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TABLE 266-2 Initial Evaluation of Cardiomyopathy Clinical Evaluation Thorough history and physical examination to identify cardiac and noncardiac disorders Detailed family history of heart failure, cardiomyopathy, skeletal myopathy, conduction disorders, tachyarrhythmias, and sudden death History of alcohol, illicit drugs, chemotherapy or radiation therapy Assessment of changing ability to perform routine and desired activities Assessment of jugular venous pressure, edema, orthostatic blood pressure, adequacy of perfusion Laboratory Evaluation Electrocardiogram Chest radiograph Two-dimensional and Doppler echocardiogram Magnetic resonance imaging for evidence of myocardial inflammation and fibrosis Chemistry: Serum sodium, potassium, calcium, magnesium Fasting glucose (glycohemoglobin in diabetes mellitus) Creatinine, blood urea nitrogen Albumin, total protein, liver function tests Lipid profile Thyroid-stimulating hormone Serum iron, transferrin saturation Urinalysis Creatine kinase isoforms Cardiac troponin level Hematology: Hemoglobin/hematocrit White blood cell count with differential Total eosinophil count if abnormal % on differential Erythrocyte sedimentation rate Evaluation When Specific Diagnoses Are Suspected Respiratory pathogen panel during acute respiratory syndromes Diagnosis of other specific infections such as: Human immunodeficiency virus Chagas’ disease (Trypanosoma cruzi) Lyme disease (Borrelia burgdorferi) and other tick-borne diseases Toxoplasmosis Trichinosis Genetic counseling and testing with multigene cardiomyopathy panel Serologies for active rheumatologic disease Endomyocardial biopsy including sample for electron microscopy when suspecting specific diagnosis with therapeutic implications Catheterization with coronary angiography in patients who have evidence of ischemia/infarction and are candidates for intervention ■ ■FURTHER READING Arbelo E et al: 2023 ESC guidelines for the management of cardiomy opathies. Eur Heart J 44:3503, 2023. Elliott P: Towards a new classification of cardiomyopathies. Curr Cardiol Rep 25:229, 2023. Kontorovich AR: Approaches to genetic screening in cardiomy opathies: Practical guidance for clinicians. JACC Heart Fail 11:133, 2023. Merlo M et al: Clinical application of CMR in cardiomyopathies: Evolving concepts and techniques: A position paper of myocardial and pericardial diseases and cardiac magnetic resonance work ing groups of Italian Society of Cardiology. Heart Fail Rev 28:77, 2023.

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Cardiomyopathies CHAPTER 267 Each of the traditional morphologic forms of cardiomyopathy, hyper trophic, dilated, and restrictive, can be caused or modified by under lying genetic factors (Table 267-1). Estimates for the prevalence of a genetic etiology for cardiomyopathy continue to rise, with increasing availability of genetic testing and attention to the family history. Wellrecognized in hypertrophic cardiomyopathy, heritability is also pres ent in at least 30% of dilated cardiomyopathy (DCM) without other clear etiology. Careful family history should elicit information about not only known cardiomyopathy and heart failure, but also family members who have had sudden death, often incorrectly attributed to a “heart attack,” who have had atrial fibrillation or pacemaker implanta tion by middle age, or who have muscular dystrophy. Genetic Cardiomyopathies Most familial cardiomyopathies are inherited in an autosomal domi nant pattern, with occasional autosomal recessive, matrilineal (mito chondrial), and X-linked inheritance (Table 267-1). Missense variants with amino acid substitutions and truncating variants are the most common genetic abnormalities in cardiomyopathy. Expressed mutant proteins may interfere with function of the normal allele through a dominant negative mechanism. Variants introducing a premature stop codon (nonsense) or shift in the reading frame (frameshift) may create a truncated or unstable protein, the lack of which causes cardiomyopa thy (haploinsufficiency). In some forms of genetic DCM, both haplo insufficiency and the dominant negative effect of a truncated allele may contribute to pathophysiology. Deletions or duplications of an entire exon or gene are uncommon causes of cardiomyopathy, except for the dystrophinopathies. Many different genes have been implicated in human cardiomyopa thy (locus heterogeneity), and many pathogenic or likely pathogenic variants (i.e., variants) within those genes have been associated with disease (allelic heterogeneity). Although most identified variants are “private” to individual families, several specific variants are found repeatedly, either due to a founder effect or recurrent variants at a com mon residue. While most patients with genetic cardiomyopathy have a single rare, “high effect,” disease allele, there is a growing appreciation for the effect of multiple less rare “intermediate effect” alleles on pen etrance and expression. While the additive effects of multiple common alleles/variants captured as a polygenic risk score have shown greatest utility in common diseases such as atherosclerosis, they may also pro vide insight into the subset of patients with primary cardiomyopathy without an identifiable “high effect” allele. Genetic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of cardiomyopathy is rarely present at birth and, in some individuals, may never mani fest. Related individuals who carry the same variant may differ in the severity and rate of progression of cardiac dysfunction and associ ated rhythm disorders, indicating the important role of other genetic, epigenetic, and environmental modifiers in disease expression. Sex appears to play a role, as penetrance and clinical severity may be greater in men for most cardiomyopathies. The clinical course of a patient usu ally cannot be predicted based on which variant is present; thus, cur rent therapy is based on the phenotype rather than the genetic defect. Currently, the greatest utility of genetic testing for cardiomyopathy is to inform family evaluations. However, genetic testing can provide risk stratification in some forms of cardiomyopathy and occasion ally enables the detection of a disease for which specific therapy is indicated, such as the replacements for defective metabolic enzymes in Fabry’s disease and Gaucher’s disease. Moreover, clinical trials are interrogating the role of gene therapies for cardiomyopathy, which will provide greater impetus for genetic testing.

