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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

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Abstract—Classifications of heart muscle diseases have proved to be exceedingly complex and in many respects contradictory. Indeed, the precise language used to describe these diseases is profoundly important. A new contemporary and rigorous classification of cardiomyopathies (with definitions) is proposed here. This reference document affords an important framework and measure of clarity to this heterogeneous group of diseases. Of particular note, the present classification scheme recognizes the rapid evolution of molecular genetics in cardiology, as well as the introduction of several recently described diseases, and is unique in that it incorporates ion channelopathies as a primary cardiomyopathy. (*Circulation*. 2006;113:1807-1816.)

Key Words: AHA Scientific Statements ■ cardiomyopathies ■ arrhythmias ■ terminology ■ genetics

Cardiomyopathies are an important and heterogeneous group of diseases. The awareness of cardiomyopathies in both the public and medical communities historically has been impaired by persistent confusion surrounding definitions and nomenclature. Classification schemes, of which there have been many,¹⁻⁸ are potentially useful in drawing relationships and distinctions between complex disease states for the purpose of promoting greater understanding; indeed, the precise language used to describe these diseases is profoundly important.

However, many classifications offered in the literature and in textbooks are to some degree contradictory in presentation. The last formal effort at developing a consensus for a classification of cardiomyopathies was 11 years ago (1995) in the form of a very brief document under the auspices of the World Health Organization (WHO).¹ However, with the identification of several new disease entities over the past decade, dramatic advances in diagnosis, and precise knowl-

edge of causation, some disease definitions have become outdated and render the WHO classification obsolete in many respects.¹ The past decade has witnessed a rapid evolution of molecular genetics in cardiology⁹⁻¹⁴ and the emergence of ion channelopathies as diseases predisposing to potentially lethal ventricular tachyarrhythmias that are characterized by mutations in ion channel proteins leading to dysfunctional sodium, potassium, calcium, and other ion channels.

These considerations provide the opportunity to develop a new and rigorous framework and classification of cardiomyopathies. Therefore, it is timely to assemble this expert consensus panel under the auspices of the American Heart Association to construct a contemporary reference document for the classification of cardiomyopathies that relies substantially on recent advances made in the characterization of diseases affecting the myocardium, supported by previously published guidelines that direct clinical practice.¹⁵⁻¹⁷ This new classification scheme affords a large measure of clarity

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to this area of investigation and is intended to facilitate interaction among the clinical and research communities in assessing these complex diseases. Although we would expect this classification to take the place of the WHO document, as new data continue to emerge, the proposed classification scheme undoubtedly will itself require revision in the future.

The contemporary definitions of cardiomyopathies presented here are in concert with the molecular era of cardiovascular disease and have direct clinical applications and implications for cardiac diagnosis. However, the classification of cardiomyopathies presented herein is not intended to provide precise methodologies or strategies for clinical diagnosis. Rather, the classification of cardiomyopathies represents a scientific presentation that offers new perspectives to aid in understanding this complex and heterogeneous group of diseases and basic disease mechanisms.

General Considerations

Historical Context

The concept of heart muscle diseases has a notable and evolving history. In the mid 1850s, chronic myocarditis was the only recognized cause of heart muscle disease.² In 1900, the designation of primary myocardial disease was introduced, and it was not until 1957 that the term “cardiomyopathy” was used for the first time. Over the subsequent 25 years, a number of definitions for cardiomyopathies were advanced in concert with an increasing awareness and understanding of these diseases. Indeed, in the original 1980 WHO classification,³ cardiomyopathies were defined only as “heart muscle diseases of unknown cause,” reflecting a general lack of information available about causation and basic disease mechanisms. In 1968, the WHO defined cardiomyopathies as “diseases of different and often unknown etiology in which the dominant feature is cardiomegaly and heart failure.”² The updated and most recent WHO definition in 1995¹ was “diseases of myocardium associated with cardiac dysfunction” and included newly recognized arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) and primary restrictive cardiomyopathy for the first time.

Pitfalls

Classifications for heart muscle disease have proved to be exceedingly complex. Indeed, through the years, a variety of systematic classifications have been presented that were designed for physicians and biomedical scientists and based on a variety of premises, including origin, anatomy, physiology, primary treatments, method of diagnosis, biopsy histopathology, and symptomatic state. However, an inevitable limitation of any classification is the considerable overlap encountered between categories into which diseases have been segregated. Therefore, although the objective is a classification that can be appreciated by all interested parties and disciplines, it is acknowledged that each has shortcomings and that no past, present, or future classification of cardiomyopathies is likely to satisfy the purposes of all users.

In particular, the popular classification of “hypertrophic-dilated-restrictive cardiomyopathies” has major limitations and underscores the particular difficulties in this regard by

mixing anatomic designations (ie, hypertrophic and dilated) with a functional one (ie, restrictive). Consequently, confusion may arise because the same disease could appear in 2 categories. Furthermore, such a classification fails to recognize the heterogeneity of clinical expression now attributable to many of these diseases. For example, hypertrophic cardiomyopathy (HCM) and infiltrative and storage cardiomyopathies are characterized by often substantial left ventricular (LV) hypertrophy with increased wall thickness in the absence of ventricular dilatation, but they also are frequently associated with restriction to diastolic filling. Knowledge of the genetic basis for HCM and other cardiomyopathies has led to the identification of some individuals with a disease-causing gene mutation but without evidence of LV hypertrophy. Indeed, gene-based insights into pathophysiology may define more subtle clinical manifestations than hypertrophy. In addition, dilated forms of cardiomyopathy have considerably increased cardiac mass (weight) with myocyte enlargement, indicative of cardiac hypertrophy even with absolute LV wall thicknesses that are within normal limits.

