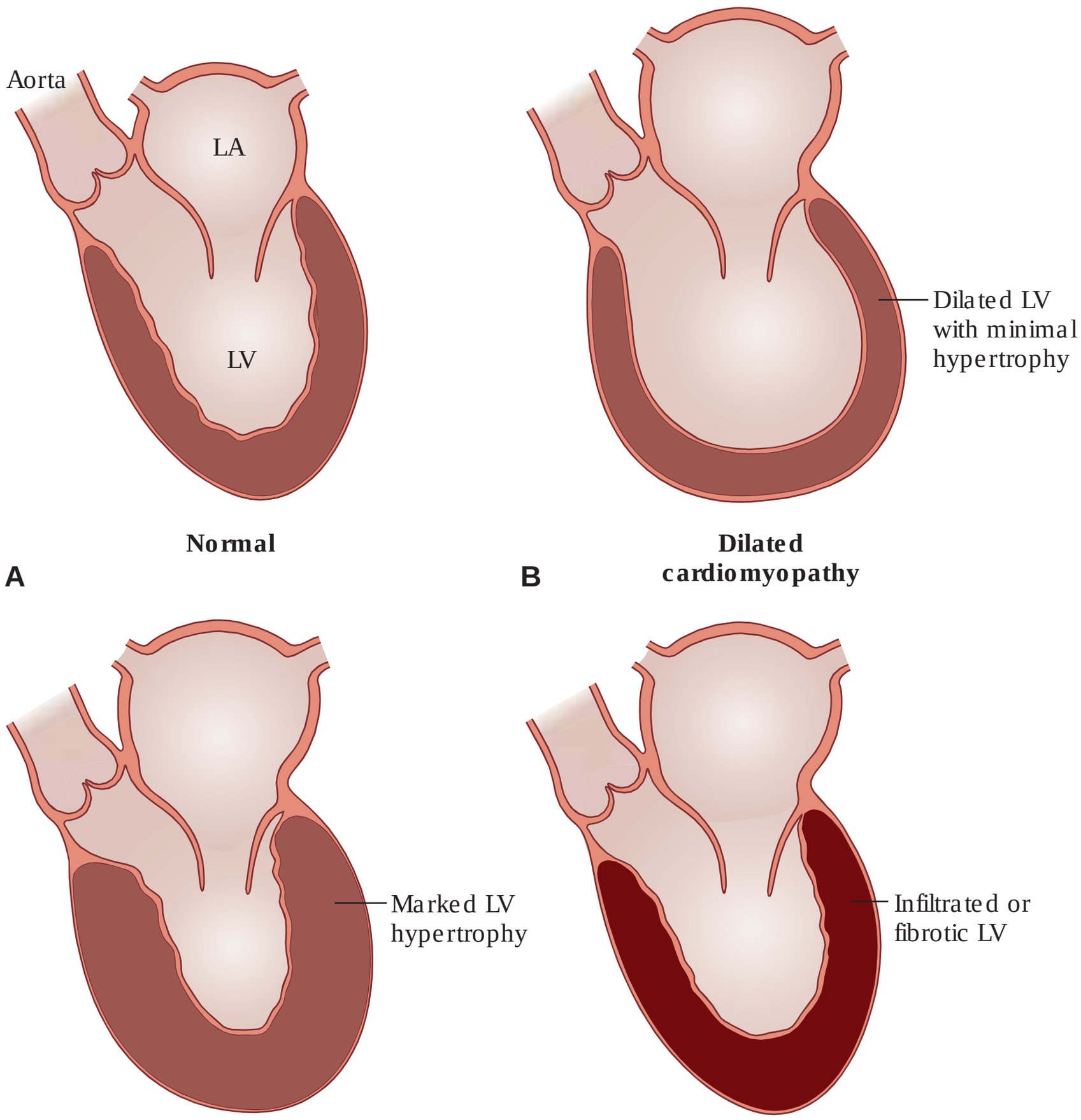


FIGURE 10-1. Anatomic appearance of the cardiomyopathies (CMPs). A. Normal heart demonstrating left ventricle (LV) and left atrium (LA). **B.** Dilated CMP is characterized by ventricular enlargement with only mildly increased thickness. **C.** Hypertrophic CMP demonstrates marked ventricular hypertrophy, either asymmetrically, or symmetrically (as drawn here). **D.** Restrictive CMP is caused by infiltration or fibrosis of the ventricles, usually without chamber enlargement. LA enlargement is common to all three types of CMP.

TABLE 10-1 Examples of Dilated Cardiomyopathies

Idiopathic
Familial (genetic)
Inflammatory
Infectious (especially viral)
Noninfectious
Connective tissue diseases
Peripartum cardiomyopathy
Sarcoidosis
Toxic
Chronic alcohol ingestion
Chemotherapeutic agents (e.g., doxorubicin, trastuzumab)
Metabolic
Hypothyroidism
Chronic hypocalcemia or hypophosphatemia
Neuromuscular
Muscular or myotonic dystrophy

ingestion, the peripartum state, specif c gene mutations, and exposure to potentially cardiotoxic antineoplastic agents, such as doxorubicin.

Acute viral myocarditis generally afflicts young, previously healthy people. Common responsible infecting organisms include coxsackievirus group B, parvovirus B19, and adenovirus, among many others. Viral myocarditis is usually a self-limited illness with full recovery, but for unknown reasons, some patients progress to DCM. It is hypothesized that myocardial destruction and f brosis result from immune-mediated injury triggered by viral constituents. Nonetheless, immunosuppressive drugs have not been shown to improve the prognosis of this condition. Transvenous ventricular biopsy during acute myocarditis may demonstrate active inflammation, but specif c viral genomic sequences have been demonstrated in only a minority of patients.

DCM develops in a small number of people who consume alcoholic beverages excessively and chronically. Although the pathogenesis of the condition is unknown, ethanol is thought to impair cellular function by impacting mitochondrial oxidative function, myof lament protein synthesis, cytosolic calcium levels, and myocyte apoptosis. While its clinical presentation and histologic features are similar to those of other dilated cardiomyopathies, alcoholic cardiomyopathy is important to identify because it is potentially reversible; cessation of ethanol consumption can lead to dramatic recovery of ventricular function.

Peripartum cardiomyopathy is a form of DCM that presents with heart failure symptoms between the last month of pregnancy and up to 6 months postpartum. Risk factors include older maternal age, being African American, and having multiple pregnancies. A unifying etiology of this condition has not yet been identif ed. Ventricular function returns to normal in approximately 50% of affected women in the months following pregnancy, but recurrences of DCM with subsequent pregnancies have been reported.

Other potentially reversible causes of DCM include toxic drug exposures, metabolic abnormalities (such as hypothyroidism), and certain inflammatory etiologies, including sarcoidosis and connective tissue diseases.

Several familial forms of DCM have been identif ed and are believed to be responsible for 20% to 30% of what were once classif ed as idiopathic DCM. Autosomal dominant, autosomal recessive, X-linked, and mitochondrial patterns of inheritance have been described, leading to defects in contractile force generation, force transmission, energy production, and myocyte viability. Identif ed mutations occur in genes that code for cardiac cytoskeletal, myof brillar, and nuclear membrane proteins (Table 10-2).

TABLE 10-2 Familial Forms of Dilated and Hypertrophic Cardiomyopathies

Protein	Mutations Identif ed in DCM	Mutations Identif ed in HCM
Cytoskeletal proteins		
Desmin	√	
Dystrophin	√	
Myosin-binding protein C	√	√
Sarcoglycans	√	
Titin	√	√
Myof brillar proteins		
β-Myosin heavy chain	√	√
Cardiac troponin T	√	√
Cardiac troponin I	√	√
Cardiac troponin C	√	√
α-Tropomyosin	√	√
Essential myosin light chain		√
Cardiac actin	√	√
Nuclear membrane protein		
Lamin A/C	√	

Pathology

Marked enlargement of all four cardiac chambers is typical of DCM (Fig. 10-2), although sometimes the disease is limited to the left or right side of the heart. The thickness of the ventricular walls may be increased, but chamber dilatation is out of proportion to any concentric hypertrophy. Microscopically, there is evidence of myocyte degeneration with irregular hypertrophy and atrophy of myofibers. Interstitial and perivascular fibrosis is often extensive.

