Circulation

AHA SCIENTIFIC STATEMENT

Cardiomyopathy in Children: Classification and Diagnosis

A Scientific Statement From the American Heart Association

ABSTRACT: In this scientific statement from the American Heart Association, experts in the field of cardiomyopathy (heart muscle disease) in children address 2 issues: the most current understanding of the causes of cardiomyopathy in children and the optimal approaches to diagnosis cardiomyopathy in children. Cardiomyopathies result in some of the worst pediatric cardiology outcomes; nearly 40% of children who present with symptomatic cardiomyopathy undergo a heart transplantation or die within the first 2 years after diagnosis. The percentage of children with cardiomyopathy who underwent a heart transplantation has not declined over the past 10 years, and cardiomyopathy remains the leading cause of transplantation for children >1 year of age. Studies from the National Heart, Lung, and Blood Institute–funded Pediatric Cardiomyopathy Registry have shown that causes are established in very few children with cardiomyopathy, yet genetic causes are likely to be present in most. The incidence of pediatric cardiomyopathy is ≈1 per 100 000 children. This is comparable to the incidence of such childhood cancers as lymphoma, Wilms tumor, and neuroblastoma. However, the published research and scientific conferences focused on pediatric cardiomyopathy are sparcer than for those cancers. The aim of the statement is to focus on the diagnosis and classification of cardiomyopathy. We anticipate that this report will help shape the future research priorities in this set of diseases to achieve earlier diagnosis, improved clinical outcomes, and better quality of life for these children and their families.

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Cardiomyopathy is rare in children but, once diagnosed, carries a substantial risk of morbidity and mortality.[1,2] Cardiomyopathy is the primary indication for heart transplantation during childhood, particularly among children >1 year of age.[2–5] The causes of pediatric cardiomyopathies are heterogeneous and range from genetic variations that affect basic myocardial processes to systemic diseases that lead to diffuse myocardial injury. Risk factors for poor outcomes in pediatric cardiomyopathy include pathogenesis, clinical characteristics, and structural abnormalities affecting geometry and function, and specific risk factors vary by phenotype. The complex interactions among genetics, environmental factors, and the response to myocardial injury in pediatric cardiomyopathies are becoming elucidated through basic, translational, and clinical research. This statement is designed to give an overview of the current understanding of the classification and diagnosis of primary and acquired pediatric cardiomyopathies, about which, although much has been learned, much more remains unknown.

INCIDENCE OF PRIMARY CARDIOMYOPATHY IN CHILDREN AND ADOLESCENTS

Population-based studies in the United States, Finland, and Australia estimate the incidence of primary cardiomyopathies in children to be 1 case per 100 000 person-years in children <20 years of age.[1,2,6] The lowest estimate, from Finland, was 0.7 cases per 100 000 person-years but includes only idiopathic cardiomyopathy.[6] The highest estimate, from Australia, was 1.24 cases per 100 000 person-years, but this report included only children up to 10 years of age, the period when cardiomyopathy is most commonly diagnosed.[2] The estimate from the United States was 1.1 cases per 100 000 person-years, but the incidence was 8 times higher (8.3 cases per 100 000 person-years) in children diagnosed at <1 year of age.[1]

Incidence rates were generally higher in male individuals, blacks, and Aboriginal Australian children.[1,2] In these large population-based studies, cardiomyopathy subtypes were classified by myocardial morphofunctional phenotype. About 50% of cases in children and adolescents were characterized as dilated cardiomyopathy (DCM), with 10% to 25% of cases in this category attributable to acute myocarditis.[2,7,8] Hypertrophic cardiomyopathies (HCMs) make up 35% to 50% of cases, and restrictive cardiomyopathies (RCMs) make up <5% of cases in children.[1,2,6] The incidence of HCM was 3 times higher in children <1 year of age than in older children.[9] Left ventricular (LV) myocardial noncompaction (LVNC) accounted for ≈5% of cases.[10]

CLASSIFICATION OF CARDIOMYOPATHIES

Several classifications of the cardiomyopathies have been published. The original World Health Organization classification, published in 1980, classified the cardiomyopathies only by phenotype and included only 3 categories: *dilated*, *hypertrophic*, and *restrictive*. The World Health Organization also recommended limiting these terms to idiopathic disease, whereas *specific heart muscle disease* was recommended as the terminology for those instances in which the cause was known.[11] Several subsequent publications by the World Health Organization and other organizations[12–15] also maintained phenotype as the primary basis for classification but included subcategories that specified pathogenetic and genotypic categories and, in some instances, recommended that genetics should be the primary basis for classification.[16] The evolution of these classifications has recently been reviewed by McKenna et al,[17] including the various potential methods of categorization such as primary (isolated to the heart) versus secondary (multisystem) disease, genetic (sarcomeric HCM) versus acquired (myocarditis), structural (noncompaction) versus functional (restrictive), and mechanical versus electrical. The review by McKenna et al presented, but did not attempt to resolve, the inconsistencies in terminology between the published systems of the American Heart Association (AHA), the American College of Cardiology (ACC), and the European Society of Cardiology (ESC).[18,19]

The MOGE(S) classification[20] was developed from the need to describe cardiomyopathies by integrating multiple characteristics of the disease: the morphofunctional phenotype, organ involvement, genetic or familial inheritance pattern, and etiology (genetic or nongenetic). Functional status (S), based on the ACC/AHA stage (A–D) and New York Heart Association functional classes (I–IV), can also be included. Functional classes for cardiac disease in adults have had limited utility in children and are therefore generally not used. An important issue in any classification system is determining what should be included in the hierarchy. Currently, the published classification systems vary substantially in part because of differences in terminology. The terminology for some of the heart muscle diseases remains in flux because of uncertainties in the science, for example, in the mitochondrial disorders with overlapping phenotypes. Terminology has also changed in response to an evolving understanding of the social implications of some terms such as the stigmatizing potential of the term *LEOPARD* (lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, deafness) syndrome, which led to its replacement by *Noonan syndrome with multiple*

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lentigines. However, some of the inconsistencies in terminology among the published classification systems have no apparent rationale.

Perhaps the most important of these inconsistencies is the contradictory recommendations for the secondary forms of HCM. The ESC recommends including both primary and secondary forms of HCM under the umbrella of HCM, an approach virtually universal in pediatric cardiology. In the ESC classification, cardiomyopathies are defined by their morphofunctional phenotype and then subdivided by pathogenesis (familial-genetic and nonfamilial-nongenetic) independently of the presence of extracardiac disease.[19] The AHA/ACC definition of HCM is identical to that of the ESC, defining HCM on the basis of phenotype (cardiac hypertrophy that cannot be explained by hemodynamic causes), but the AHA/ACC document nonetheless recommends excluding all secondary forms of this phenotype such as Noonan syndrome from categorization as a form of HCM.[19] The AHA/ACC recommendations state categorically, "Use of the term HCM is not appropriate to describe these and other patients with LV hypertrophy that occurs in the context of a multisystem disorder."[21] The AHA/ACC consensus statement goes on to state that "nomenclature that describes patients as 'Noonan hypertrophic cardiomyopathy' [sic] is discouraged, whereas 'Noonan syndrome with LV hypertrophy' or 'Noonan syndrome with cardiomyopathy' is preferred." [21] The AHA/ACC committee does not explain why it excluded diseases that meet its phenotypic definition of HCM and why its classification conflicts with the classifications for the other cardiomyopathies, in which the top-level categories in the classification, including DCM and RCM, are based on morphofunctional phenotype independently of cause, with pathogenetic classification occurring at lower levels in the hierarchy. Adopting the recommendation to exclude all secondary forms of the HCM phenotype would result in the absence of all forms of secondary HCM on the HCM tree, despite the fact that these diseases meet the definition of HCM as expressed in both the ESC and ACC/AHA recommendations. Virtually all the literature on heart disease associated with Noonan syndrome has used the term HCM, and the functional consequences for clinical and literature database searches are not discussed. Alternative terminology, such as *Noonan syndrome with LV hypertrophy* as recommended by the AHA/ACC, is inexact because it does not distinguish between secondary hypertrophy and cardiomyopathy.

Our consensus was therefore to use a classification system based on a hierarchy incorporating the required elements of the MOGE(S) classification. Given the deviation from existing standards for disease classification systems and the lack of justification for such a deviation, this statement follows the ESC approach and uses a classification based on morphofunctional characteristics as the top-level category and pathogenetic characteristics as lower-level categories. The morphofunctional phenotype is the highest category in the hierarchy because it is the basis for diagnosis and management. For example, patients who carry a known pathogenic gene are not considered to have the disease in the absence of the phenotype. Similarly, several electrocardiographic and imaging findings have been identified in carriers of sarcomeric gene mutations associated with HCM,[22–24] but symptoms and adverse outcomes are not seen in the absence of the phenotype, so the presence of disease is based on the presence of the phenotype. Therefore, in this statement, the proposed classification of the cardiomyopathies is a hierarchy based on the structural and functional phenotype with genetic and nongenetic causes as subcategories.

MORPHOLOGICAL EVALUATION OF PEDIATRIC CARDIOMYOPATHIES

Imaging is integral to diagnosing and classifying the cardiomyopathies on the basis of the primacy of the morphofunctional phenotype to our hierarchical approach. Cardiac anatomy, including myocardial structural or valvular abnormalities, coronary artery abnormalities, and function, needs to be assessed to ascertain the presence of a cardiomyopathy and to assign the highest subcategory in the hierarchy: DCM, HCM, RCM, noncompaction, or arrhythmogenic cardiomyopathy. Findings need to be compared with other clinical assessments to determine whether any concurrent hemodynamic conditions or other factors (eg, arrhythmias) are responsible for the presentation or whether the myocardial pathology genuinely warrants designation as a cardiomyopathy. Multimodality imaging is often required for screening, diagnosis, risk stratification, prognosis, and treatment.[25–27]

Echocardiography

In addition to anatomic observations such as measures of chamber dimensions, volumes, and wall dimensions,[28] echocardiography allows the functional assessment of myocardial performance, including Doppler traces of ventricular contractility (dP/dt), systolic-to-diastolic ratio,[29] myocardial performance index, tissue Doppler imaging, and measurements of myocardial deformation (strain and strain rate).[30]

Key measurements for morphological classification purposes include the LV end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), LV end-diastolic volume, and LV posterior wall and septal thicknesses, all expressed as *z* scores to adjust for patient

size.[31–33] A higher LVEDD or LV end-diastolic volume, combined with lower LV functional variables, suggests a dilated, hypokinetic phenotype. Greater wall thicknesses and the pattern of thickening suggest a hypertrophic phenotype and its subtypes in the hierarchy. The thickness-to-dimension ratio can help distinguish between idiopathic DCM (IDCM) and myocarditis and reflects changes in patients with anthracycline cardiomyopathy. The ratio of the short-axis dimension to the long-axis dimension can reflect a transition to a more spherical shape.