Furthermore, some diseases do not have a uniformly static expression and may evolve, as a consequence of remodeling, from one category to another during their natural clinical course; eg, HCM, amyloid, and other infiltrative conditions may progress from a nondilated (often hyperdynamic) state with ventricular stiffness to a dilated form with systolic dysfunction and failure. Finally, because quantitative assessments of ventricular size represent a continuum and patients can vary widely in their degree of dilatation (including often minimal cavity enlargement early in a disease process), it often is difficult to rigidly distinguish dilated and nondilated forms of cardiomyopathy. This ambiguity also may arise with some rare, or newly identified, cardiac diseases in young patients for which few quantitative cardiac dimensional data are available. Indeed, as new cardiomyopathies have been defined (often by genomics) and knowledge of pathological disease spectrums has evolved, the dilated-hypertrophic-restrictive classification has become less tenable and useful and probably should be abandoned.

General etiologic classifications of cardiomyopathies also are problematic, given that diseases with the same (or similar) phenotypes can harbor diverse origins and mechanisms. For example, dilated cardiomyopathy (DCM) has been reported to have genetic, infectious, autoimmune, and toxic causes (and in some cases remains “idiopathic”), all leading to the final common pathway of ventricular dilatation and systolic dysfunction. Alternatively, functional (ie, physiological) classifications, seemingly most useful to clinicians with relevance to treatment considerations, are in fact of limited value because management strategies are dynamic and inevitably evolve for these diseases.

Although the panel regards the present AHA classification scheme as the best available “snapshot” at this point in time, it has been formulated to simplify terminology and to represent a flexible “living document” that is amenable to new information and future revision, particularly as the molecular biology of cardiomyopathies evolves.

Definitions and Proposed Contemporary Classification (2006)

Definitions

The expert consensus panel proposes this definition: *Cardiomyopathies are a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic. Cardiomyopathies either are confined to the heart or are part of generalized systemic disorders, often leading to cardiovascular death or progressive heart failure-related disability.*

Within this broad definition, cardiomyopathies usually are associated with failure of myocardial performance, which may be mechanical (eg, diastolic or systolic dysfunction) or a primary electrical disease prone to life-threatening arrhythmias. Indeed, the ion channelopathies (long-QT syndrome [LQTS] and Brugada syndrome among others) are primary electrical diseases without gross or histopathological abnormalities in which the functional and structural myocardial abnormalities responsible for arrhythmogenesis are at the molecular level in the cell membrane itself. Therefore, the basic pathological abnormality in these diseases is not identifiable by either conventional noninvasive imaging or myocardial biopsy during life or even by autopsy examination of tissue. Nevertheless, the panel believes that it is justifiable to include the ion channelopathies in the present contemporary classification of cardiomyopathies on the basis of the scientifically reasonable (but largely hypothetical) assertion that ion channel mutations are responsible for altering biophysical properties and protein structure, thereby creating structurally abnormal ion channel interfaces and architecture.

Consequently, the genomic and molecular orientation of this proposed cardiomyopathy classification represents a distinct and major departure from prior efforts. It is predicated on the view that causative mutations in genes encoding proteins regulating the transport of ions (such as sodium, potassium, and calcium) across the cell membrane are ultimately responsible for a structural disease state that triggers primary life-threatening ventricular tachyarrhythmias.

Although the present classification relies substantially on contemporary molecular biology, taking into account cellular levels of expression of encoded proteins and underlying gene mutations (and that many cardiomyopathies are now known to be familial), it probably is premature and inadvisable at this time to preferentially formulate a classification that is entirely dependent on genomics. The molecular genetics of myocardial disease is not yet completely developed, and more complex genotype-phenotype relationships will continue to emerge for these diseases. For example, several sarcomeric gene mutations are now known to cause both DCM and HCM. Furthermore, troponin I mutations have been reported to cause both HCM and a restrictive form of cardiomyopathy.

It is also important to specify those disease entities that have not been included as cardiomyopathies in the present contemporary classification. These include pathological myocardial processes and dysfunction that are a direct consequence of other cardiovascular abnormalities such as that

which occurs with valvular heart disease, systemic hypertension, congenital heart disease, and atherosclerotic coronary artery disease producing ischemic myocardial damage secondary to impairment in coronary flow. Therefore, the commonly used term “ischemic cardiomyopathy,” referring to myocardial ischemia and infarction, is not supported by this panel, nor is it part of the formal classification scheme. The following conditions also have not been considered as part of this cardiomyopathy classification: metastatic and primary intracavitary or intramyocardial cardiac tumors, diseases affecting endocardium with little or no myocardial involvement, and the imprecisely defined entity of hypertensive HCM.