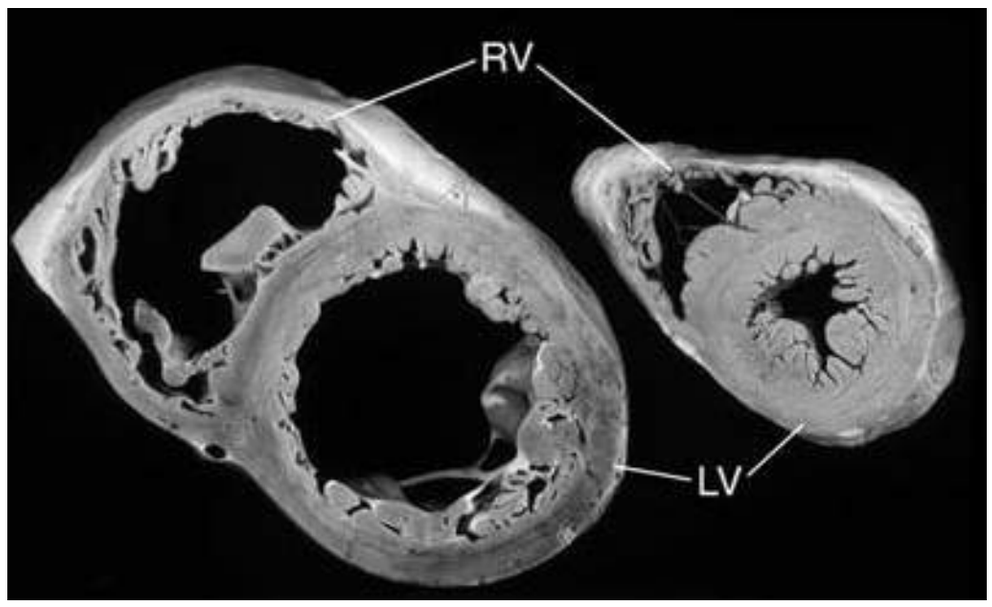


FIGURE 10-2. Transverse sections of a normal heart (right) and a heart from a patient with dilated cardiomyopathy (DCM). In the DCM specimen, there is biventricular dilatation without a proportional increase in wall thickness. LV, left ventricle; RV, right ventricle. (Modified from Emmanouilides GC, ed. Moss and Adams' Heart Disease in Infants, Children, and Adolescents. 5th ed. Baltimore, MD: Lippincott Williams & Wilkins; 1995:86.)

Pathophysiology

The hallmark of DCM is ventricular dilatation with decreased contractile function (Fig. 10-3). Most often in DCM, both ventricles are impaired, but sometimes dysfunction is limited to the LV and even less commonly to the right ventricle (RV).

As ventricular stroke volume and cardiac output decline because of impaired myocyte contractility, two compensatory effects are activated: (1) the Frank–Starling mechanism, in which the elevated ventricular diastolic volume increases the stretch of the myofibers, thereby increasing the subsequent stroke volume; and (2) neurohormonal activation, initially mediated by the sympathetic nervous system (see Chapter 9). The latter contributes to an increased heart rate and contractility, which help to buffer the fall in cardiac output. These compensations may render the patient asymptomatic during the early stages of ventricular dysfunction; however, as progressive myocyte degeneration and volume overload ensue, clinical symptoms of heart failure develop.

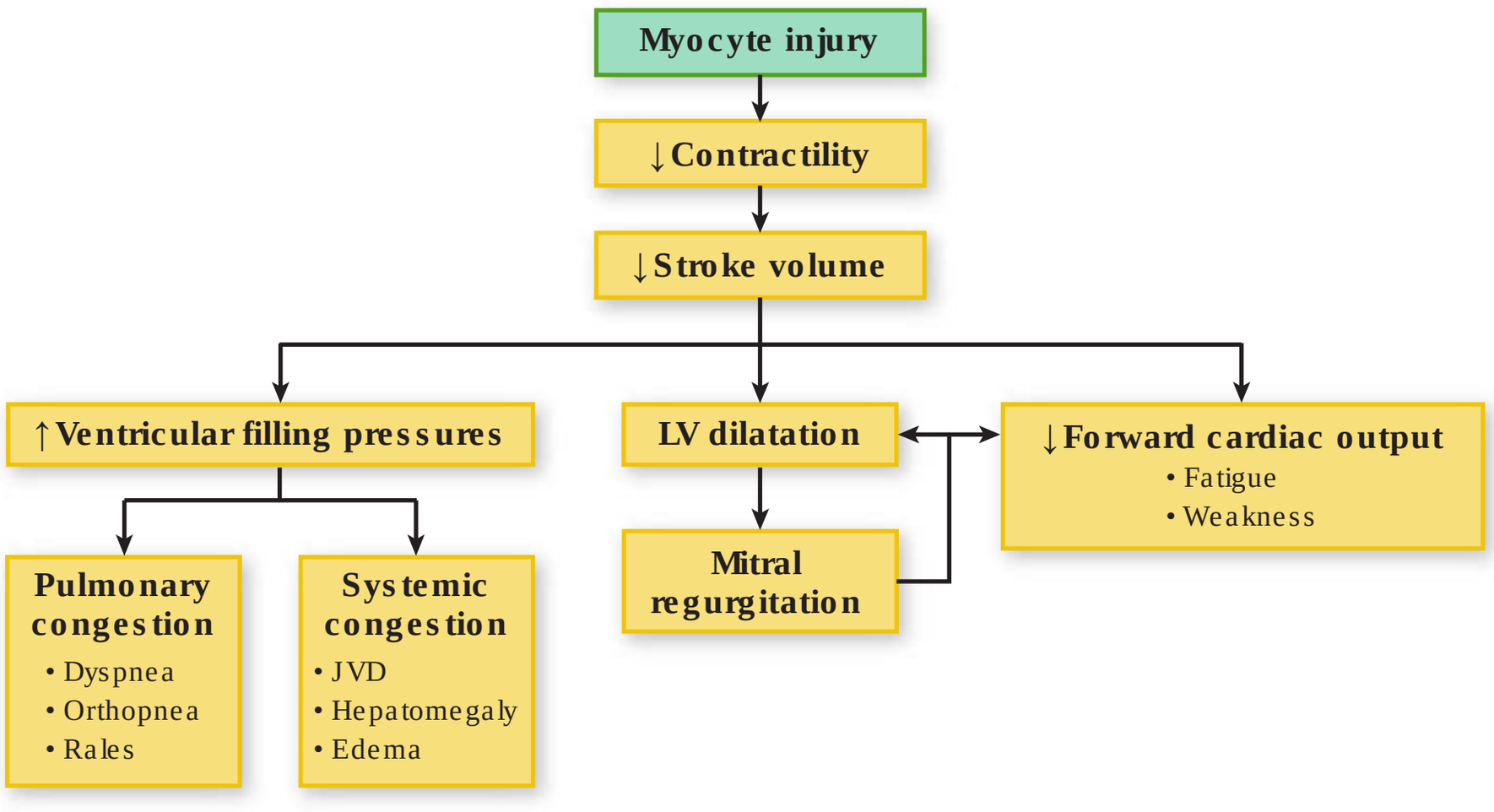


FIGURE 10-3. Pathophysiology of dilated cardiomyopathy. The reduced ventricular stroke volume results in decreased forward cardiac output and increased ventricular filling pressures. The listed clinical manifestations follow. JVD, jugular venous distention.

With a persistent reduction of cardiac output, the decline in renal blood flow prompts the kidneys to increase secretion of renin. This activation of the renin–angiotensin–aldosterone axis increases peripheral vascular resistance (mediated through angiotensin II) and intravascular volume (because of increased aldosterone). As described in Chapter 9, these effects are also initially helpful in buffering the fall in cardiac output.

Ultimately, however, the "compensatory" effects of neurohormonal activation prove detrimental. Arteriolar vasoconstriction and increased systemic resistance render it more difficult for the LV to eject blood in the forward direction, and the rise in intravascular volume further burdens the ventricles, resulting in pulmonary and systemic congestion. In addition, chronically elevated levels of angiotensin II and aldosterone directly contribute to pathologic myocardial remodeling and fibrosis.

As the cardiomyopathic process causes the ventricles to enlarge over time, the mitral and tricuspid valves may fail to coapt properly in systole, and valvular regurgitation ensues. This regurgitation has three detrimental consequences: (1) excessive volume and pressure loads are placed on the atria, causing them to dilate, often leading to atrial fibrillation; (2) regurgitation of blood into the left atrium further decreases forward stroke volume into the aorta and systemic circulation; and (3) when the regurgitant volume returns to the LV during each diastole, an even greater volume load is presented to the dilated LV.

Clinical Findings

The clinical manifestations of DCM are those of congestive heart failure. The most common symptoms of low forward cardiac output include fatigue, light-headedness, and exertional dyspnea associated with decreased tissue perfusion. Pulmonary congestion results in dyspnea, orthopnea, and paroxysmal nocturnal dyspnea, whereas chronic systemic venous congestion causes ascites and peripheral edema. Because these symptoms may develop insidiously, the patient may complain only of recent weight gain (because of interstitial edema) and shortness of breath on exertion.

Physical Examination

Signs of decreased cardiac output are often present and include cool extremities (owing to peripheral vasoconstriction) and low arterial pressure. Pulmonary venous congestion results in auscultatory rales (crackles), and basilar chest dullness to percussion may be present because of pleural effusions. Cardiac examination shows an enlarged heart with leftward displacement of the apical impulse. On auscultation, a third heart sound (S3) is common as a sign of poor systolic function. The murmur of mitral valve regurgitation is often present as a result of the significant left ventricular dilatation (see Chapter 8). If right ventricular heart failure has developed, signs of systemic venous congestion may include jugular vein distention, hepatomegaly, ascites, and peripheral edema. Right ventricular enlargement and contractile dysfunction are often accompanied by the murmur of tricuspid valve regurgitation.