TABLE 267-1 Selected Genetic Defects Associated with Cardiomyopathy GENE PRODUCT INHERITANCE CARDIAC PHENOTYPE Sarcomere ACTC1 (cardiac actin) AD HCM, DCM Yes MYH7 (β

myosin heavy chain) AD HCM, DCM, LVNC Yes Skeletal myopathy PART 6 Disorders of the Cardiovascular System MYBPC3 (myosin binding protein C) AD HCM Yes TNNT2 (cardiac troponin T) AD HCM, DCM, LVNC Yes TNNI3 (cardiac troponin I) AD, AR HCM, DCM, RCM Yes TTN (Titin) AD DCM Yes TPM1 (α-tropomyosin) AD HCM, DCM Yes TNNC1 (cardiac troponin C) AD DCM Yes MYL2 (myosin regulatory light chain) AD HCM Yes Skeletal myopathy MYL3 (myosin essential light chain) AD HCM Yes Z-disk and cytoskeleton DES (desmin) AD RCM, DCM Yes Skeletal myopathy FLNC (filamin C) AD DCM Yes Skeletal myopathy NEXN (nexilin) AD DCM Yes VCL (vinculin) AD DCM Yes Nuclear membrane LMNA (lamin A/C) AD, AR CDDC Yes Skeletal myopathy EMD (emerin) X-linked CDDC No Skeletal myopathy, contractures Excitationcontraction coupling PLN (phospholamban) AD DCM, ARVC Yes SCN5A (NAV 1.5) AD CDDC Yes Note other variants associated with Brugada syndrome RYR2 (cardiac ryanodine receptor) AD ARVC Yes CASQ2 (calsequestrin 2) AR ARVC Yes Cellular metabolism PRKAG2 (γ-subunit of AMP kinase) AD HCM+ Yes LAMP2 (lysosomal associated membrane protein) X-linked HCM+ Nob Danon's disease: skeletal myopathy, cognitive impairment TAZ (tafazzin) X-linked DCM, LVNC No Barth's syndrome: skeletal myopathy, cognitive impairment, neutropenia FXN (frataxin) AR HCM No Friedreich's ataxia: ataxia, diabetes mellitus type 2 TMEM43 (transmembrane protein 43) AD ARVC Yes GLA (α-galactosidase-A) X-linked HCM+ No Fabry's disease: renal failure, angiokeratomas and painful neuropathy Mitochondria Mitochondrial DNA Maternal transmission Sarcolemmal membrane DMD (dystrophin) X-linked DCM Nob Duchenne's and Becker's muscular dystrophy DMPK (dystrophica myotonica protein kinase) AD DCM No Myotonic dystrophy type 1 Desmosome DSP (desmoplakin), JUP (plakoglobin) AD, AR ARVC, DCM Yes Carvajal syndrome (AR), Naxos syndrome (AR), "woolly hair" and hyperkeratosis of palms and soles DSG2 (desmoglein 2), DSC2 (desmocollin 2), PKP2 (plakophilin 2) AD ARVC Yes Other examples RBM20 (RNA binding motif 20) AD DCM Yes BAG3 (BCL2-associated athanogene 3) AD DCM Yes ALPK3 (α-kinase 3) AR HCM Yes aIndicates that the usual clinical presentation is of isolated cardiomyopathy; however, occasionally present extracardiac manifestations are also provided. bIndicates that isolated cardiac phenotype can occur in women with the X-linked defects. Abbreviations: AD, autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CDDC, conduction disease with dilated cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; HCM+, HCM with preexcitation; LVNC, left ventricular noncompaction; MELAS, (mitochondrial) myopathy, encephalopathy, lactic acidosis, and strokelike episodes syndrome; MERRF, myoclonic epilepsy with ragged red fibers; RCM, restrictive cardiomyopathy. The genetic architecture of hypertrophic, dilated, arrhythmogenic, and restrictive cardiomyopathy are overlapping, summarized in Table 267-1 and Fig. 267-1 and detailed in the subsequent sections organized by phenotype. For any patient with suspected or proven genetic disease, family members should be considered and evaluated in a longitudinal fashion.