Changes in these measures (LV dilatation, wall thinning, and spherical shape) usually represent unfavorable remodeling, whereas the converse (reverse remodeling) is important in determining the effect of relieving potentially mitigating hemodynamic factors (eg, aortic stenosis).[34,35] Estimating LV mass to determine and monitor LV hypertrophy is important but challenging in the absence of normal ranges, and multiple methods exist to do so.[36] The key is the ability to determine deviations from normal to ascertain the presence of a hypertrophic phenotype and to account for somatic growth in sequential studies to ascertain progression (from increasing LV hypertrophy to noncompensatory LV dilation and thinning), stability, or regression.[37] Dilated atria in the presence of normal or small ventricular sizes and wall thicknesses and preserved systolic function in the absence of marked valvular regurgitation may indicate a restrictive phenotype or mixed disease, if dilation is combined with measures of LV hypertrophy.

LV systolic function is most commonly assessed by echocardiography as shortening fraction (normal range, 28%–38%) and ejection fraction (normal, >55%). Any values below normal would be classified as hypokinetic and, if combined with chamber dilation, a dilated hypokinetic phenotype.[22,38] Systolic function is often preserved in hypertrophic and restrictive phenotypes until the disease is advanced, potentially transitioning to a mixed phenotype.

The various Doppler-based time interval assessments can aid in classification, but as a second-tier characteristic and not tied to morphology per se but instead to differences in normal time intervals of systole and diastole. These assessments depend on loading conditions and are fraught with challenges and problems with reproducibility.[39,40] Ventricular dP/dt may help characterize single ventricles and morphological right ventricles (RVs). The myocardial performance index and the systolic-to-diastolic ratio are most useful in classifying dilated and restrictive phenotypes.[41,42]

Tissue Doppler imaging of longitudinal ventricular function (S′, E′, A′), reported as *z* scores, can be abnormal (reduced) before a change in circumferential function is reflected in the systolic functional measures described above.[43] Early changes have been variably reported in subclinical anthracycline-related cardiomyopathy and familial DCM (FDCM).[44,45]

Strain measures (global, longitudinal, and radial) are more sensitive indicators of systolic dysfunction.[46] Persistent abnormalities have been found in patients with DCM with reverse remodeling and improved ejection fraction while on medical therapy.[47] Detecting early changes allows early diagnosis of anthracycline-related cardiomyopathy in both children and adults.[48,49] Subclinical changes have been reported in patients with normal ejection fractions and familial, genetic, or other predispositions to DCM, potentially contributing to a phenotypic diagnosis.

Assessing diastolic function with a combination of Doppler patterns of mitral valve inflow, pulmonary venous flow, and tissue Doppler imaging of the mitral valve annulus can detect compliance and relaxation abnormalities and restrictive physiology and can be important for classifying a restrictive phenotype.[50] Measures of early diastolic dysfunction are evident in HCM phenotypes and can precede phenotypic hypertrophy in gene-positive patients.[51] However, assessing diastolic function in children is challenging. Reproducibility and interobserver consistency are limited, and the results are poorly associated with invasive hemodynamics and often do not discriminate between cardiomyopathy phenotypes.[40,44]

The appearance of the myocardium contributes to morphological diagnosis and classification, most notably for LVNC, which is characterized by prominent LV trabeculations with deep recesses communicating with the LV cavity and a thin, compacted epicardial layer.[52] LVNC can be isolated or seen in a mixed phenotype or with congenital heart disease. Attempts to standardize assessment and diagnosis have included measuring the ratio of noncompacted to compacted myocardium and the depths of intertrabecular recesses. However, diagnosis remains challenging except in the most severe cases.[53] Abnormalities of the mitral valve, mitral valve apparatus, and the LV outflow tract contribute to identifying the HCM morphological phenotype. Patterns of hypertrophy in HCM (eg, apical) should be sought but are more challenging to measure with echocardiography.[25]

Normal RV morphology and physiology differ from those in the LV, but assessment is important in diagnosing and classifying cardiomyopathies and could reflect biventricular involvement. Imaging RV morphology, specifically RV wall motion abnormalities, size, and function, is important for diagnosing and classifying arrhythmogenic cardiomyopathy.[27] Although echocardiography is a first-line tool, assessing the RV is challenging and requires targeted views of the RV, measurements (eg, RV outflow tract dimension, fractional area of change), and advanced techniques (eg, tricuspid annular plane systolic excursion, RV strain).[54]

Magnetic Resonance Imaging

Abnormal chamber dimensions, wall thicknesses, and ventricular mass can be determined by cardiac magnetic resonance imaging (cMRI), help define a specific morphological phenotype, and move the classification farther down the hierarchy.[55] In addition, cMRI can provide functional assessment of myocardial performance, including flow rates, shunts, and regional wall motion abnormalities.[56] Tissue characterization of fibrotic scar, interstitial fibrosis, edema, and hyperemia can help determine the cause of cardiomyopathy (eg, IDCM versus myocarditis). In addition, cMRI is better than echocardiography for characterizing patterns of myocardial hypertrophy and thus further distinguishing the different types of HCM, in addition to characterizing the presence and pattern of fibrosis in tissue with late gadolinium enhancement.[57,58] Morphological features of the myocardium observed on cMRI and the noncompacted-to-compacted ratio can contribute to the classification of LVNC, and fibrosis assessment adds prognostic information.[59] Fibrosis, especially in patients with muscular dystrophies and anthracycline exposure, is important in early identification of cardiac involvement. T2*-based cMRI is important in assessing cardiomyopathies secondary to iron overload. cMRI improves the accuracy of the measurements of RV wall motion, size, and function and can detect fibrofatty replacement of the myocardium in arrhythmogenic cardiomyopathy.

Computed Tomography

Cardiac computed tomography (CT), a second-tier imaging choice, is most useful to delineate anatomic and coronary artery abnormalities, in addition to assessing the pericardium for any evidence of constriction in patients with a possible restrictive phenotype.[26] Patients with poor echocardiographic windows and contraindications to cMRI can be imaged with CT. Cardiac CT can also be useful in assessing the morphology of suspected arrhythmogenic cardiomyopathy, including RV size, RV function, regional wall motion abnormalities, and intramyocardial fat.[27]

Cardiac Catheterization

Cardiac catheterization is rarely used to assess morphology in pediatric cardiomyopathies. Instead, it is used for assessing hemodynamics, calculating pulmonary vascular resistance, obtaining endomyocardial biopsies for diagnostic purposes, and intervening in patients with amenable lesions.[50]

GENETICS OF PEDIATRIC CARDIOMYOPATHIES

Genetic testing in pediatric cardiomyopathy is a valuable part of diagnosis and classification. In a single-center study, among 42% of 63 children with cardiomyopathy, the cause was genetic, as defined by the presence of an affected first-degree family member or a positive test for an HCM or a DCM gene panel mutation.[60] Although the morphofunctional phenotype may be similar to that in adults, the causes and proportion of cases resulting from those causes differ.[8] Neuromuscular, metabolic, mitochondrial, and syndromic causes are important in children with cardiomyopathy, particularly for infants and young children.[8] In 916 children with an identified cause of cardiomyopathy, an underlying metabolic or syndromic cause was reported in more than one-third.[61] A metabolic or syndromic cause was also reported in 40% to 50% of 61 children with HCM,[1] and 8% of 1731 children with DCM in the PCMR (Pediatric Cardiomyopathy Registry) had a neuromuscular disorder (NMD).[7] Patients with these pathogeneses tend to be excluded from cardiomyopathy studies in adults, and their underlying mutations are not included in standard commercial cardiomyopathy gene panels.

Autosomal-dominant inheritance is the most common mode of inheritance in familial isolated cardiomyopathy diagnosed in childhood.[1] However, X-linked inheritance and autosomal-recessive inheritance also occur. Mutations in genes encoding sarcomeric proteins are the most common abnormalities in children with isolated HCM.[62] However, children sometimes have mutations in lysosome-associated membrane protein 2 (LAMP2; Danon disease) or γ-2 subunit of AMP-activated protein kinase (PRKAG2; cardiac glycogenosis), and their clinical courses and prognoses differ from those of children with sarcomeric HCM.[63,64]

Sarcomeric gene mutations also are associated with pediatric RCM, LVNC, and DCM.[65–69] Mutations in genes encoding cytoskeletal and desmosomal proteins are found in DCM. Desmosomal gene mutations are associated with arrhythmogenic ventricular cardiomyopathy (AVC).[70] The likelihood of finding a disease-causing mutation in isolated cardiomyopathy is highest in children with HCM and in children with an affected first-degree relative. Limited data suggest a higher likelihood of multiple disease-causing mutations in HCM that develops in childhood compared with HCM diagnosed in adulthood.[71] The frequency of specific gene mutations in pediatric cardiomyopathy and the possibility of multiple genetic hits in children with early or severe disease need to be further validated in larger pediatric cohorts.

Genetic cause can be important for understanding prognosis and has the potential to result in personalized medical care. For instance, Noonan syndrome is the leading genetic cause of infantile HCM and carries a high risk of early mortality (22% at 1 year).[72,73] Mortality is also high for children with HCM caused by inborn errors of metabolism, with a mortality rate of ≈50% within 2 years of diagnosis.[74] A medical genetics evaluation is important for correct diagnosis,

disease-specific prognosis, and disease management. A comprehensive genetic assessment can be beneficial because features of the syndromes may be overlooked at the initial presentation, particularly in infants or in critically ill children.

Indications for genetic testing include determining the cause of HCM, predicting the clinical course and severity, screening first-degree relatives, and determining recurrence risk. Before genetic testing, comprehensive genetic counseling and a complete family pedigree can provide a framework for understanding the scope and implications of testing. Genetic testing should first be performed in the individual known to have a specific cardiomyopathy phenotype and should be informed by the child's overall presentation, with a detailed examination looking for dysmorphic features, muscle weakness, scoliosis, or specific laboratory findings.

