Chapter 30
Understanding Cardiomyopathy: Practical Guidelines

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HYPERTROPHIC CARDIOMYOPATHY
Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disorder caused by mutations in 1 of the 12 sarcomeric or nonsarcomeric genes and is recognized as the most common cause of sudden cardiac death (SCD) in the young and an important substrate for disability at any age. It affects men and women equally and occurs in many races and countries. The clinical diagnosis of HCM is established most easily and reliably with two-dimensional echocardiography by demonstrating left ventricular hypertrophy (LVH) which is typically asymmetric in distribution, and showing virtually any diffuse or segmental pattern of left ventricular (LV) wall thickening. LV wall thickening is associated with a nondilated and hyperdynamic chamber, in the absence of any other cardiac or systemic disease capable of producing such a magnitude of hypertrophy, and independent of whether or not LV outflow obstruction is present. Although the usual clinical diagnostic criteria for HCM is wall thickness greater than or equal to 15 mm, genotypic and phenotypic correlations have shown that virtually any level of wall thickness can occur in the presence of a HCM mutant gene. It is of clinical importance to distinguish between obstructive or nonobstructive forms of HCM, based on the presence or absence of a LV outflow gradient under resting and/or provocative conditions.

Outflow gradients are responsible for a loud apical systolic ejection murmur. Obstruction may either be subaortic or mid-cavity in location. Subaortic obstruction is caused by systolic anterior motion (SAM) of the mitral valve leaflets and mid-systolic contact with the ventricular septum. SAM is probably attributable to a drag effect or possibly a Venturi phenomenon and is responsible not only for subaortic obstruction, but also for concomitant mitral regurgitation.

Hypertrophic cardiomyopathy disease spectrum may be divided into hemodynamic subgroups, based on the representative peak instantaneous gradients as assessed with continuous wave Doppler: (1) obstructive gradient under basal (resting) conditions, equal to or greater than 30 mm Hg; (2) latent (provocable) obstructive gradient less than 30 mm Hg under basal conditions and equal to or greater than 30 mm Hg with provocation; (3) nonobstructive—less than 30 mm Hg under both basal and provokable conditions.

Genetics
Hypertrophic cardiomyopathy is inherited as a Mendelian autosomal dominant trait and is caused by mutations in any one of the 10 genes, encoding protein components of the cardiac sarcomere, which is composed of thick or thin filaments with contractile, structural or regulatory functions. Three of the HCM causing mutant genes predominate in frequency. Beta-myosin heavy chain (the first identified), myosin-binding protein C and cardiac troponin T probably comprise more than one half of the genotyped patients to date. Seven other genes each account for fewer cases: regulatory and essential myosin light chains, titin, alpha-tropomyosin, alpha-actin, cardiac troponin I and alpha-myosin heavy chain.

Clinical Course
Adverse clinical course proceeds along one or more of the following pathways, which ultimately dictate treatment strategies: (1) high risk for premature, sudden and unexpected death; (2) progressive symptoms like exertional dyspnea, chest pain and impaired consciousness, including syncope, near syncope or presyncope, in the presence of preserved LV systolic function; (3) progression to advanced congestive heart failure (the “end-stage phase”) with LV remodeling and systolic dysfunction and (4) complications attributable to atrial fibrillation (AF) including embolic stroke.

Medical Management
Alleviation of symptoms related to heart failure is the fundamental goal of treatment. Pharmacological therapy has traditionally been the initial therapeutic approach for relieving disabling symptoms of exertional dyspnea and improving exercise capacity.

Beta-blockers are negative inotropic drugs that have traditionally been administered to HCM patients with or without obstruction, usually relying on the patient’s own subjective and historical perception of benefit. The beneficial effects of beta-blockers for symptoms of exertional dyspnea and exercise intolerance appear to be attributable largely to a decrease in the heart rate with a consequent prolongation of diastole, muscle relaxation and an increase in passive ventricular filling. These agents lessen LV contractility and myocardial oxygen demand and possibly reduce microvascular myocardial ischemia. Potential side effects include fatigue, impotence, sleep disturbances and chronotropic incompetence.