ISOLATED CARDIAC PHENOTYPEa EXTRACARDIAC MANIFESTATIONS DCM, HCM No MELAS, MERRF, Kearns-Sayre syndrome, ocular myopathy Screening generally includes both an echocardiogram and electrocar diogram (ECG). The indications and implications for confirmatory specific genetic testing vary depending on the specific variant. The profound questions raised by families about diseases shared and passed down merit serious and sensitive discussion, ideally provided by a trained genetic counselor.

FIGURE 267-1 Drawing of myocyte indicating multiple sites of abnormal gene products associated with cardiomyopathy. Major functional groups include the sarcomeric proteins (actin, myosin,

tropomyosin, and the associated regulatory proteins), the dystrophin complex stabilizing and connecting the cell membrane to intracellular structures, the desmosome complexes associated with cell-cell connections and stability, and multiple cytoskeletal proteins that integrate and stabilize the myocyte. ATP, adenosine triphosphate. (Figure adapted from Jeffrey A. Towbin, MD, University of Tennessee Health Science Center.) HYPERTROPHIC CARDIOMYOPATHY ■ ■EPIDEMIOLOGY, ETIOLOGY, AND PATHOLOGY Hypertrophic cardiomyopathy is defined as left ventricular hypertro phy that develops in the absence of causative hemodynamic factors, such as hypertension, aortic valve disease, or systemic infiltrative or storage diseases (Figs. 267-2 and 267-3). It has previously been termed hypertrophic obstructive cardiomyopathy (HOCM); however, the accepted terminology is now hypertrophic cardiomyopathy with or without obstruction. Prevalence in North America, Africa, and Asia is about 1:500. It is a leading cause of sudden death in the young and is an important cause of heart failure. Pediatric presentation is associated with increased early morbidity and mortality, and patients diagnosed as adults have decreased survival compared to age-matched individuals without hypertrophic cardiomyopathy. A sarcomere gene variant is present in ~40–50% of patients with hypertrophic cardiomyopathy and is more common in those with familial disease and characteristic asymmetric septal hypertrophy. More than nine different genes with >1500 variants have been impli cated, although ~80% of patients have a variant in either MYH7 or MYBPC3 (Table 267-1), which encode the thick myofilament of the sarcomere. Hypertrophic cardiomyopathy is characterized by age-dependent and incomplete penetrance. The defining phenotype of left ventricular hypertrophy is rarely present at birth and usually develops later in life.

CHAPTER 267 Genetic Cardiomyopathies Women appear to have lower penetrance of sarcomere variants and an older age at hypertrophic cardiomyopathy diagnosis but subsequently increased rates of heart failure and mortality thereafter. Accordingly, screening of family members should begin in childhood, usually at adolescence, and extend through adulthood. In MYBPC3 variant carriers, the average age of disease development is ~40 years, while 30% remain free from hypertrophy after 70 years. Related individuals who carry the same variant may have a different extent and pattern of hypertrophy (e.g., asymmetric vs concentric), occurrence of outflow tract obstruction, and associated clinical outcomes, although sudden death and progression to heart failure occur more commonly in fami lies with that history. At the level of the sarcomere, hypertrophic cardiomyopathy variants lead to enhanced calcium sensitivity, maximal force generation, and ATPase activity. Calcium handling is affected through modification of regulatory proteins. Sarcomere variants lead to abnormal energetics and impaired relaxation, both directly and as a result of hypertrophy. Hypertrophic cardiomyopathy is characterized by misalignment and disarray of the enlarged myofibrils and myocytes (Fig. 267-4), which can also occur to a lesser extent in other cardiac diseases. Although hypertrophy is the defining feature of hypertrophic cardiomyopathy, fibrosis and microvascular disease are also present. Interstitial fibrosis is detectable before overt hypertrophy develops and likely results from early activation of profibrotic pathways. In the majority of patients with overt cardiomyopathy, focal areas of replacement fibrosis can be readily

PART 6 Disorders of the Cardiovascular System LV Septum MV LA FIGURE 267-2 Hypertrophic cardiomyopathy. This echocardiogram of hypertrophic cardiomyopathy shows asymmetric hypertrophy of the septum compared to the lateral wall of the left ventricle (LV). The mitral valve (MV) is moving anteriorly toward the hypertrophied septum in systole. The left atrium (LA) is

enlarged. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.) Mitral valve Tricuspid valve RV free wall LV free wall RV Chamber LV Chamber IVS FIGURE 267-3 Hypertrophic cardiomyopathy. Gross specimen of a heart with hypertrophic cardiomyopathy removed at the time of transplantation, showing asymmetric septal hypertrophy (septum much thicker than left ventricular free wall) with the septum bulging into the left ventricular outflow tract causing obstruction. The forceps are retracting the anterior leaflet of the mitral valve, demonstrating the characteristic plaque of systolic anterior motion, manifest as endocardial fibrosis on the interventricular septum in a mirror-image pattern to the valve leaflet. There is patchy replacement fibrosis, and small thick-walled arterioles can be appreciated grossly, especially in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.)