Classification

Cardiomyopathies are divided into 2 major groups based on predominant organ involvement. *Primary* cardiomyopathies (genetic, nongenetic, acquired) are those solely or predominantly confined to heart muscle and are relatively few in number (Figure). *Secondary* cardiomyopathies show pathological myocardial involvement as part of a large number and variety of generalized systemic (multiorgan) disorders (Table). These systemic diseases associated with secondary forms of cardiomyopathies have previously been referred to as “specific cardiomyopathies” or “specific heart muscle diseases” in prior classifications, but that nomenclature has been abandoned here. The frequency and degree of secondary myocardial involvement vary considerably among these diseases, some of which are exceedingly uncommon and for which the evidence of myocardial pathology may be sparse and reported in only a few patients. Because many cardiomyopathies may predominantly involve the heart but are not necessarily confined to that organ, some of the distinctions between primary and secondary cardiomyopathy are necessarily arbitrary and inevitably rely on judgment about the clinical importance and consequences of the myocardial process.

Therefore, on the basis of all these considerations, the panel recommends that cardiomyopathies can be most effectively classified as primary: genetic, mixed (genetic and nongenetic), acquired; and secondary.

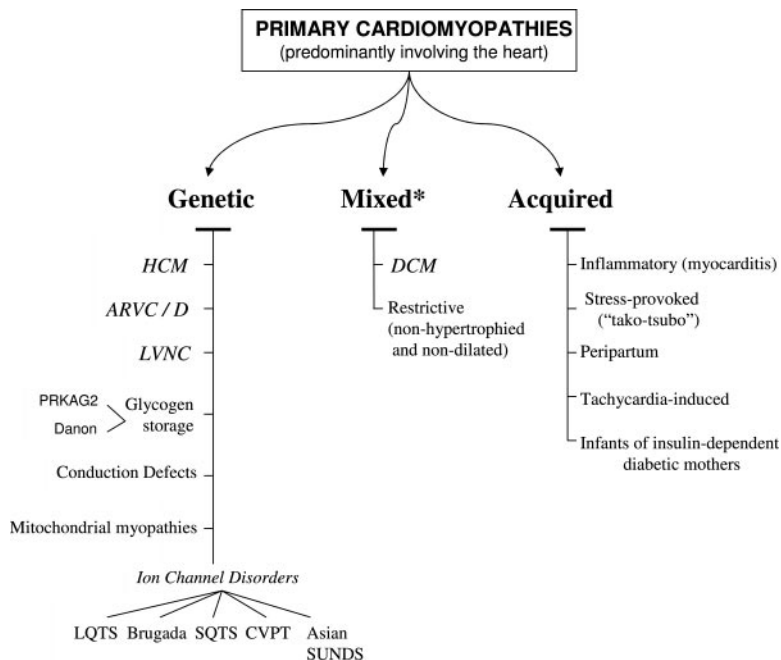
Primary Cardiomyopathies

Genetic

Hypertrophic Cardiomyopathy

HCM is a clinically heterogeneous but relatively common autosomal dominant genetic heart disease (1:500 of the general population for the disease phenotype recognized by echocardiography) that probably is the most frequently occurring cardiomyopathy. Data from the United States indicate that HCM is the most common cause of sudden cardiac death in the young (including trained athletes) and is an important substrate for heart failure disability at any age.

HCM is characterized morphologically and defined by a hypertrophied, nondilated LV in the absence of another systemic or cardiac disease that is capable of producing the magnitude of wall thickening evident (eg, systemic hypertension, aortic valve stenosis). Clinical diagnosis is customarily



Primary cardiomyopathies in which the clinically relevant disease processes solely or predominantly involve the myocardium. The conditions have been segregated according to their genetic or nongenetic etiologies. *Predominantly nongenetic; familial disease with a genetic origin has been reported in a minority of cases.

made with 2-dimensional echocardiography (or alternatively with cardiac magnetic resonance imaging) by detection of otherwise unexplained LV wall thickening, usually in the presence of a small LV cavity, after suspicion is raised by the clinical profile or as part of family screening.

When LV wall thickness is mild, differential diagnosis with physiological athlete's heart may arise. Furthermore, individuals harboring a genetic defect for HCM do not necessarily express clinical markers of their disease such as LV hypertrophy on echocardiogram, ECG abnormalities, or symptoms at all times during life, and ECG alterations can precede the appearance of hypertrophy. Indeed, virtually any LV wall thickness, even when within normal limits, is consistent with the presence of an HCM-causing mutant gene, and diagnosis can be made by laboratory DNA analysis. Furthermore, recognition of LV hypertrophy may be age related with its initial appearance delayed well into adulthood (adult morphological conversion). Most HCM patients have the propensity to develop dynamic obstruction to LV outflow under resting or physiologically provokable conditions, produced by systolic anterior motion of the mitral valve with ventricular septal contact.

HCM is caused by a variety of mutations encoding contractile proteins of the cardiac sarcomere. Currently, 11 mutant genes are associated with HCM, most commonly β -myosin heavy chain (the first identified) and myosin-binding protein C. The other 9 genes appear to account for far fewer cases of HCM and include troponin T and I, regulatory and essential myosin light chains, titin, α -tropomyosin, α -actin, α -myosin heavy chain, and muscle LIM protein. This genetic diversity is compounded by considerable intragenic heterogeneity, with >400 individual mutations now identified. These most commonly are missense mutations but include insertions, deletions, and splice (split-site) mutations encoding truncated sarcomeric proteins. The characteristic diversity of the HCM phenotype is attributable to the disease-

causing mutations and probably to the influence of modifier genes and environmental factors.