Diagnostic Studies

The chest radiograph shows an enlarged cardiac silhouette. If heart failure has developed, then pulmonary vascular redistribution, interstitial and alveolar edema, and pleural effusions are evident (see Fig. 3-5).

The electrocardiogram (ECG) usually demonstrates atrial and ventricular enlargement. Patchy fibrosis of the myofibers results in a variety of arrhythmias, most importantly atrial fibrillation and ventricular tachycardia. Conduction defects (left or right bundle branch block) are common. In addition, regions of dense myocardial fibrosis may produce localized Q waves, resembling the pattern of previous transmural myocardial infarction.

Echocardiography in DCM typically demonstrates enlargement of the affected ventricle(s) with little concentric hypertrophy, and global reduction of systolic ventricular function. Mitral and/or tricuspid regurgitation is frequently detected due to ventricular dilatation.

Cardiac catheterization or CT angiography is often performed to determine whether coexistent coronary artery disease is contributing to the impaired ventricular function. This is most useful diagnostically in patients who have symptoms of angina or evidence of prior myocardial infarction on the ECG. Typically, hemodynamic measurements show elevated right- and left-sided diastolic pressures and diminished cardiac output. A transvenous biopsy of the RV is sometimes performed in the catheterization laboratory, in an attempt to clarify the etiology of the cardiomyopathy.

Cardiac magnetic resonance imaging (MRI) (described in Chapter 3) is often helpful in the evaluation of DCM, particularly to assess for contributory myocardial inflammation (myocarditis).

Treatment

The goal of therapy in DCM is to promote reverse remodeling of dilated ventricles, enhance myocardial function, relieve symptoms, prevent complications, and improve long-term survival. Thus, in addition to treating any identified underlying cause of DCM, therapeutic considerations include those described in the following sections.

Medical Treatment of Heart Failure Symptoms

Approaches for the relief of vascular congestion and improvement in forward cardiac output are the same as standard therapies for heart failure (see Chapter 9). Initial therapy typically includes salt restriction and diuretics if volume overload is present, vasodilator therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB), and a β-blocker in hemodynamically stable patients. For patients with persistent symptoms, the addition of an aldosterone antagonist should be considered. These measures have been shown to improve symptoms and reduce mortality in patients with DCM.

Prevention and Treatment of Arrhythmias

Atrial and ventricular arrhythmias are common in advanced DCM, and approximately 40% of deaths in this condition result from ventricular tachycardia or fibrillation. It is important to maintain serum electrolytes (notably, potassium and magnesium) within their normal ranges, especially during diuretic therapy, to avoid provoking serious arrhythmias. Studies have shown that available antiarrhythmic drugs do not prevent death from ventricular arrhythmias in DCM. In fact, when used in patients with poor LV function, many antiarrhythmic drugs may worsen the rhythm disturbance. Amiodarone is the antiarrhythmic drug studied most extensively in patients with DCM. Whereas there is no convincing evidence that it reduces mortality from ventricular arrhythmias in DCM, it is the safest antiarrhythmic for treating atrial fibrillation and other supraventricular arrhythmias in this population. In contrast to antiarrhythmic drugs, the placement of an implantable cardioverter–defibrillator (ICD) does reduce arrhythmic deaths in patients with DCM. Therefore, based on large-scale randomized trials, an ICD is recommended for patients with chronic symptomatic DCM and at least moderately reduced systolic function (e.g., LV ejection fraction $\leq$35%), regardless of whether ventricular arrhythmias have been detected.

Many patients with DCM have electrical conduction abnormalities that contribute to dyssynchronous ventricular contraction and therefore reduced cardiac output. Electronic pacemakers capable of stimulating both ventricles simultaneously have been devised to better coordinate systolic contraction as an adjunct to medical therapy (termed cardiac resynchronization

therapy, as described in Chapter 9). Demonstrated benef ts of this approach include improved quality of life and exercise tolerance, fewer hospitalizations for heart failure, and reduced mortality, particularly in those with pretreatment left bundle branch block or other conduction abnormalities with a markedly prolonged QRS duration.

Prevention of Thromboembolic Events

Patients with DCM are at increased risk of thromboembolic complications for reasons that include (1) blood stasis in the ventricles resulting from poor systolic function, (2) stasis in the atria due to chamber enlargement or atrial f brillation, and (3) systemic venous stasis because of poor circulatory flow. Peripheral venous or right ventricular thrombi may lead to pulmonary emboli, whereas thromboemboli of left ventricular origin may lodge in a systemic artery, resulting in, for example, cerebral, myocardial, or renal infarctions. In DCM with heart failure, systemic anticoagulation should be considered for patients with a history of venous or systemic thromboembolism, atrial f brillation, or those with left ventricular thrombi identif ed by cardiac imaging, especially those that are mobile or protrude into the LV cavity (and are therefore more likely to embolize).

Cardiac Transplantation

In suitable highly symptomatic patients, cardiac transplantation offers a substantially better 5-year prognosis than do standard therapies for DCM described above. The 5- and 10-year survival rates after transplantation are 74% and 55%, respectively. However, the scarcity of donor hearts greatly limits the availability of this technique. As a result, other mechanical options have been explored and continue to undergo experimental ref nements, including ventricular assist devices and completely implanted artif cial hearts.

HYPERTROPHIC CARDIOMYOPATHY

With an incidence of about 1 of 500 in the general population, HCM is characterized by left ventricular hypertrophy that is not caused by chronic pressure overload (i.e., not the result of hypertension or aortic stenosis [AS]). Other terms used to describe this disease are “hypertrophic obstructive cardiomyopathy” and “idiopathic hypertrophic subaortic stenosis.” In this condition, systolic LV contractile function is vigorous but the thickened muscle is stiff, resulting in impaired ventricular relaxation and high diastolic pressures. HCM has received notoriety in the lay press because it is the most common cardiac abnormality found in young athletes in the United States who die suddenly during vigorous physical exertion.

Etiology

HCM is a familial disease in which inheritance follows an autosomal dominant pattern with variable penetrance, and hundreds of mutations in several different genes have been implicated. The proteins encoded by the responsible genes are all part of the sarcomere complex and include β-myosin heavy chain (β-MHC), cardiac troponins, and myosin-binding protein C (see Table 10-2). The incorporation of these mutated peptides into the sarcomere is thought to cause impaired contractile function. The resultant increase in myocyte stress is then hypothesized to lead to compensatory hypertrophy and proliferation of f broblasts.

The pathophysiology and natural history of familial HCM are variable and appear related to particular mutations within the disease-causing gene, rather than the actual gene involved. In fact, it has been shown that the precise genetic mutation determines the age of onset of hypertrophy, the extent and pattern of cardiac remodeling, and the person’s risk of developing symptomatic heart failure or sudden death. For example, mutations in the β-MHC gene that alter electrical charge in the encoded protein are associated with worse prognoses than other mutations.

Pathology

Although hypertrophy in HCM may involve any portion of the ventricles, asymmetric hypertrophy of the ventricular septum (Fig. 10-4) is most commonly found (approximately 90% of cases). Less often, the hypertrophy involves the ventricular walls symmetrically or is localized to the apex or mid-region of the LV.

Unlike ventricular hypertrophy resulting from hypertension in which the myocytes enlarge uniformly and remain orderly, the histology of HCM is unusual. The myocardial f bers are in a pattern of extensive disarray (Fig. 10-5). Short, wide, hypertrophied f bers are oriented in chaotic directions and are surrounded by numerous cardiac f broblasts and extracellular matrix. This myocyte disarray and f brosis are characteristic of HCM and play a role in the abnormal diastolic stiffness and the arrhythmias common to this disorder.