Methods of Genetic Testing

Genetic testing for clinical care should be pursued via a Clinical Laboratory Improvement Amendments–approved laboratory, after the performance of comprehensive genetic counseling as noted above. Methods of gene testing include Sanger sequencing, or first-generation sequencing, which is used to identify copy number variations, single gene abnormalities, and familial mutations or variants. Next-generation sequencing may involve rapid sequencing of the coding region of multiple genes in parallel and is the type of sequencing used for large gene panels such as testing for genes that are most commonly associated with isolated cardiomyopathy. Most sequencing tests provide the option to also pursue testing for large gene deletions or duplications, which can be missed by sequencing approaches. In the current era, there is a move to more quickly consider whole-exome sequencing or whole-genome testing, particularly as cost considerations improve and the desire to comprehensively assess the genome increases. Whole-exome sequencing or whole-genome testing may be performed when a patient has a constellation of features that suggest a syndrome or disease process with other extracardiac abnormalities. Trio testing, or testing the child and both parents, is useful for exome or genome sequencing because it more accurately identifies candidate gene mutations on the basis of a suspected inheritance pattern (autosomal-dominant versus autosomal-recessive pattern).

Several commercial next-generation sequencing tests are available for use in the child with cardiomyopathy. These tests include panels specific to a morphological type of cardiomyopathy and those that can identify >60 genes that cause a variety of cardiomyopathy phenotypes. These "pan" cardiomyopathy panels are indicated when the predominant phenotype is not clear or in rarer forms of cardiomyopathy such as RCM and LVNC. Cardiomyopathy panels generally test for genes associated with isolated cardiomyopathy. Separate panels can be used in the workup of neuromuscular or mitochondrial disorders in selected patients. No panel is entirely comprehensive for the child with a cardiomyopathy. Exome sequencing can be valuable in critically ill children because it is the most comprehensive test with the fastest turnaround for multiple different pathogeneses when the differential diagnosis is large. This type of testing is now possible in a matter of days to weeks and provides diagnostic information soon enough to inform clinical decision making. If widespread gene sequencing is pursued, a genetic consultation is advisable, given the likelihood of finding abnormalities of uncertain clinical importance or with implications beyond the scope of the clinician's intent for testing.

Interpreting Test Results

Genetic testing has 3 outcomes: confirmatory (identification of a known pathogenic mutation, clear cosegregation within phenotype in a family, or functional gene studies that validate pathogenicity), negative (not identifying a pathogenic mutation in genes tested), or inconclusive (lack of information to definitively classify the results as pathogenic or to definitively classify them as benign). In the inconclusive outcome, a variant is identified and further classified as likely pathogenic, a variant of unknown significance, or likely benign according to criteria put forth by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (Table 1).[75]

Some key points should be considered in the interpretation of test results. A negative or nondiagnostic test result does not exclude the diagnosis of cardiomyopathy, nor does it exclude the potential for an inherited cause for the cardiomyopathy. Finding a variant of unknown significance (a genetic mutation in a gene known to cause cardiomyopathy that has not been directly linked as causative in larger population studies) does not mean that the variant found is disease causing. Such variants, even in genes implicated in disease, cannot be used in clinical decision making for the patient or family. Variants likely to be benign can be excluded as the cause of the child's cardiomyopathy and are not used in screening other family members. Cascade genetic testing of family members is generally recommended when a pathogenic mutation known to be associated with cardiomyopathy is found in a child with cardiomyopathy. Cascade testing may be of value if mutations of unknown significance are detected because, if they are present in phenotypically normal parents and other family members, they may likely be

Table 1. Interpretation of Sequence Variants Based on Population Data, Computational and Predictive Data, Functional Studies of Variants, Cosegregation of Variant With Disease, De Novo Data From Trio Analyses

Standard Classification	Strength of Evidence	Implications for Patients With Cardiomyopathy	Implications for Family Screening
Pathogenic	Very strong or strong causal evidence	Disease causing	Phenotype-negative, asymptomatic, gene-negative family members in families in whom the pathogenic mutation has been identified do not require serial cardiac testing for cardiomyopathy.
			Gene-positive relatives require serial cardiac testing, but medical treatment or activity modification is generally indicated with onset of the disease phenotype. The special case of AVC is discussed in the text.
Likely pathogenic	Strong or moderate causal evidence	Likely disease causing	Genetic test results cannot be used in determining the need for ongoing cardiac screening.
Variant of unknown significance	Insufficient evidence to date for classification of either pathogenic or benign	Uncertain	Genetic testing is not indicated because results cannot be applied to clinical decision making.
Likely benign	Strong by 1 criterion and additional supporting evidence that the variant is benign	Unlikely to cause cardiomyopathy	Genetic testing is not indicated because results cannot be applied to clinical decision making.
Benign	Stand-alone evidence or multiple strong criteria indicating that the variant is benign	Not a cause of cardiomyopathy	Genetic testing is not indicated because results cannot be applied to clinical decision making

AVC indicates arrhythmogenic ventricular cardiomyopathy.

benign. However, this does not exclude the possibility that the family member has not yet manifested disease or that penetrance is incomplete.

Clinicians also need to understand the phenomenon of variable expression and variable penetrance of genes that cause cardiomyopathy. Different cardiomyopathy phenotypes can occur in families who carry the same genetic mutation. The timing of onset and the severity of the cardiomyopathy phenotype can vary. Expressivity varies when individuals with the same genetic mutation have different expressions of that mutation. Variable penetrance refers to the variable risk for eventually developing a cardiomyopathy in individuals known to carry a pathogenic mutation. Thus, a pathogenic mutation may be necessary but not sufficient to cause a specific heart muscle disease. For instance, HCM is more penetrant than other forms of cardiomyopathy (DCM, RCM, or arrhythmogenic RV cardiomyopathy). Modifier genes, multiple pathogenic variants, environmental factors, or lifestyle factors can also influence the morpho-functional phenotype.

Applying Test Results

Regardless of the laboratory results, involving a specialist in genetic counseling is useful for interpreting and discussing results with patients. Negative test results cannot be interpreted as the absence of a genetic cause for cardiomyopathy. The test may not have screened for the specific abnormality, or the mutation may not have been discovered at the time of testing. Over time, new genes are characterized in pedigrees or experimentally, which means that retesting a patient may be appropriate.

When no pathogenic mutation is identified, cascade screening of family members with gene testing is not indicated. Conversely, finding a pathogenic variant enables cascade screening of family members such that gene-negative relatives do not require cardiac surveillance, although gene-positive family members do. Beginning medical therapy or restricting activity in children who test positive for a pathogenic mutation but who have no echocardiographic or cMRI features of cardiomyopathy is not indicated, with 1 notable exception. Endurance and high-intensity athletics are linked to the progression of arrhythmogenic RV cardiomyopathy in desmosomal mutation carriers.[76,77]

Limitations of Genetic Testing

Genetic testing has several limitations:

- The detection rate of finding a pathogenic variant is unknown for any of the pediatric cardiomyopathies.
- Commercial panels are based mostly on data from adults.
- The signs and symptoms of systemic disease can evolve over time, which may indicate isolated myocardial disease at first, when in fact a syndrome or a systemic disorder is present. The converse may also be true for testing to diagnose syndromic disorders without cardiovascular manifestations at the time of testing. The reason is that the diagnosis of a syndrome and associated disease will then dictate the cardiovascular follow-up. Furthermore, even if there is no manifest cardiovascular disease with a diagnosed syndrome, there may be a need for cardiology follow-up.

- The potential for multiple pathogenic mutations in individuals with pediatric cardiomyopathy is unknown and may be greater than in adults.
- Children previously tested in clinical practice may require reclassification or retesting when clinical tests are updated with newly identified variants and genes.

DILATED CARDIOMYOPATHY

Definition

DCM is defined by the presence of a dilated LV with systolic dysfunction in the absence of a hemodynamic cause that can produce the existent dilation and dysfunction, including physiological (eg, sepsis) or anatomic causes with either abnormal loading conditions (eg, coarctation of the aorta) or ischemia (eg, coronary artery anomalies).[78–80] Physiological and anatomic conditions can affect the morphofunctional phenotype. If the morphofunctional phenotype is retained after appropriate intervention, then a DCM is established.

Diagnostic Criteria

The primary diagnostic criterion for DCM is a dilated LV with systolic dysfunction.[78,80] Adjusting for body size is mandatory in children; therefore, the diagnosis is based on LVEDD and LVESD *z* scores >2 on either side of the body surface area–adjusted mean value in a normal population and on reduced measures of systolic function derived from echocardiography or multimodality imaging, as summarized in the Genetics of Pediatric Cardiomyopathies section. For borderline cases, causal predisposition is used to evaluate the net probability of disease.

Echocardiography, ECG, cMRI, and cardiac catheterization all aid in diagnosing DCM and determining the functional severity of the disease (Genetics of Pediatric Cardiomyopathies section). In addition, cMRI and endomyocardial biopsy can aid in establishing a cause.

Structural and Functional Phenotypes

In addition to LV dilation, other morphological features include decreased mass-to-volume or wall thickness–to–cavity dimension ratios of the LV caused by relative or actual thinning of the ventricular walls and by the ventricle becoming more spherical (see the Genetics of Pediatric Cardiomyopathies section). Mitral regurgitation can ensue as a functional consequence of the dilated and spherical LV and the dilated mitral annulus. The RV can also have features of dilation and decreased contractility, with concomitant tricuspid regurgitation secondary to both annular dilation and elevated pulmonary pressures (see the Genetics of Pediatric Cardiomyopathies section).

Physiologically, decreased ventricular contraction leads to decreased stroke volume and cardiac output. Incomplete ventricular emptying increases end-diastolic pressure and end-systolic volume. Elevated end-diastolic pressure is transmitted to the pulmonary vasculature, and the increased hydrostatic pressure leads to pulmonary edema. Similarly, on the right side of the heart, the increased pressure is transmitted to the systemic venous circulation, causing peripheral edema, hepatic congestion, abdominal edema, and jugular venous distention.[80]

The functional phenotype includes a variety of clinical presentations from asymptomatic to RV, LV, and biventricular heart failure (HF), in addition to atrial and ventricular arrhythmias, syncope, thromboembolic complications, failure to thrive, sudden death, and jugular venous distention.[8,80,81]

Pathogenetic Classification

A wide variety of causations and associations have been described for DCM[8,20,79] (Table 2). For many forms, including familial and sarcomeric DCM, the association is variable, and not all individuals will manifest the phenotype. These pathogenetic categories include primary (idiopathic, familial, genetic mutations) and secondary (inflammatory, congenital heart disease, oncologic, toxin mediated, systemic, and syndromic) categories, which are discussed below. Congenital heart disease is sometimes associated with DCM, given the end-stage consequence of abnormal loading conditions (eg, valvular stenosis or regurgitation). As noted in the introduction, the challenge is to determine whether ventricular remodeling and dysfunction are caused by an abnormal myocardium or solely by the abnormal loading conditions. The diagnosis of DCM is most justifiable when dilation and dysfunction do not resolve after hemodynamic factors return to normal.