FIGURE 267-4 Hypertrophic cardiomyopathy. Microscopic image of hypertrophic cardiomyopathy showing the characteristic disarrayed myocyte architecture with swirling and branching rather than the usual parallel arrangement of myocyte fibers. Myocyte nuclei vary markedly in size, and interstitial fibrosis is present. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.) detected with magnetic resonance imaging (MRI). These areas of "scar" may represent substrate for the development of ventricular arrhyth mias. Increased thickness and decreased luminal area of the intramural vessels in hypertrophied myocardium contribute to microvascular ischemia and angina. Microinfarction of hypertrophied myocardium is a hypothesized mechanism for replacement scar formation. Macroscopically, hypertrophy is typically manifest as nonuniform ventricular thickening (Fig. 267-3). The interventricular septum is the typical location of maximal hypertrophy, although other patterns of hypertrophic remodeling include concentric and midventricular. Hypertrophy confined to the ventricular apex (apical hypertrophic car diomyopathy) is less often familial and has a different genetic substrate, with sarcomere variants present in only ~15%. Left ventricular outflow tract obstruction represents the most common focus of diagnosis and intervention, although diastolic dysfunction, myocardial fibrosis, and microvascular ischemia also contribute to contractile dysfunction and elevated intracardiac pressures. Obstruction is present in ~30% of patients at rest and can be provoked by exercise in another ~30%. Systolic obstruction is initiated by drag forces, which push an anteri orly displaced and enlarged anterior mitral leaflet into contact with the hypertrophied ventricular septum. Mitral leaflet coaptation may ensue, leading to posteriorly directed mitral regurgitation. To maintain stroke volume across outflow tract obstruction, the ventricle generates higher pressures, leading to higher wall stress and myocardial oxygen demand. Smaller chamber size and increased contractility exacerbate the sever ity of obstruction. Conditions of low preload, such as dehydration, and low afterload, such as arterial vasodilation, may lead to transient hypotension and near-syncope. The systolic ejection murmur of left ventricular outflow tract obstruction is harsh and late peaking and can be enhanced by bedside maneuvers that diminish ventricular volume and transiently worsen obstruction, such as the Valsalva maneuver or standing from a squatting position. ■ ■DIAGNOSIS The substantial variability of hypertrophic cardiomyopathy pathology is reflected in the diversity of clinical presentations. Patients may be diagnosed after undergoing evaluations triggered by the abnormal physical findings (murmur) or by symptoms of exertional dyspnea, angina, or syncope.

Alternatively, diagnosis may follow evaluations prompted by the detection of disease in family members. Cardiac imaging (Fig. 267-2) is central to diagnosis, for which the physical examination and ECG are insensitive. The identification of a diseasecausing variant in a proband can focus family evaluations on variant carriers, but this strategy requires a high degree of certainty that the

variant is truly pathogenic and not a benign DNA variant. Biopsy is not recommended to diagnose hypertrophic cardiomyopathy but can be used to exclude infiltrative and metabolic diseases. Rigorous athletic training (athlete's heart) may cause intermediate degrees of physiologic hypertrophy difficult to differentiate from mild hypertrophic cardio myopathy. Unlike hypertrophic cardiomyopathy, hypertrophy in the athlete's heart regresses with cessation of training and is accompanied by supernormal exercise capacity (VO2max >50 mL/kg per min), mild ventricular dilation, and normal diastolic function. TREATMENT Hypertrophic Cardiomyopathy Management focuses on treatment of symptoms and prevention of sudden death and stroke (Fig. 267-5). Left ventricular outflow tract obstruction can be controlled medically in the majority of patients. β-Adrenergic blocking agents and L-type calcium channel block ers (e.g., verapamil) are first-line agents that reduce the severity of obstruction by slowing heart rate, enhancing diastolic filling, and decreasing contractility. Persistent symptoms of exertional dyspnea or chest pain can be controlled occasionally with the addition of disopyramide, an antiarrhythmic agent with potent negative ino tropic properties. The recently introduced small-molecule cardiac myosin inhibitors mavacamten (U.S. Food and Drug Administra tion approved) and aficamten (under investigation) have shown high efficacy in the treatment of symptomatic obstructive hyper trophic cardiomyopathy, including in patients with persistent symptoms despite treatment with a beta blocker and/or those Hypertrophic Cardiomyopathy In all patients, evaluate risk for sudden death No Titrate beta blocker and/or calcium channel blocker If high, consider ICD Evidence of fluid retention? If low, follow with serial evaluation Use diuretics with caution to avoid hypovolemia, particularly in presence of outflow gradient Reevaluate cause of symptoms FIGURE 267-5 Treatment algorithm for hypertrophic cardiomyopathy depending on the presence and severity of symptoms and the presence of an intraventricular gradient with obstruction to outflow. Note that all patients with hypertrophic cardiomyopathy should be evaluated for atrial fibrillation and risk of sudden death, whether or not they require treatment for symptoms. ICD, implantable cardioverter-defibrillator; LV, left ventricular.