Verapamil was introduced as another negative inotropic agent for the treatment of HCM, and has been widely used empirically in both the nonobstructive and obstructive forms, with a reported benefit for many patients, including those with a component of chest pain. Verapamil may occasionally harbor a potential for clinically important adverse consequences and has been reported to cause death in a few HCM patients with severe disabling symptoms (orthopnea and paroxysmal nocturnal dyspnea) and markedly-elevated pulmonary arterial pressure, in combination with marked
The negative inotropic and Type IA antiarrhythmic agent disopyramide produces symptomatic relief in patients with severe resting obstruction, because of a decrease in SAM, outflow obstruction and mitral regurgitant volume. Anticholinergic side effects such as dry mouth and eyes, constipation, indigestion and difficulty in micturation may be reduced by long-acting preparations through which cardioactive benefits are more sustained. Because disopyramide may cause accelerated atrioventricular (AV) nodal conduction and thus increase ventricular rate during AF, supplemental therapy with beta-blockers in low doses to achieve normal resting heart rate has been advised.

**Infective Endocarditis Prophylaxis**

There is a small risk for bacterial endocarditis, which appears largely confined to those patients with LV outflow tract obstruction under resting conditions or with intrinsic mitral valve disease. The site of the valvular vegetation is usually the thickened anterior mitral leaflet, although cases have been reported with lesions on the outflow tract (endocardial contact plaque) or on the aortic valve. Therefore, the American Heart Association (AHA) recommendation should be applied to HCM patients with evidence of outflow obstruction under resting or exercise conditions, at the time of dental or selected surgical procedures that create a risk for blood-borne bacteremia.

**Pregnancy and Hypertrophic Cardiomyopathy**

There is no evidence that patients with HCM are generally at increased risk during pregnancy and delivery. Absolute maternal mortality is very low and most pregnant HCM patients undergo normal vaginal delivery without the necessity for cesarean section.

**Surgical Therapy**

When medical therapy proves insufficient to control symptoms, and the quality of life becomes unacceptable to the patient, other treatment options are thought of 5% of all HCM patients in non-referral settings (but up to 30% in tertiary referral populations), are generally regarded as candidates for surgery. These patients have particularly marked outflow gradients (peak instantaneous gradient is usually ≥ 50 mm Hg), as measured with continuous wave Doppler echocardiography, either under resting or basal conditions and/or with provocation, preferably utilizing physiologic exercise. In addition, these patients have severe limiting symptoms, usually of exertional dyspnea and chest pain that are regarded in adults as the New York Heart Association (NYHA) functional classes III and IV, refractory to maximum medical therapy. Ventricular septal myectomy operation (also known as the Morrow procedure) has become established as a proven approach for amelioration of outflow obstruction and the standard therapeutic option, and the gold standard for both adults and children with obstructive HCM and severe drug-refractory symptoms. Myectomy is performed through an aortotomy and involves the resection of a carefully defined, relatively small amount of muscle from the proximal septum, extending from near the base of the aortic valve to beyond the distal margins of mitral leaflets, thereby enlarging the LV outflow tract. As a consequence, in the vast majority of patients, significant mechanical impedance to ejection and mitral valve SAM is abolished immediately. This normalizes LV systolic pressures, abolishes mitral regurgitation and ultimately, reduces left ventricular end-diastolic pressure (LVEDP). Such an abrupt relief of the gradient with surgery is advantageous in patients with severe functional limitations.

**Alcohol Septal Ablation**

A second option to surgery is alcohol septal ablation technique. This catheter interventional treatment involves the introduction of absolute alcohol into a target septal perforator branch of the left anterior descending coronary artery for the purpose of producing a myocardial infarction within the proximal ventricular septum. Septal ablation mimics the hemodynamic consequences of myectomy by reducing the basal septal thickness and excursion (producing akinetic or hypokinetic septal motion), enlarging the LV outflow tract, and thereby, lessening the SAM of the mitral valve and mitral regurgitation.

**Risk Stratification**

The highest risk for SCD has been associated with the following: (1) prior cardiac arrest or spontaneously occurring and sustained ventricular tachycardia (VT); (2) family history of a premature HCM-related SCD, particularly if sudden and in a close relative; (3) identification of a high-risk mutant gene; (4) unexplained syncope, particularly in young patients or when exertional or recurrent; (5) nonsustained VT (of 3 beats or more and of at least 120 beats/minute) evident on ambulatory (Holter) electrocardiogram (ECG) recordings; (6) abnormal blood pressure response during upright exercise which is attenuated or hypotensive, indicative of hemodynamic instability, and of greater predictive value in patients less than 50 years old or if hypotensive and (7) extreme LVH with maximum wall thickness of 30 mm or more, particularly in adolescents and young adults.

**Prevention**

Treatment strategies to prophylactically reduce the risk for SCD or delay progression of congestive symptoms have been predicated on the administration of drugs such as beta-adrenergic blockers, verapamil and Type IA antiarrhythmic agents (i.e. quinidine, procainamide), to those patients perceived to be at high risk. Low dose (< 300 mg) amiodarone has been associated with improved survival in HCM, but this agent requires careful monitoring. The implantable cardioverter-defibrillator (ICD) is the most effective and reliable treatment option available, harboring the potential for absolute protection and altering the natural history of this disease and it is strongly warranted for secondary prevention in those patients with prior cardiac arrest or sustained and spontaneously occurring VT.