In addition, nonsarcomeric protein mutations in 2 genes involved in cardiac metabolism have recently been reported to be responsible for primary cardiac glycogen storage diseases in older children and adults with a clinical presentation mimicking (or indistinguishable from) that of sarcomeric HCM. One of these conditions involves the gene encoding the γ -2-regulatory subunit of the AMP-activated protein kinase (PRKAG2), associated with variable degrees of LV hypertrophy and ventricular preexcitation. The other involves the gene encoding lysosome-associated membrane protein 2 (LAMP-2), resulting in Danon-type storage disease. Clinical manifestations are limited largely to the heart, usually with massive degrees of LV hypertrophy and ventricular preexcitation. These disorders are now part of a subgroup of previously described infiltrative forms of LV hypertrophy such as Pompe disease, a glycogen storage disease caused by α -1,4 glycosidase (acid maltase deficiency) in infants, and Fabry's disease, an X-linked recessive disorder of glycosphingolipid metabolism caused by a deficiency of the lysosomal enzyme α -galactosidase A, resulting in intracellular accumulation of glycosphingolipids. Undoubtedly, many other mutations causing cardiac hypertrophy by disrupting sarcomere, metabolic, and other genes remain to be identified.

A number of other diseases associated with LV hypertrophy involve prominent thickening of the LV wall, occurring mostly in infants and children ≤ 4 years of age, which may resemble or mimic typical HCM caused by sarcomere protein mutations. These cardiomyopathies include secondary forms such as Noonan syndrome, an autosomal dominant cardiofacial condition associated with a variety of cardiac defects (most commonly, dysplastic pulmonary valve stenosis and atrial septal defect) resulting from mutations in PTPN11, a gene encoding the nonreceptor protein tyrosine phosphatase

SHP-2 genes. At present, the causes of most cases of pediatric cardiomyopathies are unknown.

Other diseases in this category are mitochondrial myopathies resulting from mutations encoding mitochondrial DNA (including Kearns-Sayre syndrome) or mitochondrial proteins associated with ATP electron transport chain enzyme defects that alter mitochondrial morphology. Also included in these considerations are metabolic myopathies representing ATP production and utilization defects involving abnormalities of fatty acid oxidation (acyl CoA dehydrogenase deficiencies) and carnitine deficiency, as well as infiltrative myopathies, ie, glycogen storage diseases (type II; autosomal recessive Pompe disease), Hunter's and Hurler's diseases, and the transient and nonfamilial cardiomyopathy as part of generalized organomegaly, recognized in infants of insulin-dependent diabetic mothers. In older patients, a number of systemic diseases have been associated with hypertrophic forms of cardiomyopathy; these include Friedreich's ataxia, pheochromocytoma, neurofibromatosis, lentiginosis, and tuberous sclerosis.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

ARVC/D is an uncommon form of inheritable heart muscle disease (estimated 1:5000) with a relatively recent description (\approx 20 years ago). ARVC/D involves predominantly the right ventricle with progressive loss of myocytes and fatty or fibrofatty tissue replacement, resulting in regional (segmental) or global abnormalities. Although frequently associated with myocarditis (enterovirus or adenovirus in some cases), ARVC/D is not considered a primary inflammatory cardiomyopathy. In addition, evidence of LV involvement with fibrofatty replacement, chamber enlargement, and myocarditis is reported in up to 75% of patients.

ARVC/D has a broad clinical spectrum, usually presenting clinically with ventricular tachyarrhythmias (eg, monomorphic ventricular tachycardia). A recognized cause of sudden cardiac death in the young, it is also regarded as the most common cause of sudden death in competitive athletes in Italy. Noninvasive clinical diagnosis may be confounding, without an easily obtained single test or finding that is definitively diagnostic, and generally requires an integrated assessment of electrical, functional, and anatomic abnormalities. Diagnosis often requires a high index of suspicion, frequently triggered by presentation with arrhythmias, syncope, or cardiac arrest, as well as global or segmental chamber dilatation or wall motion abnormalities.

Noninvasive tests used to diagnose ARVC/D, in addition to personal and family history, include 12-lead ECG, echocardiography, right ventricular angiography, cardiac magnetic resonance imaging, and computerized tomography. Endomyocardial biopsy from the right ventricular free wall is a sensitive diagnostic marker when fibrofatty infiltration is associated with surviving strands of myocytes. ECGs most commonly show abnormal repolarization with T-wave inversion in leads V₁ through V₃ and small-amplitude potentials at the end of the QRS complex (epsilon wave); Brugada syndrome-like right bundle-branch block and right precordial ST-segment elevation accompanied by polymorphic ventric-

ular tachycardia also have been reported in a small subpopulation of ARVC/D patients.

In most cases, ARVC/D shows autosomal dominant inheritance, albeit often with incomplete penetrance. Autosomal dominant ARVC/D has been mapped to 8 chromosomal loci, with mutations identified thus far in 4 genes: the cardiac ryanodine receptor RyR2, which is also responsible for familial catecholaminergic polymorphic ventricular tachycardia (CPVT); desmoplakin; plakophilin-2; and mutations altering regulatory sequences of the transforming growth factor- β gene, which has a role in inflammation. Two recessive forms have been described in conjunction with palmoplantar keratoderma and woolly hair (Naxos disease) and with Carvajal syndrome, caused by mutations in junctional plakoglobin and desmoplakin, respectively. Although the function of desmosomal proteins to anchor intermediate filaments to desmosomes implicates ARVC/D as a primary structural abnormality, there is also a link to ion channel dysfunction.