considering septal reduction therapy. The principal risk of cardiac myosin inhibitors is a transient reduction in left ventricular ejec tion fraction (LVEF), which warrants frequent echocardiographic monitoring.

Patients with or without obstruction may develop heart failure symptoms due to fluid retention and require diuretic therapies for venous congestion. Severe medically refractory symptoms develop in ~5% of patients, for whom septal reduction therapy with surgical myectomy or alcohol septal ablation may be effec tive. Developed over 60 years ago, surgical myectomy effectively relieves outflow tract obstruction by excising part of the septal myocardium involved in the dynamic obstruction. In selected patients, perioperative mortality is extremely low with excellent long-term survival free from recurrent obstruction and symp toms. Mitral valve repair or replacement is usually unnecessary as associated eccentric mitral regurgitation resolves with myectomy alone. Alcohol septal ablation in patients with suitable coronary anatomy can relieve outflow tract obstruction via a controlled infarction of the proximal septum, which produces similar peri

procedural outcomes and gradient reduction as surgical myec tomy. Although head-to-head comparisons between the two septal reduction therapies do not exist, septal ablation is relegated pri marily to patients who wish to avoid surgery or who have limiting comorbidities. Neither procedure has been shown to improve outcomes other than symptoms. With both procedures, the most common complication is the development of complete heart block necessitating permanent pacing. However, ventricular pacing as a primary therapy for outflow tract obstruction is ineffective and not generally advised. CHAPTER 267 Genetic Cardiomyopathies Symptomatic? Yes Yes Persistent symptoms Outflow gradient? No Yes Try mavacamten or disopyramide Evidence of severe progressive LV dysfunction? No Yes Refractory severe symptoms Rarely, consider cardiac transplantation Consider procedure Septal ablation Septal myectomy

Patients with hypertrophic cardiomyopathy have an increased risk of sudden cardiac death from ventricular tachyarrhythmias. Vigorous physical activity and competitive sports have been his torically prohibited; however, recent studies have failed to identify a relationship between exertion and ventricular arrhythmias in hypertrophic cardiomyopathy, empowering patients and provid ers to make shared decisions about exercise. Factors that increase the risk of sudden death from a baseline of 0.5% per year are pre sented in Table 267-2. As sudden death has not been reduced by medical or procedural interventions, traditionally an implantable cardioverter-defibrillator has been advised for patients with one or more major risk factors and advised on a selected basis for patient with more than one modifying risk factor. Nevertheless, the posi tive predictive value of most risk factors is low, and many patients receiving a defibrillator never receive an appropriate device therapy. A complementary approach to sudden death risk stratification and discussion with patients is the application of an externally validated European Society of Cardiology risk score using major criteria from Table 267-2 and continuous variables such as outflow tract gradi ent and left atrial size. Shared decision-making around implantable

PART 6 Disorders of the Cardiovascular System TABLE 267-2 Risk Stratification for Sudden Death in Hypertrophic Cardiomyopathy MAJOR RISK FACTOR SCREENING TECHNIQUE History of cardiac arrest or spontaneous sustained ventricular tachycardiaa History Syncope Nonvagal, often with or after exertion History Family history of sudden cardiac death Family history Left ventricular apical aneurysm Generally applicable to patients with apical hypertrophy Echocardiography with contrast, cardiac magnetic resonance imaging LV thickness >30 mm Present in <10% of patients Echocardiography or cardiac magnetic resonance imaging LV systolic dysfunction (ejection fraction <50%) Present in <10% of patients Echocardiography or cardiac magnetic resonance imaging Variables Utilized in the European Society of Calculator for Estimated Risk of Sudden Death LV outflow tract gradient Peak gradient measured at rest or with the Valsalva maneuver, mmHg Echocardiography Left atrial diameter Diameter measured in the parasternal long axis, mm Echocardiography LV thickness Maximal wall thickness, mm Echocardiography Age Syncope, family history, nonsustained ventricular tachycardia As above As above Modifying Risk Factors Late gadolinium enhancement As a percentage of myocardial mass Cardiac magnetic resonance imaging Spontaneous nonsustained ventricular tachycardia

> 3 beats at rate >120 Exercise or 24-h to 48-h ambulatory recording aImplantable cardioverter-defibrillator advised for patients with prior arrest or