**Recommendations for Athletes**

Young patients with HCM should be restricted from intense competitive sports to reduce the risk of SCD that may be associated with such extreme lifestyle. A linkage has been established between SCD and intense exertion, in trained athletes with underlying cardiovascular disease (including HCM) and SCD. There is indirect and circumstantial evidence that the removal of young athletes from the competitive arena reduces the risk for SCD.
Restrictive cardiomyopathy (RCM) is characterized by increased stiffness of the ventricles, leading to compromised diastolic filling with preserved systolic function. These changes may develop in association with local inflammatory or systemic, infiltrative or storage disease. Usually patients develop severe symptoms of heart failure over a short period of time, and the majority die within a few years following diagnosis, unless they receive a cardiac transplant.

Clinical Picture
Restrictive cardiomyopathy patients present with dyspnea, fatigue and limited exercise capacity. They may experience palpitation accompanied by dizziness due to supraventricular arrhythmias (SVT). Thromboembolic complications are common and may be the initial presentation of the condition. In children, RCM may present with failure to thrive, fatigue and even syncope. In advanced cases, patients develop raised jugular venous pressures, peripheral edema, liver enlargement and ascites. Chest radiograph usually shows a normal-sized heart with enlarged atria and variable degrees of pulmonary congestion. The ECG exhibits large P waves indicating biatrial enlargement accompanied by various ST segment and T wave abnormalities. Echocardiography typically reveals biatrial enlargement, a normal or slightly impaired systolic function and mitral inflow Doppler velocities indicative of severe diastolic dysfunction. These include increased ratio of early diastolic filling to atrial filling, decreased E deceleration time and decreased isovolumic relaxation time (IVRT). Invasive pressure measurements within the ventricles during cardiac catheterization are characterized by an early diastolic dip quickly followed by a plateau, also called the “square root sign.” Usually, the diastolic pressure of both ventricles is elevated with the highest plateau being in the left ventricle.

Differentiation of RCM from constrictive pericarditis is important, as patients suffering from the latter condition may recover completely following surgical removal of the fibrotic pericardium. However, the distinction between the two conditions may be difficult. Patients with restriction will not have sufficient respiratory variation. Cardiac magnetic resonance (CMR) and computed tomography (CT) may be useful to assess pericardial thickness, whereas magnetic resonance imaging (MRI) with late enhancement may facilitate diagnosis of infiltrative myocardial disease, for example, amyloidosis. During invasive investigation, it is possible to obtain simultaneous pressure measurements in the ventricles, and both conditions are characterized by rapid early diastolic filling with diastolic dip and plateau waveform. There may be a pressure difference between LVEDP and right ventricular end-diastolic pressure (RVEDP) in RCM, which is considered significant if diastolic pressure is more than 5–7 mm Hg, in contrast to constrictive pericarditis, in which the pressures tend to be equal in both ventricles. Nonetheless, no technique is totally reliable and in some patients it is necessary to perform a diagnostic pericardiectomy.

Prognosis
Restrictive cardiomyopathy carries a poor prognosis, particularly in children, despite optimal medical treatment. Several studies have reported that 66–100% die or receive a cardiac transplant within a few years of diagnosis. The outcome is highly correlated to symptoms and signs of heart failure. Embolic stroke is a common complication as a consequence of large atria and SVT. Therefore, prophylactic anticoagulant therapy should be considered in all RCM patients with enlarged atria even before SVT has developed.

Cardiac Amyloidosis
Cardiac amyloidosis has been classified as a RCM, as deposits of amyloid within the heart typically result in restrictive filling patterns. However, this condition is also characterized by increased ventricular wall thickness and impaired systolic function. Echocardiography often reveals a remarkable homogenous granular sparkling of the myocardium, and valves are often thickened due to amyloid infiltration. In addition, the ECG of patients with cardiac amyloidosis often shows low voltage in standard leads. Cardiac biopsies show typical features of amyloid deposits. A variety of diseases are associated with sporadic occurrence of cardiac amyloidosis, whereas hereditary appearances most often are caused by mutations in the genes for transthyretin and apolipoprotein A1.