Primary DCM

In the absence of an identified familial mutation, a diagnosis of a primary DCM cannot be based on clinical presentation or morphological imaging findings alone. Secondary causes of DCM (see Secondary DCM) must be excluded before a patient can be classified as having a primary DCM.[20,79]

Idiopathic DCM

IDCM is a diagnosis of exclusion and is estimated to occur in 50% to 70% of children with cardiomyopathy.[8,80] This proportion has decreased as further investigation of patients or families has led to reclassifying some cases of IDCM as FDCMs. Most cases of IDCM are believed to have a genetic cause. No specific morphological or functional characteristics distinguish FDCM from IDCM.

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Table 2. Causes of DCM

Primary DCM
Familial/genetic
Sarcomeric
Mitochondrial diseases
Neuromuscular disorders
Laminopathies
Secondary DCM
Inflammatory
Toxins
Iron
Lead
Cobalt
Arsenic
Anthracycline
Radiation
Metabolic disorders
Endocrinopathies
Thyroid disorders
Catecholamine-secreting tumor
Parathyroid disease
Diabetes mellitus
Fatty acid oxidation disorders
Carnitine deficiency
Malonyl coenzyme decarboxylase deficiency
GSDs
GSD type II (Pompe disease)
GSD type IV (Andersen disease)
Lysosomal storage disorders
Gaucher disease
Mucopolysaccharidoses
Sphingolipidoses
Nutritional disorders
Thiamine deficiency
Selenium deficiency
Protein energy malnutrition
Structural heart diseases
Valvular heart disease
Ischemia: coronary artery anomalies, coronary artery injury
Single ventricle
Pulmonary diseases

DCM indicates dilated cardiomyopathy; and GSD, glycogen storage disease.

Familial DCM

FDCM is estimated to occur in 30% to 50% of cases. Autosomal-dominant inheritance is the most common mode of inheritance, although X-linked and autosomal-recessive inheritance also occurs.[70] Candidate cytoskeletal and Z disk–encoding genes include δ-sarcoglycan, β-sarcoglycan, desmin, lamin A/C, metavinculin, muscle LIM protein, titin, α-actinin-2, nebulette, myopalladin, and ZASP (Z band alternatively spliced PDZ domain protein). Mutations in cytoskeletal genes are hypothesized to lead to abnormalities in force transmission (desmin, δ-sarcoglycan, metavinculin, and muscle LIM protein).

Diagnosis not only is based on clinical presentation and morphological findings on imaging but also requires a detailed family history and genetic evaluation.[20] A patient can be classified as having FDCM without an identified specific genetic mutation on the basis of family pedigree alone if multiple family members are affected, hence the importance of screening first-degree relatives in the absence of finding a nonfamilial (or secondary) cause. Genetic heterogeneity can complicate the diagnosis of FDCM and partially contributes to the reclassification of patients with IDCM as family members are identified over time or as causal genetic mutations are identified on updated DCM genetic panels.[70]

DCM Associated With Sarcomeric Mutations

Sarcomeric mutations account for 10% to 20% of inherited DCM.[22] The general comments above on FDCM apply to sarcomeric DCM, with the exception of the genes involved. Sarcomere-encoding genes include actin, troponin T, β-myosin heavy chain, myosin binding protein C, α-tropomyosin, phospholamban, and *SCN5A*. Mutations in these genes are believed to result in a defect in force generation in the myocyte.

DCM Associated With NMD

Cardiomyopathy is a common finding and a leading cause of morbidity and mortality in children with NMDs.[82] NMDs are a broad category of disease with a wide spectrum of cardiac involvement. Cardiomyopathy often develops in certain NMDs such as Duchenne and Becker muscular dystrophies, Barth syndrome, Friedreich ataxia, limb-girdle muscular dystrophies, and myofibrillar myopathies, but it occurs less commonly in other NMDs such as Emery-Dreifuss and myotonic dystrophies.[83–88] Conduction abnormalities such as heart block are common in Emery-Dreifuss muscular dystrophy and can lead to symptoms of palpitations, syncope, or even sudden death. Although the dilated phenotype is the most common manifestation of cardiomyopathy in NMDs other than Friedreich ataxia, hypertrophic, restrictive, and mixed forms have also been described. The phenotypic features of many of the NMDs are similar, but the management may be different, making genetic testing important in establishing a correct diagnosis.

The NMDs may be inherited in autosomal-dominant, autosomal-recessive, or X-linked recessive patterns. They may also result from mitochondrial or spontaneous DNA mutations. Children with NMDs should undergo cardiac evaluation, including echocardiography and ECG, at the time of diagnosis. Recommendations

for follow-up and cardiac surveillance vary and depend on the genetic diagnosis. The AHA's recent consensus statement on managing cardiac involvement in NMDs contains more detailed information.[82]

DCM Caused by Laminopathy

Mutations in the LMNA gene may cause a wide spectrum of diseases referred to as laminopathies, including peripheral neuropathy, skeletal muscle disorders, progerias, and DCM.[89] The LMNA gene encodes nuclear lamins A and C, which are intermediate filament proteins important in the structural support of the nucleus. The autosomal-dominant form of Emery-Dreifuss syndrome is caused by a mutation of LMNA and is characterized by skeletal muscle weakness and DCM.[90] LMNA gene mutations may also cause DCM in patients with limb-girdle muscular dystrophy type 1B and in patients with no skeletal muscle disease.[91,92] Cardiac conduction abnormalities are common and include sinus bradycardia, atrioventricular block, atrial fibrillation, and ventricular tachycardia (VT).[93] Conduction defects often precede the onset of HF symptoms and may be the first clinical signal of cardiac disease.

About one-third of patients experience dysrhythmias before 20 years of age, but only 10% show features of HF by 30 years of age.[93] LV or biventricular chamber dilation with depressed systolic function is often seen on echocardiography. Apical LV aneurysm and noncompacted myocardium have also been described.[94,95] A high rate of sudden death has been reported in patients with DCM secondary to LMNA mutations.[93] In fact, sudden death is more likely to occur than death resulting from HF. Cardiac conduction defects and DCM with or without skeletal muscle disease are suspicious for LMNA mutations. Genetic testing should be performed to confirm mutations in LMNA.

DCM Related to Mitochondrial Diseases

Primary mitochondrial disorders, which can arise from either mitochondrial (mtDNA) or nuclear (nDNA) gene mutations that affect cellular oxidative phosphorylation, impair energy metabolism. Given that the heart is highly energy dependent, it is not surprising that up to 40% of cases of these disorders include a cardiomyopathy phenotype.[96,97] Some include a DCM phenotype at presentation, whereas others may progress from hypertrophic or noncompacted to DCM over time.

Carnitine palmitoyl transferase II deficiency is a primary mitochondrial disease that can manifest as DCM; others include Kearns-Sayre syndrome, MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes), MERFF (myoclonic epilepsy with ragged red fibers), NADH-coenzyme Q reductase (complex I) deficiency, and cytochrome C oxidase deficiency.[98,99] When a primary mitochondrial disease is suspected, screening laboratory tests should include plasma lactate, blood glucose, urine organic acids, and plasma amino acids.[100] Skeletal muscle biopsy, molecular testing (including both nDNA sequencing and mtDNA gene sequencing), and ancillary testing for other organ involvement may also be indicated.[100,101]

Barth syndrome is a disease that affects the mitochondria through a defect in cardiolipin, a key component of the mitochondrial inner membrane.[102] It most often presents in boys with growth failure, cyclic neutropenia, and cardiomyopathy, which may be a dilated, hypertrophic, LVNC, or mixed phenotype (see the Types of LVNC section). An abnormal urine organic acid screen usually shows elevated concentrations of 3-methylglutaconic acid. The diagnosis is confirmed by depressed concentrations of cardiolipin in muscle, cultured fibroblasts, or platelets or a mutation identified on the *TAZ* (G4.5) gene on the X chromosome.

Friedreich ataxia may also be broadly categorized as a mitochondrial disorder because it is caused by a genetic mutation that leads to a deficiency in the mitochondrial protein frataxin.[103] Although it is most commonly associated with a hypertrophic phenotype (see also HCM Caused by Infiltrative and Other Nonsarcomeric Diseases), on rare occasions, children have presented with a dilated phenotype.

Secondary DCM

The DCM phenotype has several causes, as explained above. The distinguishing features of secondary DCM are that the identifiable causes themselves can sometimes be treated and that, although there is often a metabolic or genetic basis, the manifestation of these causes affects multiple organ systems, not just the heart. The phenotypic expression also markedly overlaps in the course of the disease. For instance, the cardiovascular system can be completely normal at diagnosis, and a severe DCM develops later. The morphology of the cardiomyopathy can also evolve from 1 variety to another or have combined, so-called mixed, phenotypes. Therefore, the manifestation can also differ greatly between adults and children. However, the disorders described here largely have a dilated morphology with systolic dysfunction, hence their placement in this classification. Describing each disease completely is beyond the scope of this statement. (See selected references for a more comprehensive review of each disease.) Here, we present the unique highlights as they pertain to the diagnosis in children.

In terms of a diagnostic approach to secondary DCM, this group of disorders is obviously quite broad. Some primary conditions leading to remodeling and injury to the heart, such as mechanical malfunction of valves, are obvious. More subtle diagnoses require an index of suspicion. Thus, when an underlying primary condition is suspected or diagnosed, it is important to consider the associated cardiomyopathy. Conversely, when an incidental DCM is identified, considering an

underlying pathogenic process is crucial. One practical diagnostic clue is the age of the patient. By the teenage years, whether the heart disease is an isolated condition (see Primary DCM) should be more evident. As a corollary, primary DCM is expected to be more prevalent in adults. The acquired cardiomyopathies such as those secondary to myocarditis, cancer, or pulmonary disease would also be more apparent from the history and from cardiac-specific diagnostic tools such as endomyocardial biopsy and advanced imaging. Similarly, structural heart disease should be quite apparent. The challenge in differentiating a primary DCM from a secondary DCM is in the presentation in the younger patient; although rare, the probability of a metabolic or genetically driven condition underlying the cardiomyopathy in this age group is higher. This possibility is a reason that secondary cardiomyopathies need to be classified in a cardiomyopathy statement.