> sustained ventricular tachycardia regardless of other risk factors if life expectancy is estimated to be >1 year. The European Society of Cardiology risk calculator can be found at https://doc2do.com/hcm/webHCM.html and provides an estimated 5-year risk of cardiac arrest. Patients with estimated risk of ≥6% are generally advised placement of an implantable cardioverter-defibrillator; those with risk between 4 and 6% can be considered for implant, and implant is not advised when risk is <4%. Emerging risk factors merit further clinical validation. Abbreviation: LV, left ventricle.

cardioverter-defibrillator implantation for primary prevention has emphasized discussions of estimated risk levels rather than dichoto mous yes–no criteria. Long-term use of a defibrillator may be associated with serious device-related complications, particularly in young active patients. Refinement of sudden death risk through the application of contemporary technologies such as cardiac MRI is ongoing. Atrial fibrillation is common in patients with hypertrophic cardiomyopathy and may lead to hemodynamic deterioration and embolic stroke. Rapid ventricular response is poorly tolerated and may worsen outflow tract obstruction. β-Adrenergic blocking agents and L-type calcium channel blockers slow atrioventricular (AV) nodal conduction and improve symptoms; cardiac glyco sides should be avoided, as they may increase contractility and worsen obstruction. Even with adequate rate control, symptoms exacerbated by atrial fibrillation may persist due to loss of AV syn chrony and may require restoration of sinus rhythm. Disopyramide and amiodarone are the preferred antiarrhythmic agents, with radiofrequency ablation considered for medically refractory cases. Anticoagulation to prevent embolic stroke in atrial fibrillation is recommended. ■ ■PROGNOSIS The general prognosis for hypertrophic cardiomyopathy is better than in early studies of referral populations, but mortality remains higher than in an age-matched population without cardiomyopathy. The sud den death risk is <1% per year; however, up to 1 in 20 patients will progress to overt systolic dysfunction with a reduced ejection fraction (<50%) with or without dilated remodeling (i.e., “burned out” or endstage hypertrophic cardiomyopathy). These patients may suffer from low cardiac output and have an increased risk of death from progres sive heart failure and sudden death unless they undergo timely cardiac transplantation. GENETIC DILATED AND ARRHYTHMOGENIC CARDIOMYOPATHY ■ ■EPIDEMIOLOGY, ETIOLOGY, AND PATHOLOGY As outlined in Chap. 266, an enlarged left ventricle with reduced systolic function as measured by LVEF characterizes DCM, which is considered to be present when the LVEF is ≤0.50 and/or the left ven tricular diastolic dimension is >95% predicted for age and sex. In some patients with reduced LVEF, the left ventricular dilation is minimal, sometimes referred to as nondilated or minimally dilated cardiomy opathy (Figs. 267-6, 267-7, and 267-8). While diverse etiologies may cause DCM and arrhythmogenic car diomyopathy (ACM), familial clustering is present in ~30–40% of cases and monogenic etiologies can be identified in ~25%. Sarcomere variants are most associated with hypertrophic cardio myopathy; however, they are also implicated in DCM. The most com mon genetic causes of DCM are truncating variants of the giant protein titin, encoded by TTN, which maintains sarcomere structure and acts as a key signaling molecule. As cytoskeletal proteins play crucial roles in the structure, connec tion, and stability of the myocyte, multiple defects in these proteins can lead to dilated cardiomyopathy (Fig. 267-1). For example, desmin forms intermediate filaments that connect the nuclear and plasma membranes, Z-lines, and the intercalated disks between muscle cells. Desmin variants impair the transmission of force and signaling for both

cardiac and skeletal muscle and may cause combined cardiac and skeletal myopathy, more commonly with a restrictive phenotype (RCM) than dilated phenotype (DCM). Defects in the sarcolemmal membrane proteins are associated with DCM. The best known is dystrophin, encoded by the X chromosome gene DMD, abnormalities of which cause Duchenne's and Becker's muscle dystrophy. This protein provides a network that supports the sarcolemma and also connects to the sarcomere. The progressive func tional defect in both cardiac and skeletal muscle reflects vulnerability

FIGURE 267-6 Dilated cardiomyopathy. This gross specimen of a heart removed at the time of transplantation shows massive left ventricular dilation and moderate right ventricular dilation. Although the left ventricular wall in particular appears thinned, there is significant hypertrophy of this heart, which weighs >800 g (upper limit of normal = 360 g). A defibrillator lead is seen traversing the tricuspid valve into the right ventricular apex. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.) LV RV LA RA FIGURE 267-7 Dilated cardiomyopathy. This echocardiogram of a young man with dilated cardiomyopathy shows massive global dilation and thinning of the walls of the left ventricle (LV). The left atrium (LA) is also enlarged compared to normal. Note that the echocardiographic and pathologic images are vertically opposite, such that the LV is by convention on the top right in the echocardiographic image and bottom right in the pathologic images. RA, right atrium; RV, right ventricle. (Image courtesy of Justina Wu, MD, Brigham and Women's Hospital, Boston.)