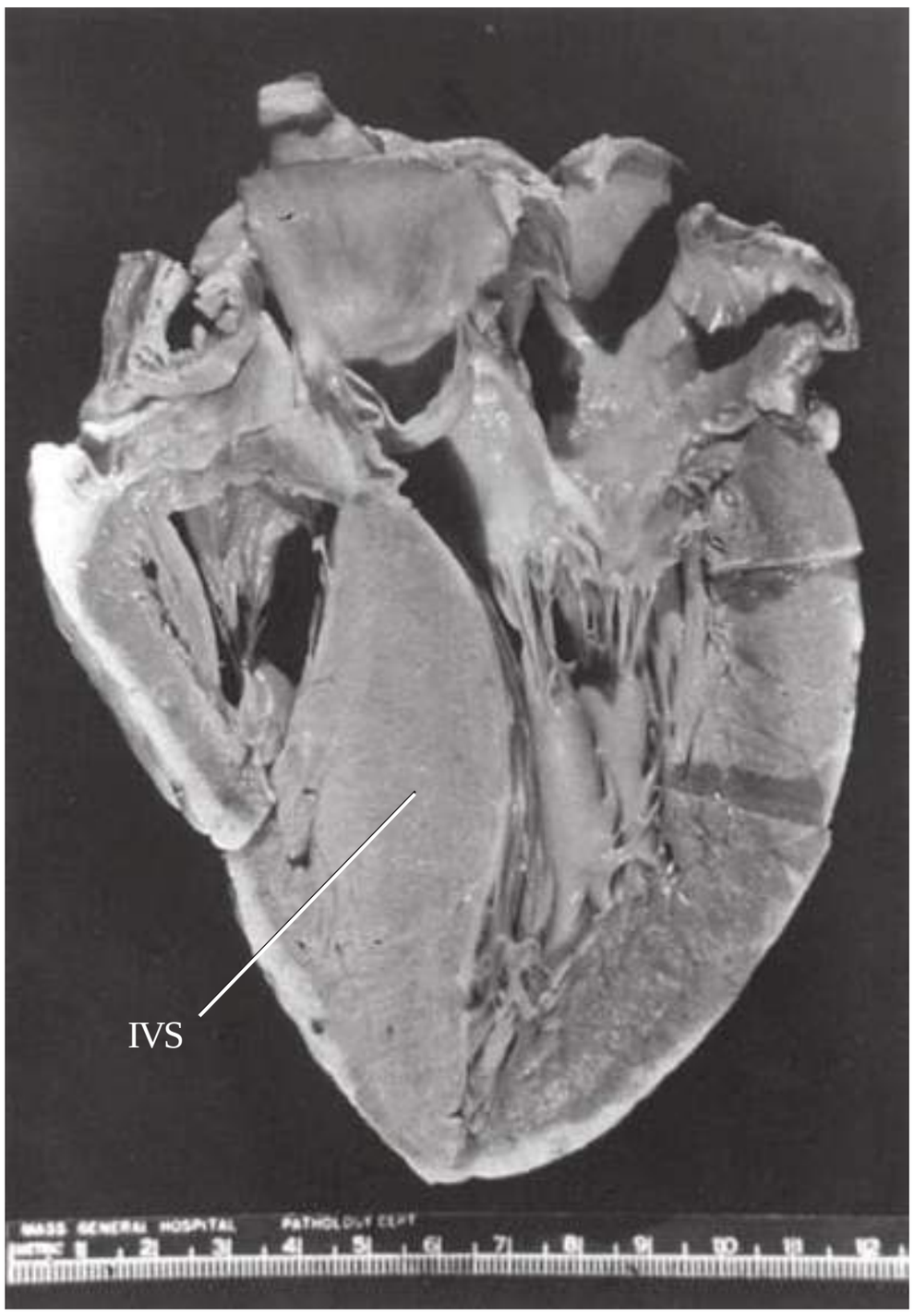


FIGURE 10-4. Postmortem heart specimen from a patient with hypertrophic cardiomyopathy. Marked left ventricular hypertrophy is present, especially of the interventricular septum (IVS).

Pathophysiology

The predominant feature of HCM is marked ventricular hypertrophy that reduces the compliance and diastolic relaxation properties of the chamber, such that f lling becomes impaired (Fig. 10-6). Patients who have asymmetric hypertrophy of the proximal interventricular septum may display additional f ndings related to transient obstruction of left ventricular outflow during systole. It is useful to consider the pathophysiology of HCM based on whether such systolic outflow tract obstruction is present.

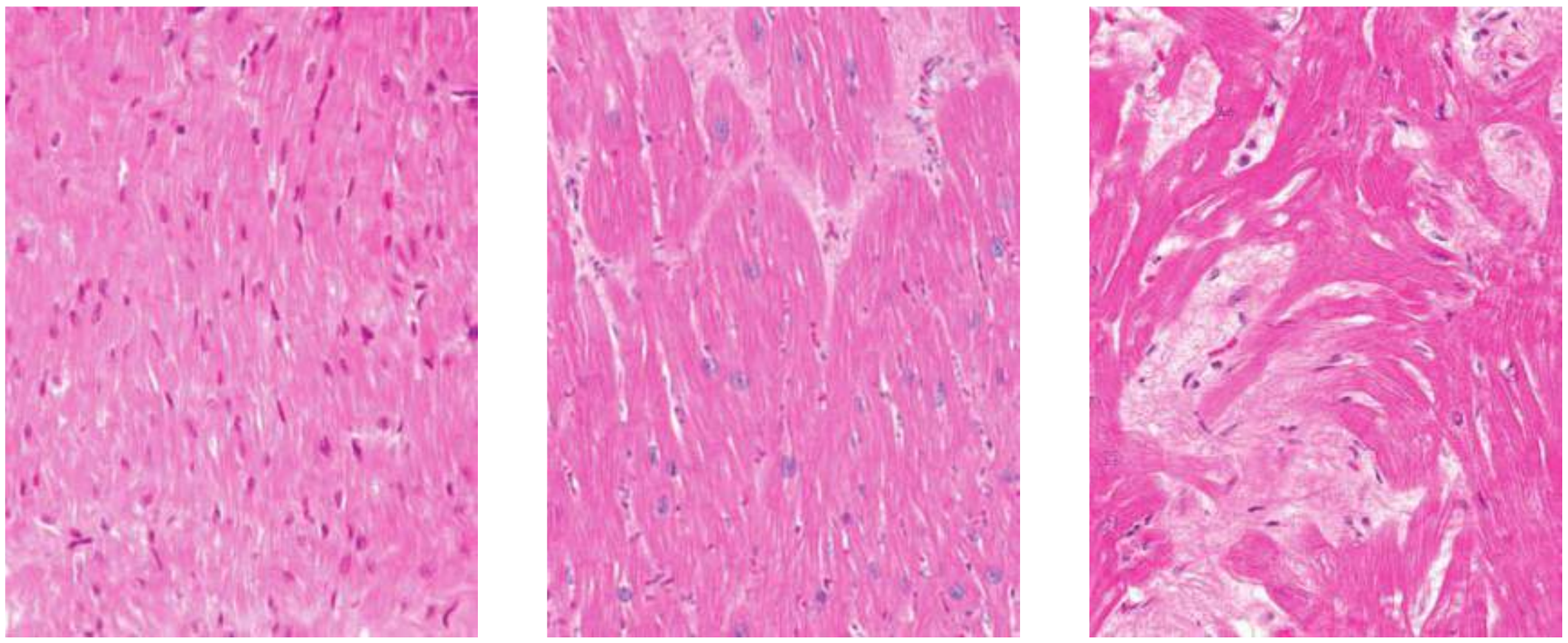


FIGURE 10-5. Light microscopy of hypertrophic myocardium. A. Normal myocardium. **B.** Hypertrophied myocytes in a patient with valvular heart disease. **C.** Myocyte disarray with f brosis in a patient with hypertrophic cardiomyopathy.