Inflammatory DCM

Inflammatory DCM can be classified as infectious or noninfectious. Because noninfectious causes are rare in children, we refer readers to Table 3. We focus here on viral myocarditis because it is the most common cause of inflammatory DCM in children.

Viral myocarditis is a good example of how the morphology of the ventricle can change in the course of a disease. In the acute and fulminant phases, the LV does not have to be dilated, despite marked dysfunction. However, over time, the phenotype ascribed to myocarditis remodels into a dilated form with hypokinesis.[105] In the seminal work describing the incidence of newly diagnosed DCM in children in North America, only 34% of the 1426 patients in the cohort had a known cause.[8] Among these patients, 485 cases, 46% (222 of 485), were presumed to be myocarditis. Attributing the cause of the myocarditis to a viral organism is not straightforward. A definitive diagnosis of viral myocarditis requires finding inflammation and injury in the myocardium severe enough to convincingly affect the morphology and function.[106] A biological marker of a virus may be found in the myocardium. In clinical practice, neither criterion is easily met, especially in acutely ill children in whom invasive procedures to obtain myocardial specimens or advanced noninvasive imaging to detect inflammation may be unobtainable. Given these difficulties of proving inflammation in the myocardium or an infectious cause, the terms supposed myocarditis or presumed myocarditis are used.

To diagnose inflammation, results from an endomyocardial biopsy are still the reference standard. The original Dallas criteria, if met, require a histological diagnosis of myocarditis that includes myocyte necrosis.[107] However, lymphocytic infiltrate, with or without monocytic cells, and immunohistochemistry showing $CD3^+$ lymphocytes even without myocyte degeneration are associated with clinical myocarditis and are the criteria established by the ESC.[108] However, a negative biopsy does not necessarily rule out myocarditis. Furthermore,

Table 3. Causes of Inflammatory Cardiomyopathy

	Causal Agent or Exposure
Commonly reported	
Infectious causes	
Bacterial	
Fungal	
Viral	Adenoviruses, enteroviruses, herpes simplex virus, varicella-zoster virus, human cytomegalovirus, Epstein-Barr virus, human herpesvirus 6, influenza A and B viruses, HIV, parvovirus B19
Rickettsial	
Spirochete	*Borrelia burgdorferi*
Noninfectious causes	
Autoimmune diseases	
Hypersensitive reactions	Dermatomyositis, hypereosinophilic syndrome, Kawasaki disease, lupus erythematodes, rheumatoid arthritis
Drug reactions	
Toxic reactions to drugs	Penicillin, ampicillin, cephalosporins, tetracyclines, sulfonamides, anthracyclines
Other exposures	
Rarely reported	
Infectious causes	
Bacterial	Chlamydia, *Corynebacterium diphtheria,* legionella, *Mycobacterium tuberculosis,* mycoplasma, staphylococcus, *Streptococcus A, Streptococcus pneumonia*
Fungal	Actinomyces, aspergillus, candida, *Cryptococcus helminthic: Echinococcus granulosus, Trichinella spiralis protozoal: Toxoplasma gondii, Trypanosoma cruzi*
Viral	Variola virus, vaccinia virus, mumps virus, measles virus, rubella virus, hepatitis C virus, coronavirus, respiratory syncytial virus
Rickettsial	*Coxiella brunetti, Rickettsia typhi*
Spirochete	Leptospira, *Treponema pallidum*
Noninfectious causes	
Autoimmune diseases	Celiac disease, Churg-Strauss syndrome, Crohn disease, giant-cell myocarditis, lymphofollicular myocarditis, sarcoidosis, scleroderma, ulcerative colitis
Hypersensitive reactions	Antiphlogistics, benzodiazepines, clozapine, loop and thiazide diuretics
Drug reactions	Methyldopa, smallpox vaccine, tetanus toxoid, tricyclic antidepressants
Toxic reactions to drugs	Amphetamines, catecholamines, cocaine, cyclophosphamide, 5-fluorouracil, phenytoin, trastuzumab, ethanol
Other exposures	Arsenic, copper, iron, radiotherapy, thyrotoxicosis

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not only can inflammation be regional and spotty, but also the amount of inflammation indicated by traditional criteria, such as edema, amount of lymphocytic infiltrate, and myocyte necrosis, is not necessarily associated with a response to treatment or outcome. Hence, alternative diagnostic methods have been used. cMRI is now an accepted modality for diagnosing myocarditis.

An international consensus group has issued the Lake Louise criteria for diagnosing myocarditis using cMRI.[109] Its recommendations are based on expert opinion, relying on clinical and cMRI data without confirmation by pathology from biopsy. Two of the 3 following criteria are required for a diagnosis of myocardial inflammation: regional or global increased intensity of T2-weighted images indicating edema, increased global myocardial early gadolinium enhancement T1-weighted images as a sign of hyperemia and capillary leak, or late gadolinium enhancement T1-weighted images with nonischemic regional distribution (not attributable to epicardial occlusive disease) indicating myocardial injury.

A rigorous prospective study of 129 consecutive adults with suspected myocarditis that compared the Lake Louise cMRI criteria and T1 and T2 mapping with biventricular endomyocardial biopsy as the reference standard found associations between biopsies and the Lake Louise criteria. However, the associations between T1 (myocyte injury, hyperemia, intracellular and extracellular edema) and T2 (edema) mapping techniques with biopsy were even stronger.[110] One potential reason is that delayed enhancement (myocardial injury or scarring) can be seen in DCM. Therefore, if DCM is in the differential diagnosis, delayed enhancement, which is included in the Lake Louise criteria, may have a higher false-positive rate. If no heart disease other than myocarditis is in the differential diagnosis, the use of delayed enhancement may be acceptable, but T1 mapping and T2 mapping were still shown to be superior to the T1-weighted and T2-weighted techniques used in the Lake Louise criteria.

The largest study incorporating cMRI in children was retrospective and involved 13 hospitals and 143 patients.[111] A number of different tissue characterization techniques were used to diagnose myocarditis among the centers, which illustrated the lack of consensus on magnetic resonance imaging (MRI) criteria at the time. The reference standard for the diagnosis of myocarditis was presumed because it was based on the clinical diagnosis reported by the managing physician. The sensitivity of MRI to diagnose myocarditis in children was 82%, although its inherent limitations are as described above.

Among the numerous causes of inflammatory cardiomyopathy in children, virus-mediated myocarditis is common (Table 3). Highly sensitive and specific assays based on polymerase chain reactions in blood, respiratory secretions, and tissue, including the myocardium, can often identify an organism, supporting a diagnosis of myocarditis (Table 3). Adenovirus and enterovirus were the predominant organisms in North America[112] in an early era, and parvovirus and human herpesvirus 6 are more common in more recent eras.[113–115] Unlike polymerase chain reaction, viral serologies are unlikely to be helpful because they are obtained solely from blood and indicate prior exposure to an organism as opposed to active viremia or presence of virus in the tissue of interest. It would not be surprising to observe serological conversion from past exposure in many children in some of the viruses described above. In young infants, serologies can also be passively acquired from the mother.

Identifying viruses by polymerase chain reaction from the blood or body secretions can also provide a presumptive diagnosis of viral myocarditis when other clinical information is supportive.[116] The other blood biomarker that supports a diagnosis of myocarditis is troponin. Because acute coronary syndrome and acute myocardial strain such as that caused by pulmonary embolism or recreational drug use are uncommon in children, an elevated troponin concentration can support a diagnosis of myocarditis when other causes of ischemia are not likely, especially if the concentration is in the range indicating myocardial infarction.

Unlike for cMRI, no well-conducted prospective studies have assessed the ability of troponin concentrations to accurately diagnose myocarditis with histology as the reference standard. However, several studies support its additive utility. Cardiac troponin T concentrations were elevated in 28 of 80 adults with clinically suspected myocarditis, but a histological diagnosis was made in only 5, and all 5 had elevated troponin concentrations.[117] Adding immunohistochemistry to the biopsy review revealed myocarditis in 26 of 28 patients with elevated troponin concentrations and in 23 of 52 patients without elevated concentrations. In a later study that examined the association of cMRI results with biopsy results in the diagnosis of myocarditis, an elevated troponin concentration was required for enrollment.[118] In this study of preselected patients, a good association (κ=0.70) was reported between biopsy and cMRI results, suggesting that troponin concentrations can be used in triage, although, as stated before, many adults presenting with chest pain and elevated troponin concentrations are more likely to have ischemia from coronary artery disease.

There is lack of data on the use of C-reactive protein or erythrocyte sedimentation rate to aid the diagnosis of myocarditis. Although they are good markers of systemic inflammation such as in autoimmune diseases or infections, they are not tissue specific. Furthermore, concomitant viral or bacterial infections are common

during childhood, and the quest remains how best to identify specific involvement of the myocardium.

Smaller studies in children have reported elevated troponin concentrations in myocarditis.[119–122] Given the trend to reduce the reliance on biopsy in the diagnostic workup in children,[123] noninvasive testing will continue to be used in clinical practice.

In summary, a complete history and physical examination should be performed to detect cardiovascular symptoms of HF, ischemia, recent infection, and systemic inflammation and to elicit a history of toxin exposure, travel, drug use, and family history. Autoimmunity and hypersensitivity should also be considered in the history and physical examination. If myocarditis is suspected, ECG, troponin concentrations, and echocardiography can help rule out other causes of cardiovascular disease and to determine whether cMRI, biopsy, or both should be obtained. If a biopsy can be safely obtained, viral polymerase chain reaction of the specimen should be performed, acknowledging that a positive viral polymerase chain reaction without histological changes can serve only as supportive and not as definitive proof of myocarditis. Local expertise in acquiring and interpreting the results of cMRI can be a barrier to its use, especially if edema and hyperemia are needed to differentiate myocarditis from noninflammatory cardiomyopathy or no myocardial disease such as pericarditis. cMRI will not identify the cause of the myocarditis. Additional tests such as viral polymerase chain reaction from the blood or respiratory secretions can support the diagnosis of an underlying infectious process, but they cannot prove direct myocardial involvement on their own. Therefore, the diagnostic criterion for myocarditis is the presence of inflammation in the myocardium by histopathology or cMRI. The criterion for viral myocarditis is the demonstration of viral presence in the inflamed myocardium, which would have to be from an endomyocardial biopsy. Presumed myocarditis or viral myocarditis would be ≥1 of the surrogate features described above.