CHAPTER 267 Genetic Cardiomyopathies FIGURE 267-8 Dilated cardiomyopathy. Microscopic specimen of a dilated cardiomyopathy showing the nonspecific changes of interstitial fibrosis and myocyte hypertrophy characterized by increased myocyte size and enlarged, irregular nuclei. Hematoxylin and eosin–stained section, 100× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women's Hospital, Boston.) to mechanical stress. Defects in the sarcolemmal channel proteins (channelopathies) are generally associated with primary arrhythmias, but variants in SCN5A, the α subunit of the Nav 1.5 ion channel pro tein, distinct from those that cause the Brugada or long QT syndromes, have been implicated in DCM with conduction disease. Nuclear membrane protein defects in cardiac and skeletal muscle occur in either autosomal (lamin A/C) or X-linked (emerin) pat terns. These defects are associated with a high prevalence of atrial and ventricular arrhythmias and conduction system disease, which can occur in some family members without or before detectable cardiomy opathy and underlie gene-specific risk stratification for sudden death and different utilization criteria for primary prevention implantable cardioverter-defibrillators in these patients. Intercalated disks contribute to intracellular connections, allowing mechanical and electrical coupling between cells and also connec tions to desmin filaments within the cell. Variants in proteins of the desmosomal complex compromise attachment of the myocytes, which can become disconnected and die via activation of Wnt/β-catenin and proinflammatory signaling pathways, to be replaced by fat and fibrous tissue. These areas are highly arrhythmogenic and may dilate to form aneurysms. Although more often noted in the right ventricle (arrhyth mogenic right ventricular cardiomyopathy), this condition can be restricted to the left ventricle (especially when secondary to truncating variants in DSP, which encodes desmoplakin) or affect both ventricles and has also been termed "arrhythmogenic cardiomyopathy." The recognized frequency of familial involvement in DCM has increased to >30%. Truncating variants in TTN, encoding the giant sar comeric protein titin, are the most common cause of DCM, accounting for up to 25% of familial disease. On average, men with

TTN truncat ing variants develop cardiomyopathy a decade before women, without distinctive clinical features. Variants in thick and thin filament genes account for ~8% of DCM and may manifest in early childhood. ■ ■PROGNOSIS Prognosis and therapy of DCM and ACM are dictated primarily by the stage of clinical disease and the risk for sudden death, which also varies based on disease gene (higher for patients with variants in DES, DSP, DSC2, DCG2, FLNC, LMNA, PKP2, PLN, RBM20, SCN5A, and TMEM43). The rate of progression of disease is also heritable, with marked variation based on disease gene observed (e.g., patients with TTN truncating variants frequently experience recovery with medical therapy). Medical therapy is generally guided by the phenotype, such that patients with DCM and reduced LVEF are treated with thera pies recommended for heart failure with reduced ejection fraction

(Chap. 264). As for HCM, shared decision-making is needed regarding implantable cardioverter-defibrillators. However, the specific genotype plays a greater role in decisions regarding DCM, for which some fea tures may warrant implantable cardioverter-defibrillator placement before the LVEF has declined to 0.35, such as the presence of patho genic LMNA or FLNC variants or a family history of sudden death at early ages.

PART 6 Disorders of the Cardiovascular System Arrhythmogenic right ventricular cardiomyopathy (ARVC) has an established diagnostic framework (task force criteria) that rests upon identifying and quantifying right ventricular dilation, dyski nesis, and ECG abnormalities (repolarization, depolarization, and arrhythmias) in the context of a suggestive family history of genetic test results. Overlapping with ARVC and DCM is ACM, in which ventricular arrhythmias may precede or supersede the severity of predominantly left ventricular remodeling. Unlike ARVC, consensus diagnostic criteria for ACM are lacking. Early stages of ARVC and ACM may be restricted to ventricular arrhythmias, and over years, ventricular dilation, hypokinesis, and failure may ensue. Patients with an initial presentation of right ventricular cardiomyopathy who progress to include left ventricular dysfunction are at high risk for adverse events. CARDIOMYOPATHY DUE TO INHERITED DISORDERS OF METABOLISM Multiple genetic disorders of metabolic pathways can cause myocardial disease, due to infiltration of abnormal products or cells containing them between the myocytes, and storage disease, due to their accumu lation within cells (Table 267-1). Hypertrophic cardiomyopathy may be mimicked by the myocardium thickened with these abnormal products causing “pseudohypertrophy,” usually with an abnormally short PR interval. The pseudohypertrophic phenotype is most common, but restrictive cardiomyopathy and DCM may occur. Most of these dis eases are diagnosed during childhood. Fabry’s disease results from a deficiency of the lysosomal enzyme alpha-galactosidase A caused by variants in GLA. This disorder of glycosphingolipid metabolism is an X-linked disorder that may also cause clinical disease in female carriers. Glycolipid accumulation may be limited to the cardiac tissues but usually also involves the skin, peripheral nerve, and kidney. Electron microscopy of endomyocardial biopsy tissue shows diagnostic vesicles containing concentric lamellar figures (Fig. 267-9). Diagnosis can be made through assessment of enzyme activity and/or GLA sequencing and is crucial because enzyme replacement can reduce abnormal deposits and improve cardiac and clinical function. The magnitude of clinical impact has not been well established for this therapy, which requires frequent infusions of the enzyme at a cost of >$100,000 a year. The oral chaperone therapy, migalastat, stabilizes mutant forms of alpha-galactosidase, increases enzymatic activity, and was approved for use in a subset of patients with Fabry’s disease bearing variants amenable to this therapy. Carnitine is an essential cofactor in long-chain fatty acid metabo lism. Multiple defects have been