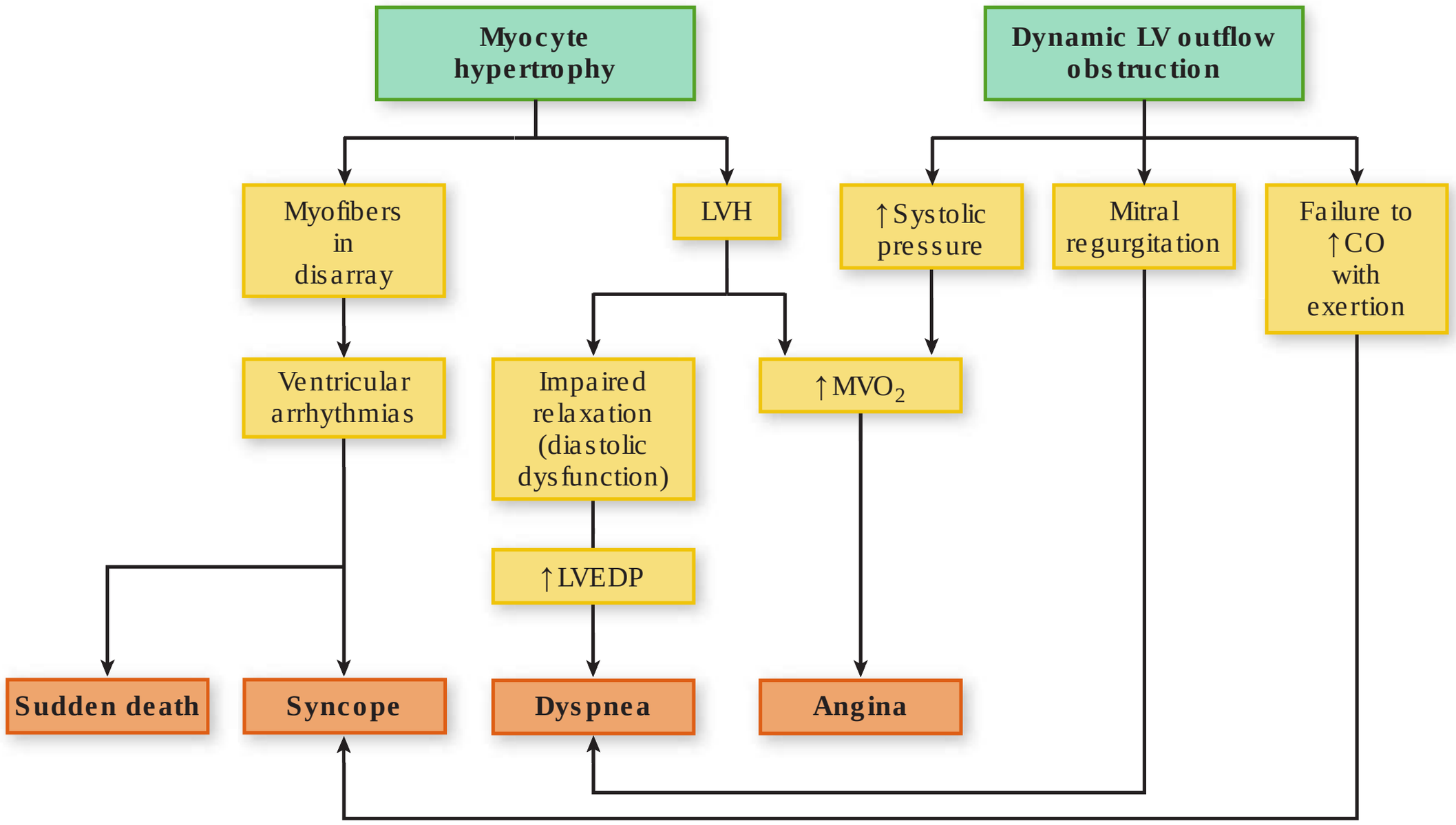


FIGURE 10-6. Pathophysiology of hypertrophic cardiomyopathy. The disarrayed and hypertrophied myocytes may lead to ventricular arrhythmias (which can cause syncope or sudden death) and impaired diastolic left ventricular (LV) relaxation (which causes elevated LV filling pressures and dyspnea). If dynamic LV outflow obstruction is present, mitral regurgitation often accompanies it (which contributes to dyspnea), and the impaired ability to raise cardiac output with exertion can lead to exertional syncope. The thickened LV wall, and increased systolic pressure associated with outflow tract obstruction, each contribute to increased myocardial oxygen consumption (MVO_2) and can precipitate angina. CO, cardiac output; LVEDP, LV end-diastolic pressure; LVH, LV hypertrophy.

HCM without Outflow Tract Obstruction

Although systolic contraction of the LV is usually vigorous in HCM, hypertrophy of the walls results in increased stiffness and impaired relaxation of the chamber. The reduced ventricular compliance alters the normal pressure–volume relationship, causing the passive diastolic filling curve to shift upward (see Fig. 9-7B). The associated rise in diastolic LV pressure is transmitted backward, leading to elevated left atrial, pulmonary venous, and pulmonary capillary pressures. Dyspnea, especially during exertion, is thus a common symptom in this disorder.

HCM with Outflow Obstruction

Approximately one third of patients with HCM manifest systolic outflow tract obstruction. The mechanism of systolic obstruction involves abnormal motion of the anterior mitral valve leaflet toward the LV outflow tract where the thickened septum protrudes (Fig. 10-7). The process is explained as follows: (1) during ventricular contraction, ejection of blood toward the aortic valve is more rapid than usual, because it must flow through an outflow tract that is narrowed by the thickened septum; (2) this rapid flow creates Venturi forces that abnormally draw the anterior mitral leaflet toward the septum during contraction; and (3) the anterior mitral leaflet approaches and abuts the hypertrophied septum, causing transient obstruction of blood flow into the aorta.

In patients with outflow obstruction, elevated left atrial and pulmonary capillary wedge pressures result from both the decreased ventricular compliance and the outflow obstruction during contraction. During systolic obstruction, a pressure gradient develops between the main body of the LV and the outflow tract distal to the obstruction (see Fig. 10-7).

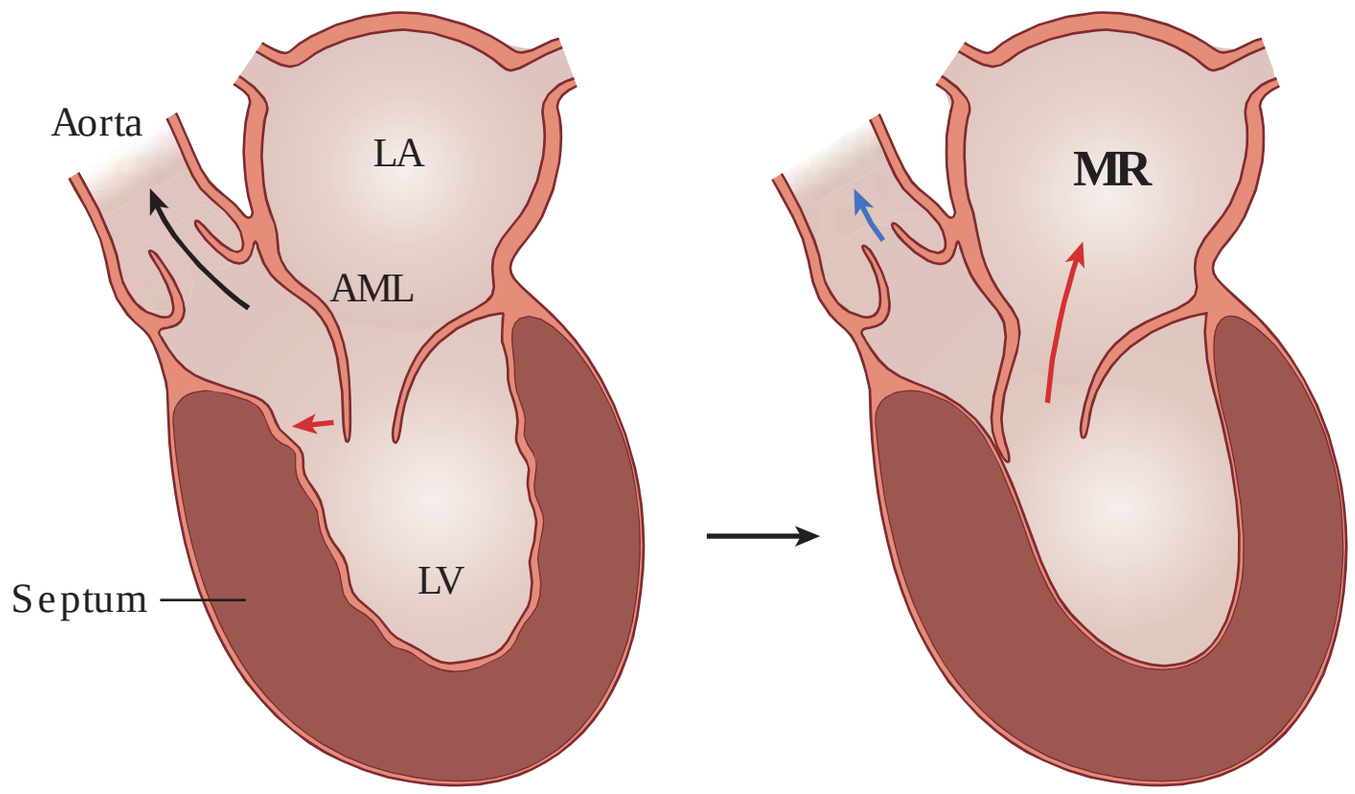


FIGURE 10-7. Pathophysiology of left ventricular (LV) outflow obstruction and mitral regurgitation (MR) in hypertrophic cardiomyopathy. Left panel. The LV outflow tract is abnormally narrowed between the hypertrophied interventricular septum and the anterior leaflet of the mitral valve (AML). It is thought that the rapid ejection velocity through the narrowed tract in early systole draws the AML toward the septum (short red arrow). **Right panel**. As the mitral valve anterior leaflet abnormally moves toward, and contacts, the septum, outflow into the aorta is transiently obstructed. Because the mitral leaflets do not coapt normally in systole, MR also results (long red arrow).

The elevated ventricular systolic pressure increases wall stress and myocardial oxygen consumption, which can result in angina (see Fig. 10-6). In addition, because obstruction is caused by abnormal motion of the anterior mitral leaflet toward the septum (and therefore away from the posterior mitral leaflet), the mitral valve does not close properly during systole, and mitral regurgitation may result. Such regurgitation further elevates left atrial and pulmonary venous pressures and may worsen symptoms of dyspnea, as well as contribute to the development of atrial fibrillation.

The systolic pressure gradient observed in obstructive HCM is dynamic in that its magnitude varies during contraction and depends, at any given time, on the distance between the anterior leaflet of the mitral valve and the hypertrophied septum. Situations that decrease LV cavity size (e.g., reduced venous return owing to intravascular volume depletion) bring the mitral leaflet and septum into closer proximity and promote obstruction. Conversely, conditions that enlarge the LV (e.g., augmented intravascular volume) increase the distance between the anterior mitral leaflet and septum and reduce the obstruction. Positive inotropic drugs (which augment the force of contraction; see Chapter 17) also force the mitral leaflet and septum into closer proximity and contribute to obstruction, whereas negative inotropic drugs (e.g., β-blockers, verapamil) have the opposite effect.

Although dynamic systolic outflow tract obstruction creates an impressive murmur and receives great attention, the symptoms of obstructive HCM appear to primarily stem from the increased LV stiffness and diastolic dysfunction that are also present in the nonobstructive form.

Clinical Findings

The symptoms of HCM vary widely in affected individuals, from none to marked physical limitations (see Fig. 10-6). The average age of presentation is the mid-20s.