LV Noncompaction

Noncompaction of ventricular myocardium is a recently recognized congenital cardiomyopathy characterized by a distinctive ("spongy") morphological appearance of the LV myocardium. Noncompaction involves predominantly the distal (apical) portion of the LV chamber with deep intertrabecular recesses (sinusoids) in communication with the ventricular cavity, resulting from an arrest in the normal embryogenesis. LV noncompaction (LVNC) may be an isolated finding or may be associated with other congenital heart anomalies such as complex cyanotic congenital heart disease.

Diagnosis is made with 2-dimensional echocardiography, cardiac magnetic resonance imaging, or LV angiography. The natural history of LVNC is largely unresolved but includes LV systolic dysfunction and heart failure (and some cases of heart transplantation), thromboemboli, arrhythmias, sudden death, and diverse forms of remodeling. Both familial and nonfamilial cases have been described. In the isolated form of LVNC, ZASP (Z-line) and mitochondrial mutations and X-linked inheritance resulting from mutations in the G4.5 gene encoding tafazzin (including association with Barth syndrome in neonates) have been reported. Noncompaction associated with congenital heart disease has been shown to result from mutations in the α -dystrobrevin gene and transcription factor NKX2.5.

Conduction System Disease

Lenegre disease, also known as progressive cardiac conduction defect, is characterized by primary progressive development of cardiac conduction defects in the His-Purkinje system, leading to widening of the QRS complex, long pauses, and bradycardia that may trigger syncope. Sick sinus syndrome is phenotypically similar to progressive cardiac conduction defect. Familial occurrence of both syndromes has been reported with an autosomal dominant pattern of inheritance. An ion channelopathy, in the form of SCN5A mutations, is thought to contribute to these conduction system defects. Wolff-Parkinson-White syndrome is familial in some cases, but information about the genetic causes is unavailable.

Ion Channelopathies

There is a growing list of uncommon inherited and congenital arrhythmia disorders caused by mutations in genes encoding defective ionic channel proteins, governing cell membrane transit of sodium and potassium ions. These ion channel disorders include LQTS, short-QT syndrome (SQTS), Brugada syndrome, and CPVT. Nocturnal sudden unexplained death syndrome in young Southeast Asian males and Brugada syndrome are based on similar clinical and genetic profiles. A small proportion (5% to 10%) of sudden infant deaths also may be linked to ion channelopathies, including LQTS, SQTS, and Brugada syndrome. Clinical diagnosis of the ion channelopathies often can be made by identification of the disease phenotype on standard 12-lead ECG. Some of these cases had previously been classified as idiopathic ventricular fibrillation, a description that persists for a syndrome in which mechanistic understanding is lacking.

Long-QT Syndrome

This condition, probably the most common of the ion channelopathies, is characterized by prolongation of ventricular repolarization and QT interval (corrected for heart rate) on the standard 12-lead ECG, a specific form of polymorphic ventricular tachycardia (torsade des pointes), and a risk for syncope and sudden cardiac death. Phenotypic expression (on the ECG) varies considerably, and $\approx 25\%$ to 50% of affected family members may show borderline or even normal QT intervals.

Two patterns of inheritance have been described in LQTS: a rare autosomal recessive disease associated with deafness (Jervell and Lange-Nielsen syndrome), which is caused by 2 genes that encode for the slowly activating delayed rectifier potassium channel (KCNQ1 and KCNE1 [minK]), and the much more common autosomal dominant disease unassociated with deafness (Romano-Ward syndrome), which is caused by mutations in 8 different genes. These include KCNQ1 (KvLQT1, LQT1), KCNH2 (HERG, LQT2), SCN5A (Na1.5, LQT3), ANKB (LQT4), KCNE1 (minK, LQT5), KCNE2 (MiRP1, LQT6), KCNJ2 (Kir2.1, LQT7, Andersen's syndrome), and CACNA1C (Ca1.2, LQT8, Timothy syndrome). Of the 8 genes, 6 encode for cardiac potassium channels, 1 for the sodium channel (SCN5A, LQT3), and 1 for the protein ankyrin, which is involved in anchoring ion channels to the cellular membrane (ANKB).

Brugada Syndrome

The Brugada syndrome is a relatively new clinical entity associated with sudden cardiac death in young people. First described in 1992, the syndrome is identified by a distinctive ECG pattern consisting of right bundle-branch block and coved ST-segment elevation in the anterior precordial leads (V_1 through V_3). The characteristic ECG pattern is often concealed and may be unmasked with the administration of sodium channel blockers, including ajmaline, flecainide, procainamide, and pilsicainide. Familial autosomal dominant and sporadic forms have been linked to mutations in an α -subunit of the cardiac sodium channel gene SCN5A (the same gene responsible for LQT3) in 20% of patients. Another locus has been reported on the short arm of chromosome 3, but no gene has been identified.

Sudden unexplained nocturnal death syndrome, found predominantly in young Southeast Asian males (ie, those from Thailand, Japan, the Philippines, and Cambodia), is a disorder causing sudden death during sleep as a result of ventricular tachycardia/fibrillation. Some cases of sudden unexplained nocturnal death syndrome resulting from SCN5A gene mutations and Brugada syndrome have been shown to be phenotypically, genetically, and functionally the same disorder.