described that lead to carnitine deficiency, causing intracellular lipid inclusions and restrictive car diomyopathy or DCM, often presenting in children. Fatty acid oxida tion requires many metabolic steps with specific enzymes that can be deficient, with complex interactions with carnitine. Depending on the defect, cardiac and skeletal myopathy can be ameliorated with replace ment of fatty acid intermediates and carnitine. Two monogenic metabolic cardiomyopathies cause increased ven tricular wall thickness without an increase of muscle subunits or an increase in contractility. Variants in the gamma-2 regulatory subunit of the adenosine monophosphate (AMP)-activated protein kinase important for glucose metabolism (PRKAG2) have been associated with a high prevalence of conduction abnormalities, such as AV block and ventricular preexcitation. Several defects have been reported in an X-linked lysosome-associated membrane protein (LAMP2). This defect can be maternally transmitted or sporadic and has occasion ally been isolated to the heart, although it often leads to a syndrome of skeletal myopathy, intellectual disability, and hepatic dysfunction

FIGURE 267-9 Fabry’s disease. Transmission electron micrograph of a right ventricular endomyocardial biopsy specimen at high magnification showing the characteristic concentric lamellar inclusions of glycosphingolipids accumulating as a result of deficiency of the lysosomal enzyme alpha-galactosidase A. Image taken at 15,000× original magnification. (Image courtesy of Robert Padera, MD, PhD, Department of Pathology, Brigham and Women’s Hospital, Boston.) referred to as Danon disease. Extreme left ventricular hypertrophy appears early, often in childhood, and can progress rapidly to end-stage heart failure with low ejection fraction. Electron microscopy of these metabolic disorders shows that the myocytes are enlarged by multiple intracellular vacuoles of metabolic by-products. Gene therapy using a viral vector to deliver functional LAMP2 to cardiomyocytes is currently under study in humans with Danon disease. RESTRICTIVE CARDIOMYOPATHY Most restrictive cardiomyopathy (RCM) is due to acquired causes, and there is increasing emphasis to diagnose amyloidosis due to transthyre tin variants (see Chap. 266). Inherited metabolic and storage diseases can cause RCM, as can variants in DES causing combined cardiac and skeletal myopathy and sarcomere variants causing an overlap of RCM and hypertrophic cardiomyopathy. ■ ■FURTHER READING Arbelo E et al: ESC guidelines for the management of cardiomyopa thies. Eur Heart J 44:3503, 2023. Gasperetti A et al: Arrhythmic risk stratification in arrhythmogenic right ventricular cardiomyopathy. Europace 25:euad312, 2023. Groh WJ et al: 2022 HRS expert consensus statement on evaluation and management of arrhythmic risk in neuromuscular disorders. Heart Rhythm 19:e61, 2022. Helms AS et al: Translation of new and emerging therapies for genetic cardiomyopathies. JACC Basic Transl Sci 7:70, 2021. Heymans S et al: Dilated cardiomyopathy: Causes, mechanisms, and current and future treatment approaches. Lancet 402:998, 2023. Ho CY et al: Genotype and lifetime burden of disease in hypertrophic cardiomyopathy insights from the Sarcomeric Human Cardiomyopa thy Registry (SHaRe). Circulation 138:1387, 2018. Lampert R et al: Vigorous exercise in patients with hypertrophic car diomyopathy. JAMA Cardiol 8:595, 2023. Mazzarotto F et al: Reevaluating the genetic contribution of mono genic dilated cardiomyopathy. Circulation 141:387, 2020. Olivotto I et al: Mavacamten for treatment of symptomatic obstruc tive hypertrophic cardiomyopathy (EXPLORER-HCM): A random ized, double-blind, placebo-controlled, phase 3 trial. Lancet 396:759, 2020. Orsborne C et al: Disease-specific therapy for the treatment of car diovascular manifestations of Fabry disease: A systemic review. Heart 110:19, 2023.

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