DCM Secondary to Exposure to Toxins

Cardiomyopathy Secondary to Iron Overload. Cardiomyopathy secondary to iron overload occurs in several clinical conditions. Primary hemochromatosis is an autosomal-recessive, inherited condition linked to mutations in various proteins involved in iron metabolism. The 4 primary types are caused by mutations in the *HFE*, *HJV*, *TfR2*, and *SLC40AI* genes.[124]

Cardiomyopathy secondary to iron overload also occurs in patients with hereditary anemias, including sickle cell disease and α- and β-thalassemias. Iron overload may be a result of multiple blood transfusions and increased intestinal absorption when erythropoiesis is ineffective.[125] Other conditions predisposing to secondary iron overload include myelodysplastic syndromes, end-stage renal disease, leukemias, sideroblastic anemia, and congenital dyserythropoietic anemia.[124] Iron-overload cardiomyopathy in children and young adults with the above conditions begins as an RCM with severe diastolic dysfunction, eventually progressing to end-stage DCM,[126] with mixed systolic and diastolic dysfunction.

In iron-overload states, iron in the circulation exceeds the transferrin iron binding capacity, resulting in highly reactive unbound iron, a potent free-radical generator. This leads to peroxidation of lipid membranes and oxidative damage to nucleic acids and calcium cycling proteins in cardiomyocytes.[127,128] Untreated, this may eventually lead to impaired diastolic function and cardiomyopathy.[127]

Chronic iron overload predisposes the child to life-threatening arrhythmias, including conduction defects, bradyarrhythmias, tachyarrhythmias, and sudden cardiac death (SCD). It can also potentiate the cardiotoxicity of anthracyclines in patients with leukemia undergoing chemotherapy.

A serum transferrin saturation >45% and a serum ferritin concentration >200 μg/L in female patients or >300 μg/L in male patients suggest primary hemochromatosis, a clinical diagnosis associated with cardiomyopathy.[129]

Commercial genetic testing for *C252Y* and *H52D* mutations in primary hemochromatosis is now available. Hemoglobin electrophoresis is also readily available for the diagnosis of congenital hemoglobinopathies.

Echocardiography, particularly tissue Doppler imaging and strain–strain rate imaging with or without speckle tracking, is useful in the early diagnosis of ventricular systolic and diastolic function.[130,131] cMRI is useful for diagnosing and monitoring iron overload. T2* relaxation is highly correlated with myocardial iron deposition and is useful for assessing responses to iron-chelation therapy.[132] T2* images are distinct from and more sensitive than T2 images in that they detect the magnetic field heterogeneity typically present in regions of iron overload. A T2* value >10 seconds is 97% sensitive and 83% specific in predicting HF from iron overload.[133]

DCM Caused by Lead Toxicity. Lead is an environmental toxin that can damage nerves, kidneys, and the cardiovascular system, among other organs.[134,135] The degree of damage depends on serum and tissue lead concentrations and the duration of exposure.[136] Compared with the many reports on lead-induced hypertension, few describe the negative effects of lead on the cardiac muscle.[137]

Lead toxicity causes short-term inflammatory changes in the myocardium similar to those in myocarditis. Histological changes consistent with subacute interstitial

myocarditis were reported in autopsies of 5 children who died of lead poisoning.[138]

DCM Caused by Cobalt Exposure. Small amounts of cobalt are present in many over-the-counter vitamin preparations and nutritional supplements.[139] Because cobalt can stimulate the production of red blood cells, it has also been used to treat refractory anemia.[140] Cobalt can increase red blood cell mass and exercise performance, and athletes have used this agent for blood doping.[141] As a result, its medicinal use has greatly declined to prevent its abuse. The effects of cobalt on the heart are deleterious at high concentrations.[142] Cobalt interferes with calcium binding to the sarcolemma; hence, it affects calcium transfer into the cardiac myocyte.[143] Cobalt interrupts the citric acid cycle and the generation of ATP by aerobic respiration. It also inhibits the activity of the enzymes in the respiratory chain and ATP production in the mitochondria.[144,145] The net result is a distinct, rapidly progressive but reversible myocardial depression. It affects both ventricular systolic and diastolic function and changes in cardiac cell structure.[146]

The typical presentation of DCM from cobalt exposure is a subacute onset of severe HF secondary to severe DCM and is marked by elevated concentrations of cardiac enzymes, low-voltage electrocardiographic changes, and lactic acidosis. If untreated, it can be rapidly progressive and fatal. The cardiomyopathy can resolve completely with early recognition and treatment.[142] Because high cobalt concentrations cause polycythemia and hypothyroidism, cobalt cardiotoxicity should be suspected in patients with the triad of DCM, hypothyroidism, and polycythemia.[142] The diagnosis of cobalt cardiomyopathy requires documented biventricular dilatation and dysfunction associated with high cobalt concentrations in blood or urine and the return of normal cardiac structure and function when cobalt exposure ceases and concentrations return to the physiological range.[142]

Cardiomyopathy Caused by Arsenic Toxicity. Arsenic exposure in children is mainly the result of consuming contaminated water and food.[147] Arsenic is toxic to the cardiovascular system and commonly leads to capillary dilation manifesting as severe hypovolemia and hypotension. Other cardiac manifestations include DCM, prolonged QT, ST-segment changes, ventricular dysrhythmias (atypical VT and ventricular fibrillation [VF]), and HF.[148–150]

Occupational exposure in older children and adults has also been reported. Long-term inhalation of arsenic trioxide can increase the risk of death resulting from cardiovascular disease in humans.[151,152] Long-term inhalation of inorganic arsenic could cause coronary vasculopathy. Several cases of myocardial infarction and arterial thickening have been reported in children who drank water containing ≈0.6 mg/L arsenic.[147] Both short-term arsenic exposure and long-term arsenic exposure alter myocardial depolarization and cause cardiac arrhythmias that may lead to HF.[153,154]

Oncological Cardiomyopathy. Childhood cancer survivorship has increased in the past few decades. Now, >80% of patients with childhood cancer survive >5 years, whereas these malignancies were nearly universally fatal before the 1960s. As survivorship has increased, so too have the late adverse effects of cancer therapies.

Survivors of childhood cancer have markedly higher risks of morbidity with reduced quality of life and mortality than their healthy counterparts.[155,156] Cardiotoxicity is an adverse event associated with many childhood cancer therapies. Survivors have substantially higher rates of the following oncological cardiotoxicities: cardiomyopathy, HF, myocardial disease, valvular disease, pericardial disease, hypertension, and early cardiac death.[38,157–159] Cardiotoxicity is the third leading cause of morbidity and mortality after cancer recurrence and secondary malignancies among childhood cancer survivors.[124,126,156,159] Thus, in addition to seeking curative treatments for the 20% of children who currently die of cancer, another focus is reducing the cardiovascular morbidities of long-term survivors.

Cancer treatments are usually multimodal and carry risks of toxicity, including cardiotoxicity. Anthracyclines such as doxorubicin, daunorubicin, and epirubicin are among the agents commonly used to treat hematologic cancers and solid tumors, including sarcomas.[160–164] Anthracyclines are also among the most cardiotoxic agents, causing either acute or subacute cardiomyopathy within a year of treatment or several years after treatment.[160,165–167] Despite the adverse cardiac effects of anthracyclines, these drugs have remained critical components and standards of care for many patients with cancer for decades.

Radiation therapy can also be cardiotoxic. Chest irradiation can cause many of the same cardiotoxicities as anthracyclines, including cardiomyopathy, pericardial disease, myocardial fibrosis, coronary artery disease, and valvular disease.[168–171] Among 91 Finnish patients treated with doxorubicin, radiation therapy, or both, anthracycline cardiotoxicity had an additive effect on abnormal systolic and diastolic function.[172] In a recent study of 48 patients who received a radiation dose of 40 Gy (range, 27–51.7 Gy), 47 had detected subclinical cardiac abnormalities.[173] Many other chemotherapeutic drugs, including alkylating agents, tyrosine kinase inhibitors, and monoclonal antibodies, are cardiotoxic.[174,175]

Risk factors for cardiac damage include female sex, younger age at diagnosis, black race, trisomy 21, choice of therapy, and lifestyle behaviors.[174–177] A total cumulative anthracycline dose >300 mg/m^2 is a significant

risk factor for late-occurring anthracycline-induced cardiotoxicity. However, adverse effects have been associated with lower cumulative doses, suggesting that any anthracycline exposure may be potentially harmful to the heart.[174,175] Cranial spinal irradiation, in addition to thoracic irradiation, can be cardiotoxic when used concurrently with anthracyclines, possibly because of its effects on the hypothalamic-pituitary pathway.[158,178,179]

Identifying the risk of cardiotoxicities in childhood cancer survivors is imperative and requires close surveillance. Biomarker concentrations during therapy may indicate potential cardiac risk.[160,179] Cardiac troponin T and NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations were associated with echocardiographic findings, including reduced LV mass and end-diastolic posterior wall thickness, as well as abnormal LV thickness-to-dimension ratio, 4 years after therapy in patients with high-risk acute lymphoblastic leukemia treated with doxorubicin.[179] These results have informed prospective randomized clinical trials assessing the tradeoff between conventional cancer management and cardiac biomarker–guided therapy to see which provides the highest quality of life over time, balancing oncological efficacy, cardiac toxicity, and late adverse effects.[179]

Preventive measures should be considered to reduce anthracycline-induced cardiotoxicity. Dexrazoxane has reduced anthracycline-related cardiotoxicity while maintaining the oncological efficacy of anthracycline and even allowing safer anthracycline dose escalation.[164,180–183] Dexrazoxane has been endorsed by the AHA and the American Academy of Pediatrics for use as a cardioprotectant among children and adolescents undergoing anthracycline-containing protocols.[184] The drug has been used as the standard of good clinical care in all Dana Farber Cancer Institute Childhood Acute Lymphoblastic Leukemia Consortium protocols involving anthracycline therapy since 2000, and since 2015, it has been mandated for inclusion in all new Children's Oncology Group protocols involving treatment with at least 150 mg/m^2 doxorubicin or anthracycline at any dose with planned radiation treatment portals that may affect the heart.[155] In 2014, the US Food and Drug Administration granted dexrazoxane pediatric orphan drug status, and in 2017, the European Medicines Authority approved its use in children for anthracycline cardioprotection in patients expected to receive a cumulative dose of >300 mg/m^2 doxorubicin or the equivalent cumulative dose of another anthracycline. This allows virtually all pediatric patients receiving anthracyclines to receive dexrazoxane starting with the first dose of anthracycline. Specifically, in August 2017, the European Medicines Authority concluded that dexrazoxane should not be contraindicated in pediatric patients at the highest risk of cardiotoxicity. The European Medicines Authority did not find data to support that dexrazoxane use in pediatric patients resulted in increased second primary malignancy, found no evidence of interference with chemotherapy, and found no data to support dexrazoxane being associated with risk for early death. Further information on this action may be found online.[185,186]

Given the progress in finding cures and improving survival in children with cancer, we must also improve prevention and treat the long-term adverse effects of cancer therapy, including adverse cardiac effects.