The most frequent symptom is dyspnea owing to elevated diastolic LV (and therefore pulmonary capillary) pressure. This symptom is further exacerbated by the high systolic LV pressure and mitral regurgitation found in patients with outflow tract obstruction.

Angina is often described by patients with HCM, even in the absence of obstructive coronary artery disease. Myocardial ischemia may be contributed to by (1) the high oxygen demand of the increased muscle mass and (2) the narrowed small branches of the coronary arteries within the hypertrophied ventricular wall. If outflow tract obstruction is present, the high systolic ventricular pressure increases myocardial oxygen demand because of the increased wall stress and contributes to ischemia.

Syncope in HCM may result from cardiac arrhythmias that arise because of the structurally abnormal myofibers. In patients with outflow tract obstruction, syncope may also be induced by exertion, when the pressure gradient is made worse by the increased force of contraction, thereby causing a transient fall in cardiac output. Orthostatic light-headedness is also common in patients with outflow tract obstruction. This occurs because venous return to the heart is reduced on standing by the gravitational pooling of blood in the lower extremities. The LV thus decreases in size and outflow tract obstruction intensifies, transiently reducing cardiac output and cerebral perfusion.

When arrhythmias occur, symptoms of HCM may be exacerbated. For example, atrial fibrillation is not well tolerated because the loss of the normal atrial "kick" further impairs diastolic filling and can therefore worsen symptoms of pulmonary congestion. Of greatest concern, the first clinical manifestation of HCM may be ventricular fibrillation, resulting in sudden cardiac death, particularly in young adults with HCM during strenuous physical exertion. Risk factors for sudden death among patients with HCM include a history of syncope, a family history of sudden death, certain high-risk HCM mutations, and extreme hypertrophy of the LV wall (>30 mm in thickness).

Physical Examination

A patient with a mild form of HCM may have a normal cardiac examination. Otherwise, a common finding is a fourth heart sound (S_4), generated by left atrial contraction into the stiffened LV (see Chapter 2). The forceful atrial contraction may also result in a palpable presystolic impulse over the cardiac apex (a "double apical impulse").

Other findings are typical in patients with systolic outflow obstruction. The carotid pulse rises briskly in early systole but then quickly declines as obstruction to cardiac outflow appears. The characteristic systolic murmur of LV outflow obstruction is rough and crescendo–decrescendo in shape, heard best at the left lower sternal border (in proximity to the turbulent flow through the narrowed outflow tract), and unlike AS, does not typically radiate to the carotid arteries. In addition, as the stethoscope is moved toward the apex, the holosystolic blowing murmur of accompanying mitral regurgitation may be auscultated. Although the LV outflow obstruction murmur may be soft at rest, bedside maneuvers that alter preload and afterload can dramatically increase its intensity and help differentiate this murmur from other conditions, such as AS (Table 10-3).

A commonly used technique in this regard is the Valsalva maneuver, produced by asking the patient to "bear down" (technically defined as forceful exhalation with the nose, mouth, and glottis closed). The Valsalva maneuver increases intrathoracic pressure, which decreases venous return to the heart and transiently reduces LV size. This action brings the

TABLE 10-3 Effect of Maneuvers on Murmurs of AS and HCM

	Valsalva	Squatting	Standing
HCM murmur	↑	↓	↑
AS murmur	↓	↑	↓

HCM, hypertrophic cardiomyopathy; AS, aortic stenosis.

hypertrophied septum and anterior leaflet of the mitral valve into closer proximity, creating greater obstruction to forward flow. Thus, during Valsalva, the murmur of HCM increases in intensity. In contrast, the murmur of AS decreases in intensity during Valsalva because of the reduced flow across the stenotic valve.

Conversely, a change from standing to a squatting position suddenly augments venous return to the heart (which increases preload) while simultaneously increasing the systemic vascular resistance. The increased preload raises the stroke volume and therefore causes the murmur of AS to become louder. In contrast, the transient increase in LV size during squatting reduces the LV outflow tract obstruction in HCM and softens the intensity of that murmur. Sudden standing from a squatting position has the opposite effect on each of these murmurs (see Table 10-3).

Diagnostic Studies

The ECG typically shows left ventricular hypertrophy and left atrial enlargement. Prominent Q waves are common in the inferior and lateral leads, representing amplif ed forces of initial depolarization of the hypertrophied septum directed away from those leads. In some patients, diffuse T wave inversions are present, which can predate clinical, echocardiographic, or other electrocardiographic manifestations of HCM. Atrial and ventricular arrhythmias are frequent, especially atrial f brillation. Ventricular arrhythmias are particularly ominous because they may herald ventricular f brillation and sudden death, even in previously asymptomatic patients.

Echocardiography is very helpful in the evaluation of HCM. The degree of LV hypertrophy can be measured and regions of asymmetrical wall thickness readily identif ed. Signs of left ventricular outflow obstruction may also be demonstrated and include abnormal anterior motion of the mitral valve as it is drawn toward the hypertrophied septum during systole, and partial closure of the aortic valve in midsystole as flow across it is transiently obstructed. Doppler recordings during echocardiography accurately measure the outflow pressure gradient and quantify any associated mitral regurgitation. Children and adolescents with apparently mild HCM should undergo serial echocardiographic assessment over time, because the degree of hypertrophy may increase during puberty and early adulthood.

Cardiac catheterization is reserved for patients for whom the diagnosis is uncertain or if percutaneous septal ablation (described in the “Treatment” section) is planned. The major feature in patients with obstruction is the f nding of a pressure gradient within the outflow portion of the LV, either at rest or during maneuvers that transiently reduce LV size and promote outflow tract obstruction. Myocardial biopsy at the time of catheterization is not necessary because histologic f ndings do not predict disease severity or long-term prognosis.

Finally, genetic testing can be helpful in establishing, or excluding, the diagnosis of HCM in family members of an affected patient when a specif c mutation in that family has been identif ed.

Treatment

β-Blockers are standard therapy for HCM because they (1) reduce myocardial oxygen demand by slowing the heart rate and the force of contraction (and therefore diminish angina and dyspnea); (2) lessen any LV outflow gradient during exercise by reducing the force of contraction (allowing the chamber size to increase, thus separating the anterior leaflet of the mitral valve from the ventricular septum); (3) increase passive diastolic ventricular f lling time owing to the decreased heart rate; and (4) decrease the frequency of ventricular ectopic beats. Despite their antiarrhythmic effect, β-blockers do not prevent sudden arrhythmic death in this condition, nor have they been shown to slow disease progression.

Certain calcium channel antagonists (e.g., verapamil) may have benef cial effects on ventricular relaxation and f lling and are sometimes useful in improving exercise capacity in patients who fail to respond to β-blockers. Patients who develop pulmonary congestion may benef t from mild diuretic therapy, but these drugs must be administered cautiously to avoid volume depletion; reduced intravascular volume decreases LV size and could exacerbate outflow tract obstruction. Vasodilators (including nitrates) similarly reduce LV size and should be avoided.

Atrial f brillation is poorly tolerated in HCM and should be controlled aggressively, most commonly with antiarrhythmic drugs. Effective and useful antiarrhythmic drugs for atrial f brillation in HCM include amiodarone and disopyramide (a class IA antiarrhythmic drug that also possesses negative inotropic properties that may help reduce LV outflow tract obstruction; see Chapter 17). Digitalis should be avoided in HCM because its positive inotropic effect increases the force of contraction and can worsen LV outflow tract obstruction.

Sudden cardiac death has a propensity to occur in patients with HCM in association with physical exertion; therefore, strenuous exercise and competitive sports should be avoided. Sudden death in this syndrome is almost always caused by ventricular tachycardia or f brillation. Although amiodarone may reduce the frequency of ventricular arrhythmias, HCM patients who are at high risk (i.e., a family history of sudden death, extreme hypertrophy with ventricular wall thickness >30 mm, unexplained prior syncopal episodes, history of high-grade ventricular tachyarrythmias) should receive an ICD. ICD therapy is life saving for both primary prevention in such patients, and for HCM patients who have already survived a cardiac arrest.

Some studies have shown clinical improvement when patients with the obstructive form of HCM are treated with a dual-chamber permanent pacemaker, the two electrodes of which are placed in the right atrium and RV. The LV outflow gradient may become reduced by this procedure, possibly by altering the normal sequence of ventricular contraction, such that septal–mitral valve apposition becomes less prominent. However, this technique seems to be useful for only a small percentage of markedly symptomatic patients.

Surgical therapy (myomectomy) is considered for patients whose symptoms do not respond adequately to pharmacologic therapy. This procedure involves excision of portions of the hypertrophied septal muscle mass and usually improves outflow tract obstruction, symptoms, and exercise capacity. Myomectomy is the “gold standard” approach to treatment of refractory symptoms in this condition. A less invasive alternative in select patients is percutaneous septal ablation, performed in the cardiac catheterization laboratory, in which ethanol is injected directly into the f rst major septal coronary artery (a branch of the left anterior descending artery), causing a small, controlled myocardial infarction. The desired and often achieved result is reduction of septal thickness and improvement in outflow tract obstruction.