Catecholaminergic Polymorphic Ventricular Tachycardia

CPVT, a disease first described by Coumel and coworkers in 1978, is characterized by syncope, sudden death, polymorphic ventricular tachycardia triggered by vigorous physical exertion or acute emotion (usually in children and adolescents), a normal resting ECG, and the absence of structural cardiac disease. Family history of 1 or multiple sudden cardiac deaths is evident in 30% of cases. The resting ECG is unremarkable, except for sinus bradycardia and prominent U waves in some patients. The most typical arrhythmia of CPVT is bidirectional ventricular tachycardia presenting with an alternating QRS axis. The autosomal dominant form of the disease has been linked to the RyR2 gene encoding for the cardiac ryanodine receptor, a large protein that forms the calcium release channel in the sarcoplasmic reticulum that is essential for regulation of excitation-contraction coupling and intracellular calcium levels. An autosomal recessive form has been linked to CASQ2, a gene that encodes for calsequestrin, a protein that serves as a major calcium-binding protein in the terminal cisternae of the sarcoplasmic reticulum. Calsequestrin is bound to the ryanodine receptor and participates in the control of excitation-contraction coupling.

Short-QT Syndrome

First described in 2000, the SQTS is characterized by a short QT interval (<330 ms) on an ECG and a high incidence of sudden cardiac death resulting from ventricular tachycardia/fibrillation. Another distinctive ECG feature of SQTS is the appearance of tall peaked T waves similar to those encountered with hyperkalemia. The syndrome has been linked to gain-of-function mutations in KCNH2 (HERG, SQT1), KCNQ1 (KvLQT1, SQT2), and KCNJ2 (Kir2.1, SQT3), causing an increase in the intensity of I_{Kr} , I_{ks} , and I_{kl} , respectively.

Idiopathic Ventricular Fibrillation

A subgroup of patients with sudden death appears in the literature with the designation of idiopathic ventricular fibrillation. However, it is likely that idiopathic ventricular fibrillation is not an independent disease entity but rather a conglomeration of conditions with normal gross and microscopic findings in which arrhythmic risk undoubtedly derives from molecular abnormalities, most likely ion channel mutations. At present, insufficient data are available to permit the classification of idiopathic ventricular fibrillation as a distinct cardiomyopathy.

Mixed (Genetic and Nongenetic)**Dilated Cardiomyopathy**

Dilated forms of cardiomyopathy are characterized by ventricular chamber enlargement and systolic dysfunction with

normal LV wall thickness; usually diagnosis is made with 2-dimensional echocardiography. DCM leads to progressive heart failure and a decline in LV contractile function, ventricular and supraventricular arrhythmias, conduction system abnormalities, thromboembolism, and sudden or heart failure-related death. Indeed, DCM is a common and largely irreversible form of heart muscle disease with an estimated prevalence of 1:2500; it is the third most common cause of heart failure and the most frequent cause of heart transplantation. DCM may manifest clinically at a wide range of ages (most commonly in the third or fourth decade but also in young children) and usually is identified when associated with severe limiting symptoms and disability. In family screening studies with echocardiography, asymptomatic or mildly symptomatic relatives may be identified.

The DCM phenotype with sporadic occurrence may derive from a particularly broad range of primary (and secondary) causes, including the following: infectious agents, particularly viruses, often producing myocarditis (coxsackievirus, adenovirus, parvovirus, HIV); bacterial; fungal rickettsial; myobacterial; and parasitic (eg, Chagas disease resulting from *Trypanosoma cruzi* infection). Other causes include toxins; chronic excessive consumption of alcohol; chemotherapeutic agents (anthracyclines such as doxorubicin and daunorubicin); metals and other compounds (cobalt, lead, mercury, and arsenic); autoimmune and systemic disorders (including collagen vascular disorders); pheochromocytoma; neuromuscular disorders such as Duchenne/Becker and Emery-Dreifuss muscular dystrophies; and mitochondrial, metabolic, endocrine, and nutritional disorders (eg, carnitine, selenium deficiencies).

About 20% to 35% of DCM cases have been reported as familial, although with incomplete and age-dependent penetrance, and linked to a diverse group of >20 loci and genes. Although genetically heterogeneous, the predominant mode of inheritance for DCM is autosomal dominant, with X-linked autosomal recessive and mitochondrial inheritance less frequent. Several of the mutant genes linked to autosomal dominant DCM encode the same contractile sarcomeric proteins that are responsible for HCM, including α -cardiac actin; α -tropomyosin; cardiac troponin T, I, and C; β - and α -myosin heavy chain; and myosin binding protein C. Z-disc protein-encoding genes, including muscle LIM protein, α -actinin-2, ZASP, and titin, also have been identified.

DCM is also caused by a number of mutations in other genes encoding cytoskeletal/sarcolemmal, nuclear envelope, sarcomere, and transcriptional coactivator proteins. The most common of these probably is the lamin A/C gene, also associated with conduction system disease, which encodes a nuclear envelope intermediate filament protein. Mutations in this gene also cause Emery-Dreifuss muscular dystrophy. The X-linked gene responsible for Emery-Dreifuss muscular dystrophy, emerin (another nuclear lamin protein), also causes similar clinical features. Other DCM genes of this type include desmin, caveolin, and α - and β -sarcoglycan, as well as the mitochondrial respiratory chain gene. X-linked DCM is caused by the Duchenne muscular dystrophy (dystrophin) gene, whereas G 4.5 (tafazzin), a mitochondrial protein of

unknown function, causes Barth syndrome, which is an X-linked cardioskeletal myopathy in infants.