DCM Secondary to Metabolic Disorders

DCM Secondary to Endocrinopathy

Hypokinetic DCMs secondary to an endocrinopathy exist but are not common in children. Akin to many pediatric cardiovascular conditions, because these cardiomyopathies are uncommon, it becomes even more important to consider them in the workup and differential diagnosis. Fortunately, most of these conditions offer clues to the diagnostician. Furthermore, because they are secondary to an underlying endocrine disease, if identified and treated early, the cardiac condition can in most cases completely resolve. The diagnostic criteria for each of these cardiomyopathies are defined by the morphofunctional phenotype of DCM in the setting of the specific endocrinopathy described.

Hypothyroidism. Thyroid hormone is important in the energetics of the myocardium, but whether congenital or acquired hypothyroidism leads to DCM is debated.[187,188] The common myxedematous findings of pericardial effusion and nonpitting edema are well described. Additional manifestations include larger birth weight, growth failure later in life, fatigue, slower heart rate, lower blood pressures, cool skin, and softer heart sounds. Ultimately, the diagnosis requires thyroid function testing and interpretation by an endocrinologist. Therefore, the diagnosis of DCM can be suspected by both the pediatrician and the cardiologist, given that the presentation can be that of HF. Nevertheless, it is unclear whether, in the modern era, subtle echocardiographic changes progress to DCM if the hypothyroidism is left untreated by thyroxine replacement therapy.[187,188]

Hyperthyroidism. In contrast to hypothyroidism, excessive production of T3 or T4 increases cardiac stimulation and work. Hence, the clinical manifestations of hyperthyroidism are tachycardia, restlessness, irritability, and widely opened eyes in the infant and hyperactivity, insomnia, tremors, palpitations, and widened pulse pressure in older children.[189] Hyperthyroidism is also in the differential diagnosis in the child who presents with atrial fibrillation without congenital heart disease because this supraventricular arrhythmia is extremely unusual in children.[190–192]

In the infant, the most common cause is Graves disease in the mother, in which anti–thyroid-stimulating

hormone antibodies are passed transplacentally to the fetus. Thus, the condition resolves unaided in infancy and usually does not have a residual cardiomyopathy. Primary hyperthyroidism would be the pathogenesis in older children. Given the unabated cardiovascular stimulation, the heart will remodel from a hyperdynamic and hypertrophic morphofunctional phenotype to one that is likely dilated and hypokinetic, similar to tachycardia-induced cardiomyopathy. However, the existence of end-stage DCM is not documented in the medical literature, probably because these patients are readily treated by the endocrinologist.[193]

Catecholamine-Secreting Tumors. Excessive catecholamine secretion from tumors derived from neuroectodermal chromaffin cells causes severe paroxysmal hypertension and other symptoms of sympathetic surge such as headache, excessive sweating, tremors, and chest pain.[194] Although autopsies of patients with pheochromocytoma have discovered myocardial abnormalities,[194] cardiomyopathy is not commonly reported in children.[195] More commonly reported in children are HCM and DCM with neuroblastomas, which can also secrete catecholamines, perhaps more insidiously leading to cardiac remodeling without the severe peripheral vascular manifestations seen in pheochromocytomas. Both HCM and DCM resolve when the neuroblastoma is treated.[195–199]

Parathyroid Disease. Cardiac dysfunction and remodeling from hypoparathyroidism are thought to arise from chronic hypocalcemia. For example, the rare condition of congenital hypoparathyroidism can result in hypocalcemia and can cause DCM.[200] Prolonged and severe vitamin D deficiency can also cause DCM in infants.[201] Primary hypoparathyroidism leading to hypocalcemia and DCM can also occur in 22q11 deletion syndrome.[202,203] In individual case reports, the cardiomyopathy was reversible by effective treatment of the underlying condition.

Diabetes Mellitus. DCM and diastolic dysfunction, as well as premature atherosclerotic coronary disease leading to ischemic cardiomyopathy,[204,205] are well known to occur in adults. Diabetes mellitus and poorly controlled hyperglycemia are well-established risk factors for adverse cardiovascular events, including HF. Early diastolic dysfunction in diabetic children has been reported in 2 well-conducted studies with age-matched control subjects.[206,207] Although epidemiological studies that included teenagers have shown the development of cardiovascular disease, including cardiomyopathy, later in life, it is unclear whether diastolic dysfunction is a predictor. DCM or ischemic cardiomyopathy secondary to diabetes mellitus[207] presenting during childhood is exceeding rare and described only by case reports. Although classified as a pathogenesis, cardiomyopathy secondary to diabetes mellitus is likely to be subclinical during childhood.

DCM Secondary to Fatty Acid Oxidation Disorders

Fatty acid oxidation disorders can lead to cardiomyopathy,[208] arrhythmias,[209] and SCD.[208-210] Not only is the manifestation of fatty acid disorders variable, but the morphology of cardiomyopathy can also be variable, mainly HCM or DCM.[211] Largely on the basis of case reports or small studies, DCM or HCM can be associated with many of these disorders. Even within these reports, the morphology of the cardiomyopathy is not always specified, making the association of the type of cardiomyopathy with other systemic or cardiovascular features difficult to identify. The exceptions are DCM, which is reported with malonyl coenzyme A (CoA) decarboxylase deficiency, and HCM, which is reported with very long-chain acyl-CoA dehydrogenase deficiency. Therefore, the information presented below also applies to HCM associated with fatty acid oxidation disorders (see the HCM Secondary to Fatty Acid Oxidation Disorders section).

Many patients present as newborns with acute HF or multisystem failure or are incidentally diagnosed by newborn screening.[212,213] This class of disorders should be considered in children with unexplained DCM, particularly in infants and newborns, and certainly in the presence of metabolic derangement. A thorough description of the biochemistry and metabolic pathways of fatty acid oxidation is beyond the scope of this statement. In brief, fatty acids of various lengths are the substrates for cellular energy production through oxidative phosphorylation. These fatty acids are transferred from the cytoplasm across the inner membrane of mitochondria. However, in the heart, long-chain fatty acids are the preferred substrate.[214,215] These lengthier fatty acids, given their more negative charge, require carnitine to shuttle across the inner membrane of the mitochondria. Carnitine palmitoyltransferase assists in transferring the acyl groups of fatty acids to L-carnitine. These steps precede β-oxidation and ATP production in the mitochondrion matrix. The diagnostic criteria for each of these cardiomyopathies are defined by the morphofunctional phenotype in the setting of the fatty acid oxidation disorder described.

DCM Secondary to Primary Carnitine Deficiency. In primary carnitine deficiency–associated cardiomyopathy,[216] the deficiency is caused by the loss of carnitine secondary to a well-described genetic disorder in the *SLC22A5* gene, which encodes the family of cation transporter type 2. Carnitine transport across all cytoplasmic membranes requires cation transporter type 2. When a mutation in the *SLC22A5* gene renders the transporter dysfunctional, carnitine is lost through the urine, and its plasma concentration is low, leading to systemic primary carnitine deficiency. Its incidence is ≈1 in 50 000 newborns in the United States, according to newborn screening data.[208] Its manifestation

can be quite variable, depending on the mutation. In infants, the presentation is quite severe, with hypoketotic hypoglycemia, hepatomegaly, elevated transaminases and creatinine kinase concentrations, and DCM or HCM.[208,217] Presentation in older children and adults is not as striking and consists mainly of DCM, muscle weakness, and arrhythmias. Similar to other fatty acid oxidation disorders, fasting can exacerbate symptoms because of the dependence on glucose as a substrate in the disorder. The condition is treatable with meticulous metabolic management.

DCM Secondary to Malonyl CoA Decarboxylase Deficiency and Other Fatty Acid Oxidation Disorders. In addition to primary carnitine deficiency, other disorders in this class can be associated with DCM. Specifically, malonyl CoA decarboxylase and trifunctional mitochondrial protein are associated with a DCM phenotype. Malonyl CoA decarboxylase deficiency can also be associated with LVNC.[218,219] As in primary carnitine deficiency, these disorders can be diagnosed by newborn screening and by considering them in the differential diagnosis of unexplained cardiomyopathy in children.

However, other disorders of fatty acid oxidation can present with DCM or HCM.[220] Many descriptions of cardiomyopathy in fatty acid oxidation disorders are case reports. Other cases are described as part of a larger study focusing on the biochemistry, genetics, or metabolism of this disease and include mention of heart disease without enough information to verify the type of cardiomyopathy included in the studies.

When fatty acid oxidation disorders associated with cardiomyopathy are considered, those predominantly associated with HCM are very long-chain acyl-CoA dehydrogenase, multiple acyl CoA dehydrogenase (glutaric academia type II), long-chain hydroxyacyl-CoA dehydrogenase, carnitine acylcarnitine translocase, carnitine palmitoyltransferase II, and carnitine-acylcarnitine translocase (see also the HCM Secondary to Fatty Acid Oxidation Disorders section). However, even when DCM appears to respond to anticongestive therapy, the possibility of these metabolic disorders should not be discarded in patients with other systemic issues.