Theoretically, infective endocarditis could develop in patients with the obstructive form of HCM because of turbulent blood flow through the LV outflow tract and the associated mitral regurgitation. However, that is rare and routine antibiotic prophylaxis for prevention of endocarditis prior to invasive dental work is not recommended in this condition by current U.S. guidelines (see Chapter 8).

Finally, genetic counseling should be provided to all patients with HCM. Because it is an autosomal dominant disease, children of affected persons have a 50% chance of inheriting the abnormal gene. First-degree relatives of patients with HCM should be screened by physical examination, electrocardiography, echocardiography, and sometimes genetic testing. Even asymptomatic HCM patients are at risk of complications, including sudden death.

Prognosis

The incidence of sudden death in HCM is 2% to 4% per year in adults and 4% to 6% in children and adolescents. It has become clear that different mutations produce vastly

different phenotypes. Some cause extreme hypertrophy in childhood without any clinical symptoms until the occurrence of sudden death; others present later in life with heart failure symptoms. Most mutations produce only mild hypertrophy and are associated with a normal life expectancy.

RESTRICTIVE CARDIOMYOPATHY

The restrictive cardiomyopathies are less common than DCM and HCM. They are characterized by abnormally rigid (but not necessarily thickened) ventricles with impaired diastolic filling but usually normal, or near normal, systolic function. This condition results from either (1) fibrosis or scarring of the endomyocardium or (2) infiltration of the myocardium by an abnormal substance (Table 10-4).

The most common recognized cause of restrictive cardiomyopathy in nontropical countries is **amyloidosis**. In this systemic disease, insoluble misfolded amyloid fibrils deposit within tissues, including the heart, causing organ dysfunction. Amyloid deposition is diagnosed histologically by the Congo red stain, which displays amyloid fibrils with a characteristic green birefringence under polarized light.

Amyloid fibrils can develop from several different proteins that distinguish the categories of disease. Primary amyloidosis is caused by deposition of immunoglobulin light chain AL fragments secreted by a plasma cell tumor (usually, multiple myeloma). In contrast, secondary amyloidosis is characterized by the presence of AA amyloid (derived from the inflammatory marker serum amyloid A) in a variety of chronic inflammatory conditions, such as rheumatoid arthritis. Less common is hereditary amyloidosis, an autosomal dominant condition in which amyloid fibrils form from point mutations in the protein transthyretin. Senile amyloidosis refers to a condition in the elderly, in which amyloid deposits, derived from transthyretin or other proteins, are found scattered throughout the vascular system, muscles, kidney, and lung. In each form of amyloidosis, cardiac involvement is marked by deposition of extracellular amyloid between myocardial fibers in the atria and ventricles, in the coronary arteries and veins, and in the heart valves.

Clinical manifestations of cardiac involvement are most common in the primary (AL) form of amyloidosis and typically relate to the development of restrictive cardiomyopathy because of the infiltrating amyloid protein. Diastolic dysfunction is the prominent cardiac abnormality; systolic dysfunction may also develop later in the disease. Orthostatic hypotension is

TABLE 10-4 Examples of Restrictive Cardiomyopathy

Noninfiltrative
Idiopathic
Scleroderma
Infiltrative
Amyloidosis
Sarcoidosis
Storage diseases
Hemochromatosis
Glycogen storage diseases
Endomyocardial disease
Endomyocardial fibrosis
Hypereosinophilic syndrome
Metastatic tumors
Radiation therapy

present in about 10% of patients, likely contributed to by amyloid deposition in the autonomic nervous system and peripheral blood vessels. Infiltration of amyloid into the cardiac conduction system can cause arrhythmias and conduction impairments, which can result in syncope or sudden death.

Pathophysiology

Reduced compliance of the ventricles in restrictive cardiomyopathy, whether due to infiltration or fibrosis, results in an upward shift of the passive ventricular filling curve (see Fig. 9-7B), leading to abnormally high diastolic pressures. This has two major consequences: (1) elevated systemic and pulmonary venous pressures, with signs of right- and left-sided vascular congestion, and (2) reduced ventricular cavity size with decreased filling, stroke volume, and cardiac output.

Clinical Findings

It follows from the underlying pathophysiology that signs of left- and right-sided heart failure are expected (Fig. 10-8). Decreased cardiac output is manifested by fatigue and decreased exercise tolerance. Systemic congestion (often more prominent than pulmonary congestion in this syndrome) leads to jugular venous distention, peripheral edema, and ascites with a large, tender liver. Arrhythmias, including atrial fibrillation, are common. Infiltrative etiologies that involve the cardiac conduction system can cause conduction blocks (described in Chapter 12).

Physical Examination

Signs of congestive heart failure are often present, including pulmonary rales, distended neck veins, ascites, and peripheral edema. Similar to constrictive pericarditis (see Chapter 14), jugular venous distention may paradoxically worsen with inspiration (the Kussmaul sign) because the stiffened RV cannot accommodate the increased venous return.

Diagnostic Studies

The chest radiograph usually shows a normal-sized heart with signs of pulmonary congestion. The ECG often displays nonspecific ST and T wave abnormalities; conduction disturbances such as atrioventricular block or a bundle branch block may be present.

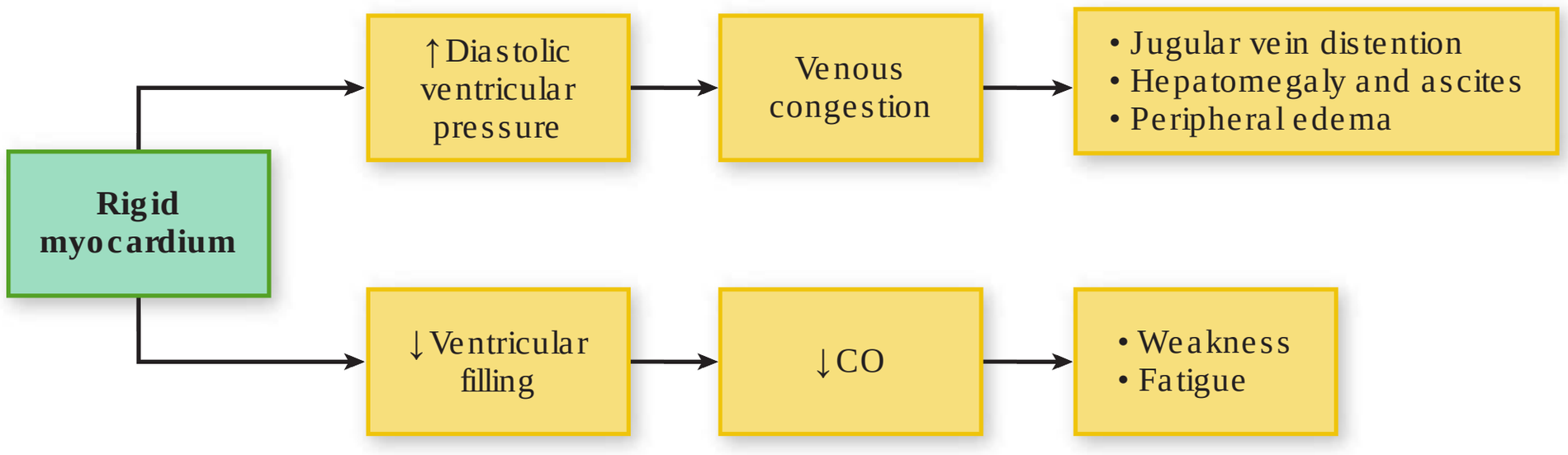


FIGURE 10-8. Pathophysiology of restrictive cardiomyopathy. The rigid myocardium results in elevated ventricular diastolic pressures and decreased ventricular filling. The resultant symptoms can be predicted from these abnormalities. CO, cardiac output.

The restrictive cardiomyopathies share nearly identical symptoms, physical signs, and hemodynamic profiles with constrictive pericarditis, as described in Chapter 14. However, it is important to distinguish these two entities because constrictive pericarditis is often correctable, whereas interventions for the restrictive cardiomyopathies are more limited.

The most useful diagnostic tools to differentiate restrictive cardiomyopathy from constrictive pericarditis are transvenous endomyocardial biopsy, computed tomography (CT), and MRI. For example, in restrictive cardiomyopathies, transvenous endomyocardial biopsy may demonstrate the cause of the condition (e.g., the presence of amyloid fibrils in amyloidosis, or iron deposits in patients with hemochromatosis [a condition of iron overload]). CT or MRI scans accurately identify the thickened pericardium present in most patients with constrictive pericarditis, a finding that is not present in states causing restrictive cardiomyopathy.

Treatment

Restrictive cardiomyopathy typically has a very poor prognosis, except when treatment can target an underlying cause. For example, phlebotomy and iron chelation therapy may be helpful in the early stages of hemochromatosis. Symptomatic therapy for all etiologies includes salt restriction and cautious use of diuretics to improve symptoms of systemic and pulmonary congestion. Unlike the dilated cardiomyopathies, vasodilators are not helpful because systolic function is usually preserved. Maintenance of sinus rhythm (e.g., converting atrial fibrillation if it occurs) is important to maximize diastolic filling and forward cardiac output. Some restrictive cardiomyopathies are prone to intraventricular thrombus formation, thus warranting chronic oral anticoagulant therapy. In the case of primary (AL) amyloidosis, chemotherapy followed by autologous bone marrow stem cell transplantation has proved effective in selected patients with early cardiac involvement.