Primary Restrictive Nonhypertrophied Cardiomyopathy

Primary restrictive cardiomyopathy as defined here is a rare form of heart muscle disease and a cause of heart failure that is characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal LV wall thickness and AV valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function. Both sporadic and familial forms have been described, and in 1 family, a troponin I mutation was responsible for both restrictive cardiomyopathy and HCM.

Acquired

Myocarditis (Inflammatory Cardiomyopathy)

Myocarditis is an acute or a chronic inflammatory process affecting the myocardium produced by a wide variety of toxins and drugs (eg, cocaine, interleukin 2) or infectious agents, most commonly including viral (eg, coxsackievirus, adenovirus, parvovirus, HIV), bacterial (eg, diphtheria, meningococcus, psittacosis, streptococcus), rickettsial (eg, typhus, Rocky Mountain spotted fever), fungal (eg, aspergillosis, candidiasis), and parasitic (Chagas disease, toxoplasmosis), as well as Whipple disease (intestinal lipodystrophy), giant cell myocarditis, and hypersensitivity reactions to drugs such as antibiotics, sulfonamides, anticonvulsants, and antiinflammatories. Endocardial fibroelastosis is a dilated cardiomyopathy in infants and children that is a consequence of viral myocarditis in utero (mumps).

Myocarditis typically evolves through active, healing, and healed stages—characterized progressively by inflammatory cell infiltrates leading to interstitial edema and focal myocyte necrosis and ultimately replacement fibrosis. These pathological processes create an electrically unstable substrate predisposing to the development of ventricular tachyarrhythmias. In some instances, an episode of viral myocarditis (frequently subclinical) can trigger an autoimmune reaction that causes immunologic damage to the myocardium or cytoskeletal disruption, culminating in DCM with LV dysfunction. Evidence for the evolution of myocarditis to DCM comes from several sources, including animal models, the finding of inflammatory infiltrates and persistence of viral RNA in endomyocardial biopsies from patients with DCM, and the natural history of patients with selected conditions such as Chagas disease. The list of agents responsible for inflammatory myocarditis overlaps with that of the infectious origin of DCM, thereby underscoring the potential interrelationship between the 2 conditions.

Myocarditis can be diagnosed by established histopathological, histochemical, or molecular criteria, but it is challenging to identify clinically. Suspicion may be raised by chest pain, exertional dyspnea, fatigue, syncope, palpitations, ventricular tachyarrhythmias, and conduction abnormalities or by acute congestive heart failure or cardiogenic shock associated with LV dilatation and/or segmental wall motion abnormalities and ST-T changes on ECG. When myocarditis is suspected from the clinical profile, an endomyocardial

biopsy may resolve an otherwise ambiguous situation by virtue of diagnostic inflammatory (leukocyte) infiltrate and necrosis (ie, the Dallas criteria) but also is limited by insensitivity and false-negative histological results. The diagnostic yield of myocardial biopsies can be enhanced substantially by molecular analysis with DNA-RNA extraction and polymerase chain reaction amplification of the viral genome. In addition to the inflammatory process, viral genome-encoded proteases appear to disrupt the cytoskeletal-sarcomeric linkages of cardiomyocytes.

Stress (“Tako-Tsubo”) Cardiomyopathy

Stress cardiomyopathy, first reported in Japan as “tako-tsubo,” is a recently described clinical entity characterized by acute but rapidly reversible LV systolic dysfunction in the absence of atherosclerotic coronary artery disease, triggered by profound psychological stress.¹⁸ This distinctive form of ventricular stunning typically affects older women and preferentially involves the distal portion of the LV chamber (“apical ballooning”), with the basal LV hypercontractile. Although presentation often mimics ST-segment-elevation myocardial infarction, outcome is favorable with appropriate medical therapy.

Others

Peripartum (postpartum) cardiomyopathy is a rare and dilated form associated with LV systolic dysfunction and heart failure of unknown cause that manifests clinically in the third trimester of pregnancy or the first 5 months postpartum and requires a high index of suspicion for diagnosis. It is regarded as a clinical entity distinct from preexisting cardiomyopathies that may be adversely affected by the stress of pregnancy. Peripartum cardiomyopathy most frequently occurs in obese, multiparous women >30 years of age with preeclampsia. This unusual cardiomyopathy is associated with complete or nearly complete recovery within 6 months in ≈50% of cases but may result in progressive clinical deterioration, heart failure, death, or transplantation.

An underrecognized and reversible dilated cardiomyopathy with LV contractile dysfunction occurs secondary to prolonged periods of supraventricular or ventricular tachycardia. Systolic function normalizes without residual impairment on cessation of the tachycardia. Dilated cardiomyopathy associated with excessive alcohol consumption is also potentially reversible on cessation of alcohol intake.

Secondary Cardiomyopathies

The most important secondary cardiomyopathies are provided in the Table. This list, however, is not intended to represent an exhaustive and complete tabulation of the vast number of systemic conditions reported to involve the myocardium. Rather, it is limited to the most common of these diseases most consistently associated with a cardiomyopathy.