Other Familial Causes
Hemochromatosis is an autosomal recessive disorder leading to iron deposition in multiple organs resulting in widespread damage. Although clinical disease expression in many cases is unpredictable, most patients present with a variety of symptoms from different organ systems, whereas only few patients have isolated cardiac manifestations and very rarely RCM. Anderson-Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the gene for alpha-galactosidase A. Glycosphingolipids accumulate in multiple organs and cause substantial morbidity and mortality, especially in men. In women, isolated affection of the heart is more frequent than in men, and affected women most often present with symptoms late in life. Typical echocardiographic findings include LHV, modest diastolic filling abnormalities and thickening of the valves. RCM in the context of Fabry disease with normal ventricular wall thickness is extremely rare. The same seems to be the case with a variety of rare hereditary glycogen storage diseases exhibiting different modes of transmission.

IDIOPATHIC DILATED CARDIOMYOPATHY (TABLES 1 AND 2)
Dilated cardiomyopathy is much more common than the other major forms of cardiomyopathy. It is a heterogeneous disease characterized by ventricular and sometimes atrial dilatation, with normal or reduced wall thickness, eventually leading to varying...
patterns have been studied, but these are quite rare. Transmission. Autosomal recessive, X-linked and mitochondrial cases are now known to exhibit an autosomal dominant pattern of sensitivity needed to demonstrate a genetic linkage. Most of these dilated cardiomyopathy the cases are found to have a familial link, and are termed genetic cause for idiopathic dilated cardiomyopathy, as some 20% of Over the past few years, much attention has been given to finding a Genetics

Incidence
Dilated cardiomyopathy has an incidence of more than 36.5 cases per 100,000 persons, and it accounts for nearly 50,000 hospitalizations and 10,000 deaths each year in the United States. The incidence has increased over the past 5–10 years, perhaps due both to the development of noninvasive diagnostic tools and to improved physician awareness. Dilated cardiomyopathy represents a major health burden. As a result, much research is underway to find better diagnostic techniques and treatment that can decrease morbidity and death. For now, dilated cardiomyopathy remains the primary indication for heart transplantation in the United States.

Genetics
Over the past few years, much attention has been given to finding a genetic cause for idiopathic dilated cardiomyopathy, as some 20% of the cases are found to have a familial link, and are termed familial dilated cardiomyopathy. Moreover, in practice, this percentage most likely represents an underestimation, as our diagnostic tools lack the sensitivity needed to demonstrate a genetic linkage. Most of these cases are now known to exhibit an autosomal dominant pattern of transmission. Autosomal recessive, X-linked and mitochondrial patterns have been studied, but these are quite rare.

TABLE 2 | Predictors of poor prognosis in idiopathic dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Biochemical features</th>
<th>Elevated levels of:</th>
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</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>Atrial natriuretic factor</td>
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<tr>
<td>Epinephrine (adrenaline)</td>
<td>Norepinephrine (noradrenaline)</td>
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<table>
<thead>
<tr>
<th>Clinical features</th>
<th>History of syncope</th>
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<tbody>
<tr>
<td>Male sex</td>
<td>New York Heart Association class IV</td>
</tr>
<tr>
<td>Older age</td>
<td>Persistent third heart sound, gallop rhythm</td>
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<tr>
<td>Signs of right heart failure</td>
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<tr>
<th>Electrocardiographic features</th>
<th>Atrial fibrillation</th>
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<tbody>
<tr>
<td>First-degree or second-degree AV block</td>
<td>Left bundle branch block</td>
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<tr>
<td>Ventricular tachycardia</td>
<td></td>
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</tbody>
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| Exercise test feature | Peak oxygen consumption < 12 mL/kg/minute |

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<tr>
<th>Hemodynamic features</th>
<th>Cardiac index</th>
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<tbody>
<tr>
<td>High right atrial pressure</td>
<td>Low mean arterial pressure</td>
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<tr>
<td>Pulmonary capillary wedge pressure &gt; 20 mm Hg</td>
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<table>
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<tr>
<th>Ventriculographic features</th>
<th>Decreased ventricular mass-volume ratio</th>
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<tr>
<td>Global diffuse wall motion abnormality</td>
<td>Low left ventricular ejection fraction</td>
</tr>
<tr>
<td>Large left ventricular end-diastolic dimension</td>
<td>Right ventricular dilatation</td>
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<tr>
<td>Spherical left ventricular geometry</td>
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<th>Chronic Viral Myocarditis</th>
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Coxsackie A and B viruses or echoviruses can cause acute myocarditis, so experts have hypothesized that idiopathic dilated cardiomyopathy results from a chronic viral myocarditis with progressive myocyte damage and eventually death.