OTHER FORMS OF CARDIOMYOPATHY

Not all forms of cardiac muscle disease fit into the traditional categories of cardiomyopathy described in this chapter. Examples of exceptions include (1) left ventricular noncompaction (LVNC), and (2) arrhythmogenic right ventricular cardiomyopathy (ARVC).

Left Ventricular Noncompaction

LVNC is a rare condition with features that overlap with hypertrophic, restrictive and dilated cardiomyopathies. It is manifest by a thickened myocardium with very prominent trabeculae and deep recesses that extend from the LV cavity into the intertrabecular spaces. The abnormal regions of myocardium typically contract poorly, often demonstrate characteristics of impaired diastolic relaxation, and predispose to rhythm disturbances and thrombus formation. Patients with this condition may present in childhood or adulthood with symptoms of heart failure (due to systolic and/or diastolic dysfunction), ventricular arrhythmias, or thromboembolism.

LVNC appears to result from arrested development of the myocardium during fetal development, though the exact mechanism has not been fully elucidated. Up to 50% of patients with this condition have affected family members, and autosomal dominant, autosomal recessive and X-linked patterns of inheritance have been found. Mutations in at least nine genes encoding sarcomere proteins have been identified in patients with LVNC (including mutations that have also been associated with hypertrophic and dilated cardiomyopathies), resulting in either the isolated disorder or a syndrome with other forms of congenital heart disease.

The diagnosis is usually established by typical features on 2-dimensional and color Doppler echocardiography or by cardiac MRI. The prognosis is variable, but is worse among symptomatic patients compared to those found to have the disorder incidentally by imaging studies. One series indicated that 60% of patients had died or required cardiac transplantation within 6 years of diagnosis, but other studies have reported less dire outcomes.

Management is aimed at treating the symptoms and complications of LVNC as there is no corrective therapy for the underlying condition itself. Depending on the clinical manifestations, approaches may include standard treatment of heart failure (Chapter 9), ICD implantation for management of life-threatening ventricular arrhythmias, chronic anticoagulation for those with accompanying atrial fibrillation or significant contractile dysfunction to prevent thromboembolism, and cardiac transplantation for those with advanced, refractory heart failure.

Arrhythmogenic Right Ventricular Cardiomyopathy

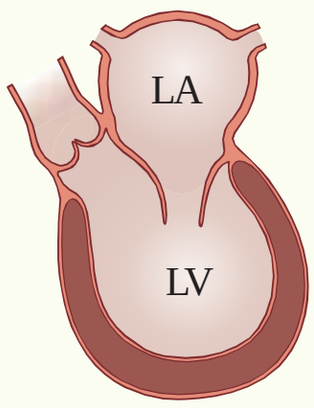
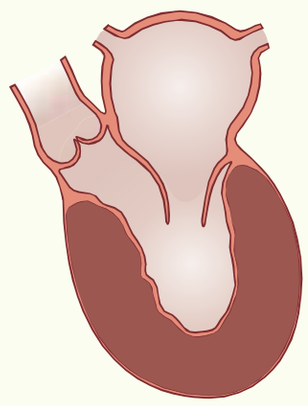
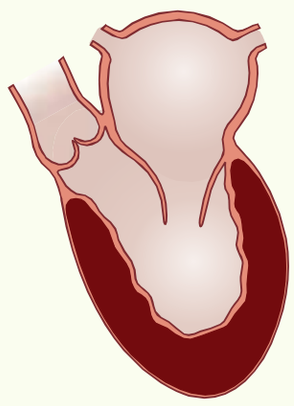
ARVC, also termed arrhythmogenic right ventricular dysplasia, is another genetic form of cardiomyopathy. It is characterized by replacement of right ventricular (and occasionally left ventricular) myocardium with adipose and fibrous tissue, resulting in rhythm disturbances and contractile dysfunction. Ventricular arrhythmias originating from the abnormal ventricle are common and may result in palpitations, syncope, and even sudden cardiac death. Symptoms often begin in the teen years, and ARVC is another cause of sudden death among young athletes.

Both autosomal dominant and recessive inheritance forms of ARVC have been identified. The majority of mutations occur in genes that encode components of desmosomes, cell membrane structures responsible for cell-to-cell adhesion, leading to fibrosis and aberrant signaling with proliferation of adipose tissue in the myocardium. Transvenous endomyocardial biopsy of the RV may demonstrate fatty or fibrofatty replacement of the myocardium, but has a high false negative rate for identifying the disorder. Thus, diagnostic criteria also rely on family history, ECG abnormalities (see Chapter 12, Box 12-1), the presence of arrhythmias emanating from the RV, morphologic abnormalities detected by imaging studies (especially cardiac MRI), and genetic testing for specific mutations. Management of ARVC typically includes ICD implantation because the disease is progressive and life-threatening ventricular tachycardia is common.

SUMMARY

- Cardiomyopathies are a group of heart muscle disorders that cause mechanical and/or electrical dysfunction of the myocardium, and often result in inappropriate ventricular hypertrophy or dilatation (Table 10-5); heart failure and cardiovascular death are common end manifestations.
- DCM is characterized by progressive ventricular chamber enlargement with impaired systolic contractile function, often leading to symptomatic heart failure, ventricular arrhythmias, and/or embolic complications.
- HCM is characterized by an abnormally thickened ventricular wall with abnormal diastolic relaxation but usually intact systolic function; dynamic LV outflow tract obstruction during systole may be present, and the most common symptoms are dyspnea and exertional angina.
- Ventricular arrhythmias in HCM may lead to sudden cardiac death.
- Restrictive cardiomyopathies are uncommon and are characterized by an abnormally stiffened myocardium (because of fibrosis or an infiltrative process) leading to impaired diastolic relaxation, but systolic contractile function is typically normal or near normal; symptoms of heart failure are typical.

TABLE 10-5 Summary of the Cardiomyopathies

	Dilated Cardiomyopathy	Hypertrophic Cardiomyopathy	Restrictive Cardiomyopathy
Ventricular morphology	Dilated LV with little concentric hypertrophy 	Marked hypertrophy, often asymmetric 	Fibrotic or infiltrated myocardium 
Etiologies	Genetic, infectious, alcoholic, peripartum	Genetic	Amyloidosis, hemochromatosis, scleroderma, radiation therapy
Symptoms	Fatigue, weakness, dyspnea, orthopnea, PND	Dyspnea, angina, syncope	Dyspnea, fatigue
Physical exam	Pulmonary rales, S_3; if RV failure present: JVD, hepatomegaly, peripheral edema	S_4; if outflow obstruction present: systolic murmur loudest at left sternal border, accompanied by mitral regurgitation	Predominantly signs of RV failure: JVD, hepatomegaly, peripheral edema
Pathophysiology	Impaired systolic contraction	Impaired diastolic relaxation; LV systolic function vigorous, often with dynamic obstruction	"Stiff" LV with impaired diastolic relaxation but usually normal systolic function
Cardiac size on chest radiograph	Enlarged	Normal or enlarged	Usually normal
Echocardiogram	Dilated, poorly contractile LV	LV hypertrophy, often more pronounced at septum; systolic anterior movement of MV with mitral regurgitation	Usually normal systolic contraction; "speckled" appearance in infiltrative disorders

LV, left ventricle; PND, paroxysmal nocturnal dyspnea; RV, right ventricle; JVD, jugular venous distension; MV, mitral valve.

Acknowledgments

Contributors to previous editions of this chapter were Christopher T. Lee, MD; Marc N. Wein, MD; Yi-Bin Chen, MD; David Grayzel, MD; and Kay Fang, MD.

Additional Reading

Arbustini E, Narula J, Tavazzi J, et al. The MOGE(S) classification of cardiomyopathy for clinicians. J Am Coll Cardiol. 2014;64:304–318.

Bhatia NL, Tajik AJ, Wilansky S, et al. Isolated noncompaction of the left ventricular myocardium in adults: A systematic overview. J Card Fail. 2011;17:771–778.

Elkayam U. Clinical characteristics of peripartum cardiomyopathy in the United States: Diagnosis, prognosis, and management. J Am Coll Cardiol. 2011;58:659–670.

Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: Executive summary. J Am Coll Cardiol. 2011;58:2703–2738.

Guan J, Mishra S, Falk RH, et al. Current perspectives on cardiac amyloidosis. Am J Physiol Heart Circ Physiol. 2012;302:H544–H552.

Maron BJ, Ommen SR, Semsarian C, et al. Hypertrophic cardiomyopathy: Present and future, with translation into contemporary cardiovascular medicine. J Am Coll Cardiol. 2014;64:83–99.

Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies: An American Heart Association scientific statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113:1807–1816.

Murray B. Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C): A review of molecular and clinical literature. J Genet Couns. 2012;21:494–504.

Sturm AC. Genetic testing in the contemporary diagnosis of cardiomyopathy. Curr Heart Fail Rep. 2013;10:63–72.