Secondary Cardiomyopathies

Infiltrative*

Amyloidosis (primary, familial autosomal dominant†, senile, secondary forms)

Gaucher disease†

Hurler’s disease†

Hunter’s disease†

Storage‡

Hemochromatosis

Fabry’s disease†

Glycogen storage disease† (type II, Pompe)

Niemann-Pick disease†

Toxicity

Drugs, heavy metals, chemical agents

Endomyocardial

Endomyocardial fibrosis

Hypereosinophilic syndrome (Löffler’s endocarditis)

Inflammatory (granulomatous)

Sarcoidosis

Endocrine

Diabetes mellitus†

Hyperthyroidism

Hypothyroidism

Hyperparathyroidism

Pheochromocytoma

Acromegaly

Cardiofacial

Noonan syndrome†

Lentiginosis†

Neuromuscular/neurological

Friedreich’s ataxia†

Duchenne-Becker muscular dystrophy†

Emery-Dreifuss muscular dystrophy†

Myotonic dystrophy†

Neurofibromatosis†

Tuberous sclerosis†

Nutritional deficiencies

Beriberi (thiamine), pellagra, scurvy, selenium, carnitine, kwashiorkor

Autoimmune/collagen

Systemic lupus erythematosus

Dermatomyositis

Rheumatoid arthritis

Scleroderma

Polyarteritis nodosa

Electrolyte imbalance

Consequence of cancer therapy

Anthracyclines: doxorubicin (adriamycin), daunorubicin

Cyclophosphamide

Radiation

*Accumulation of abnormal substances between myocytes (ie, extracellular).

†Genetic (familial) origin.

‡Accumulation of abnormal substances within myocytes (ie, intracellular).

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References

- Richardson P, McKenna W, Bristow M, Maisch B, Mautner B, O'Connell J, Olsen E, Thiene G, Goodwin J. Report of the 1995 World Health Organization/International Society and Federation of Cardiology Task Force on the Definition and Classification of Cardiomyopathies. *Circulation*. 1996;93:841–842.
- Abelmann WH. Classification and natural history of primary myocardial disease. *Prog Cardiovasc Dis*. 1984;27:73–94.
- Report of the WHO/ISFC Task Force on the Definition and Classification of Cardiomyopathies. *Br Heart J*. 1980;44:672–673.
- Mason JW. Classification of cardiomyopathies. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's the Heart, Arteries and Veins*. 10th ed. New York, NY: McGraw Hill; 2001:1941–1946.
- Wynne J, Braunwald E. The cardiomyopathies. In: Zipes DP, Libby P, Bonow RO, Braunwald ED, eds. *Braunwald's Heart Disease*. 7th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1659–1696.
- Thiene G, Angelini A, Basso C, Calabrese F, Valente M. The new definition and classification of cardiomyopathies. *Adv Clin Path*. 2000;4:53–57.
- Thiene G, Corrado D, Basso C. Cardiomyopathies: is it time for a molecular classification? *Eur Heart J*. 2004;25:1772–1775.
- Keren A, Popp RL. Assignment of patients into the classification of cardiomyopathies. *Circulation*. 1992;86:1622–1633.
- Maron BJ, McKenna WJ, Danielson GK, Kappenberger LJ, Kuhn HJ, Seidman CE, Shah PM, Spencer WH, Spirito P, Tan Cate FJ, Wigle ED, for the Task Force on Clinical Expert Consensus Documents, Committee for Practice Guidelines, European Society of Cardiology. American College of Cardiology/European Society of Cardiology clinical expert consensus document on hypertrophic cardiomyopathy: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the European Society of Cardiology Committee for Practice Guidelines. *J Am Coll Cardiol*. 2003;42:1687–1713.
- Towbin JA, Bowles NE. The failing heart. *Nature*. 2002;415:227–233.
- Antzelevitch C. Molecular genetics of arrhythmias and cardiovascular conditions associated with arrhythmias. *Heart Rhythm*. 2004;1(5C):42C–56C.
- Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, Gussak I, LeMarec H, Nademanee K, Perez Iera AR, Shimizu W, Schulze-Bahr E, Tan H, Wilde A. Brugada syndrome: report of the Second Consensus Conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. *Circulation*. 2005;111:659–670.
- Burkett EL, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol*. 2005;45:969–981.
- Chien KR. Genotype, phenotype: upstairs, downstairs in the family of cardiomyopathies. *J Clin Invest*. 2003;111:175–178.
- Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silver MA, Stevenson LW, Yancy CW, Antman EM, Smith SC Jr, Adams CD, Anderson JL, Faxon DP, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Jacobs AK, Nishimura R, Ornato JP, Page RL, Riegel B. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure): developed in collaboration with the American College of Chest Physicians and the International Society for Heart and Lung Transplantation: endorsed by the Heart Rhythm Society. *Circulation*. 2005;112:1825–1852.
- Strickberger SA, Conti J, Daoud EG, Havranek E, Mehra MR, Pina IL, Young J, for the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, Heart Rhythm Society. Patient selection for cardiac resynchronization therapy: from the Council on Clinical Cardiology Subcommittee on Electrocardiography and Arrhythmias and the Quality of Care and Outcomes Research Interdisciplinary Working Group, in collaboration with the Heart Rhythm Society. *Circulation*. 2005;111:2146–2150.
- Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RJ, Antman EM, Alpert JS, Gregoratos G, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC Jr, for the American College of Cardiology/American Heart Association Task Force on Practice Guidelines/North American Society for Pacing and Electrophysiology Committee to Update the 1998 Pacemaker Guidelines. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation*. 2002;106:2145–2161.
- Sharkey SW, Lesser JR, Zenovich AG, Maron MS, Lindberg J, Longe TF, Maron BJ. Acute and reversible cardiomyopathy provoked by stress in women from the United States. *Circulation*. 2005;111:472–479.