Clinical Features
Patients often present with symptoms relating to LV or biventricular failure, including generalized fatigue, weight loss and loss of appetite. Patients who present in the later stages of heart failure tend to have progressive shortness of breath on exertion, peripheral edema, orthopnea and paroxysmal nocturnal dyspnea as the most common signs and symptoms. Less frequently, idiopathic dilated cardiomyopathy may present with syncope, chest pain, thromboembolism, dysrhythmias and rarely, sudden death. These are seen most often in patients who are diagnosed late in the disease course.

Chest Radiography
Radiographs usually show cardiomegaly with or without pulmonary vascular congestion depending on the degree of heart failure.

Electrocardiography
Electrocardiograms are usually normal in asymptomatic patients with dilated cardiomyopathy. However, ECGs in symptomatic patients often show conduction defects, atrial dysrhythmias and ventricular hypertrophy. The test is worth performing in any patient suspected of having dilated cardiomyopathy, because evidence of ischemia, hypertrophy or conduction system disease helps direct further testing to rule out known causes of these changes.

Echocardiography
Echocardiography is useful in any patient suspected of having any form of dilated cardiomyopathy. It helps rule out known causes of dilated cardiomyopathy, such as valvular heart disease, in which four-chamber dilatation is seen with an impaired LV ejection fraction (< 40%).

Exercise Testing, Coronary Angiography
Exercise testing should be included as part of the workup to assess for coronary artery disease. It may also help in evaluating functional capabilities in patients with previously diagnosed idiopathic dilated cardiomyopathy. Coronary angiography may also be required to definitively exclude ischemic heart disease as a cause of dilated cardiomyopathy. Idiopathic dilated cardiomyopathy remains a possible diagnosis even if none of the major degrees of dilatation may be out of proportion to the extent of ischemia. Dobutamine echocardiography and radionuclide imaging also help to distinguish ischemic cardiomyopathy from idiopathic dilated cardiomyopathy.

Viral Serologic Testing
It may be helpful in patients with chronic immunosuppression (i.e. human immunodeficiency virus, cancer). While it is useful in patients with suspected acute viral myocarditis, it is not routinely recommended in patients with suspected dilated cardiomyopathy, because the results of serologic testing do not influence the treatment.

Endomyocardial Biopsy
It should be reserved for patients with suspected infiltrative disease of the myocardium, such as hemochromatosis or amyloidosis. It may
Cardiology

also be considered in patients with fulminant heart failure, to exclude giant cell myocarditis, which requires early and aggressive treatment.

Treatment

The treatment of idiopathic dilated cardiomyopathy is similar to that of other types of low output heart failure with systolic impairment. Lifestyle modification is important, with thorough patient education about proper diet and exercise and the need to avoid all cardiotoxins (e.g. alcohol). Angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, diuretics, digoxin, antiarrhythmics and anticoagulation are all used to some extent in the medical management of all types of heart failure including idiopathic dilated cardiomyopathy.

Angiotensin-Converting Enzyme Inhibitors

By suppressing the activation of the renin-angiotensin aldosterone system, thereby decreasing both preload and afterload, and by preventing, slowing, or perhaps even reversing remodeling, ACE inhibitors are paramount in the treatment of idiopathic dilated cardiomyopathy. At present, enalapril, captopril, lisinopril, quinapril, ramipril and fosinopril are all approved for the treatment of low-output heart failure due to any cause.

Beta-Blockers

Beta-blockers have become standard treatment for chronic compensated heart failure, complementing the use of ACE inhibitors. By dampening the adrenergic neurohormonal release, beta-blockers have also been shown in numerous studies to decrease cardiovascular morbidity and mortality in heart failure.

Antiarrhythmics and Implantable Cardiac Defibrillator

Many patients with idiopathic dilated cardiomyopathy experience some type of dysrhythmia, such as SVT or nonsustained VT. As maintaining sinus rhythm is essential to maximize cardiac output and reduce the occurrence of emboli, treatment of SVT in these patients does not differ from that in any other clinical setting. Nonsustained VT, a very common entity in these patients, usually requires no treatment, whereas symptomatic sustained VT may require placement of an implantable cardiac defibrillator.

Cardiac Transplantation

When all other treatment options prove unsuccessful and the patient is deemed to have terminal-stage heart failure, heart transplantation may be considered. Idiopathic dilated cardiomyopathy remains the primary indication for heart transplantation in the United States. Success rates are high and continue to improve. Cardiac transplantation seems to be of more benefit in patients with idiopathic dilated cardiomyopathy than in patients with dilated cardiomyopathy due to a known cause. Unfortunately, the scarcity of donor hearts currently limits the use of this treatment option.