DCM Caused by Glycogenosis

Given that glycogen storage diseases (GSDs; glycogenosis) typically present with a hypertrophic morphofunctional phenotype, details of this class of cardiomyopathies are described in the HCM Caused by GSDs section. GSD cardiomyopathy retains a listing under DCM also because it can evolve into a dilated phenotype with systolic dysfunction.

DCM Caused by Lysosomal Storage Disorders

Lysosomal storage disorders are a broad group of metabolic diseases caused by enzyme deficiencies that result in the accumulation or storage of various substances in tissues throughout the body. Several lysosomal disorders lead to abnormalities of the myocardium, valves, coronary arteries, and conduction system. Gaucher disease is a lysosomal storage disorder caused by a deficiency of the enzyme glucocerebrosidase, causing glucocerebroside to accumulate in the brain, lungs, liver, bone marrow, spleen, and cardiovascular system. Gaucher disease has 3 types, each based on a genetic mutation, with a spectrum of neurologic disease.[221] Calcification of the mitral and aortic valve leaflets with reduced excursion has been described in children.[222] Calcification of the ascending aorta has also been reported.[223] Although rare, severe DCM with hepatosplenomegaly may occur.[224] Confirmation of a diagnosis of Gaucher disease requires testing for enzyme deficiency or genetic analysis.

DCM Caused by Mucopolysaccharidoses. The mucopolysaccharidoses are lysosomal storage disorders caused by a deficiency in the enzyme activity necessary to metabolize glycosaminoglycans. This deficiency leads to deposition of glycosaminoglycans in the connective tissues, skin, bone, and cornea. Cardiovascular abnormalities occur in 60% to 100% of children with mucopolysaccharidoses.[225,226] Valvular disease is the most common cardiac pathology and usually manifests as thickened and rolled mitral valve leaflets with an abnormal subvalvular apparatus, causing mitral regurgitation. The aortic valve is also commonly affected. LV hypertrophy with diastolic dysfunction and pulmonary hypertension (PH) has also been described. DCM occurs less frequently (10%–20%) and is usually not associated with depressed ventricular systolic function.

DCM Caused by Sphingolipidoses. The sphingolipidoses, including Anderson-Fabry disease, are lysosomal storage disorders characterized by abnormal metabolism of sphingolipids caused by deficient enzyme activity. Progressive ventricular hypertrophy is the classic cardiac manifestation of the Anderson-Fabry disease (see the HCM Caused by Lysosomal Storage Disease section), although in the later stages of the disease, the chambers may enlarge and systolic function may be depressed.[227]

DCM Caused by Nutritional Disorders

Cardiomyopathy Caused by Thiamine Deficiency

Thiamine is important in normal oxidative phosphorylation in the citric acid cycle and therefore myocardial energy production. The phosphorylated form of thiamine is an important cofactor for enzymes involved in metabolizing carbohydrates and branched-chain amino acids.[228] In the presence of thiamine deficiency, pyruvate and its precursor, lactate, build up in the blood. Beriberi heart disease, caused by severe thiamine (vitamin B_1) deficiency, is common in parts of Asia. The

staple diet in this region consists mainly of polished rice, which is deficient in thiamine. In the United States, the mandatory use of thiamine-enriched bread has virtually abolished the disease, except in the malnourished.[229] Several studies have suggested that subclinical thiamine deficiency is common among hospitalized patients with cardiomyopathy and HF, especially if they are treated with loop diuretics.[230] LV dysfunction and cardiomyopathy improved in these patients after thiamine supplementation.[230] Thiamine deficiency can also occur as a complication of total parenteral nutrition if adequate thiamine supplements are not provided.[231]

Thiamine deficiency initially presents as a high-output state secondary to vasodilation.[232] This state is followed by eventual depression of myocardial function and the development of a low-output state.[230] Beriberi in infants becomes clinically apparent between the 2 and 3 months of age and affects mainly infants who are exclusively breastfed by women with a thiamine-deficient diet.[233] The clinical features are variable and may include a fulminant cardiac syndrome with cardiomegaly, tachycardia, a loud piercing cry, cyanosis, dyspnea, and vomiting.[234] Diagnosis is made from a careful dietary history, low blood thiamine concentrations, low erythrocyte thiamine transketolase activity, and the presence of high blood lactate concentrations.[235] T2-weighted cMRI is invaluable in the diagnosis by revealing diffuse myocardial edema in patients with wet beriberi.[236]

Cardiomyopathy Caused by Selenium Deficiency

Selenium deficiency has been reported to cause DCM and HF. Selenium deficiency decreases the activity of glutathione peroxide, which increases free radicals that are toxic to cardiac myocytes.[237] The disease is also known as Keshan disease, after a Chinese county where an endemic cardiomyopathy affecting children and women of childbearing age was linked to selenium deficiency.[238,239] The disease was eventually associated with local diets, which were nearly devoid of selenium. An animal model of Keshan disease in selenium-deficient mice infected with coxsackievirus has been developed, lending more credence to the function of selenium deficiency in the development of cardiomyopathy.[239]

Selenium deficiency has also been described in children on total parenteral nutrition. These solutions were historically not supplemented with selenium, and several cases of selenium deficiency and cardiomyopathy were reported in patients receiving long-term total parenteral nutrition.[240] Selenium deficiency has also been described in a child with lymphangiomatosis secondary to loss of selenium in the chylous fluid.[241] Selenium is important in the antioxidant defenses of the body[242] and probably in the antioxidant defenses in cardiomyocytes.[243] In 1 study, rats with the highest selenium intake recovered cardiac function and had significantly smaller infarcts and a lower incidence of postischemic ventricular arrhythmias.[244]

Cardiomyopathy Caused by Kwashiorkor (Protein Energy Malnutrition)

Severe acute malnutrition is associated with 1 of 2 classic syndromes, marasmus (wasting syndrome, or total calorie malnutrition) and kwashiorkor (protein calorie malnutrition), and sometimes a combination of the 2 (marasmic kwashiorkor).[245] Children with kwashiorkor have mild DCM and a precarious fluid balance. Saline infusions may increase venous pressure and lead to acute HF, whereas a decrease in blood volume can compromise tissue perfusion.[246] Children with severe malnutrition may exhibit cardiovascular abnormalities, including hypotension, cardiac arrhythmias, cardiomyopathy, cardiac failure, and even sudden death.[247] Cardiac myocytes atrophy during starvation, as do other muscles in the body.[248]

Echocardiographic studies have shown decreased LV mass in patients with protein energy malnutrition. In addition, LV systolic functions are reduced, especially in children losing >40% of their expected weight.[249] Protein energy malnutrition is an independent risk factor for death in patients with HF.[250] In a comparison of 44 children with kwashiorkor with normal, healthy age- and sex-matched control subjects, Olowonyo et al[251] showed that, in patients with kwashiorkor, mean values for LVEDD (29.2 [SD, 3.8] mm), LVESD (20.9 [SD, 2.8] mm), posterior ventricular wall thickness (5.42 [SD, 0.57] mm), and shortening fraction (28.2% [SD, 4.3%]) were significantly lower than the corresponding values obtained from the control subjects (38.0 [SD,5.8] mm, $P<0.001$; 27.6 [SD,4.5] mm, $P<0.001$; 7.07 [0.71] mm, $P<0.001$; and 31.4% [4.5%], $P<0.05$, respectively).

Among the various factors implicated as causes of death in kwashiorkor are arrhythmia and HF from ventricular dysfunction.[252] The small ventricular volume, coupled with reduced wall thickness secondary to myocardial infiltration and cardiomyocyte necrosis, results in increased wall stress when challenged with fluid.[253,254]

DCM Secondary to Structural Cardiac Disease

A dilated systemic or subpulmonary ventricle with systolic dysfunction in a patient with congenital heart disease can occur in a wide variety of settings. Most often, the condition occurs with valvular disease, particularly the mitral (or systemic atrioventricular valve) or aortic valve in either a biventricular or single-ventricle circulation. It is often seen in single-ventricle circulation in which, over time and even without residual anatomic lesion, ventricular function declines. Ventricular dysfunction can develop postoperatively. The issue as it relates to cardiomyopathy is whether the abnormal morphology and function in this setting are related to hemodynamic problems or to an underlying myocardial

abnormality (see Classification of Cardiomyopathies). Certainly, if an underlying hemodynamic problem is not addressed over time, irreversible myocardial injury can occur, despite reducing a hemodynamically important anatomic abnormality. In this case, the condition would be defined as cardiomyopathy. Hence, in many patients, only time will tell. As a corollary, the challenge is often being able to predict preoperatively which patients will not recover normal morphology and function despite adequate surgical repair. This challenge is most relevant in patients with valvular disease, for whom robust data are available in adults to assist clinicians in determining the timing of mitral and aortic valve repair.[255] Unfortunately, such is not the case in children and in all age groups with single-ventricle circulation.

In terms of diagnosis, in addition to a thorough history and physical examination, the surgical history should be reviewed carefully. A complete 2-dimensional (2D) Doppler echocardiographic examination is recommended, with attention to chamber size and estimated filling pressures, gradients, and the presence of PH. Multivalvular disease and multiple congenital heart defects are not unusual. If the anatomy is not clear from a 2D transthoracic echocardiogram, 3-dimensional imaging of the valve of interest or transesophageal echocardiography may be necessary. cMRI or CT can also be used to evaluate extracardiac anatomy and RV structure and function. Describing the comprehensive imaging of congenital heart disease or echocardiographic interrogation of valves is beyond the scope of this statement.[256–258]

In valvular disease, if the hemodynamic characteristics, severity of the valvular dysfunction, and ability of the ventricle to compensate are unclear, stress testing may be necessary. Similarly, measuring B-type natriuretic peptide concentrations as a surrogate for HF severity and ventricular wall stress may aid in the assessment. These measures of ventricular function and remodeling are relevant to congenital heart disease because anatomic structural abnormalities often confound the diagnosis of DCM. It is obviously preferable to have clinical or biological markers that can suggest the development of DCM postoperatively, but at minimum, early diagnosis of ventricular dysfunction and of noncompensatory remodeling in the setting of congenital heart disease can assist the decision about the timing of surgical or catheter-based interventions to prevent the development or progression of DCM.

Isolated valvular disease or dysfunction can also be secondary to an underlying DCM. Differentiating between functional and anatomic mitral valve disease can be difficult because some changes to the mitral valve can be seen in DCM with long-standing functional mitral regurgitation. However, if the features of DCM existed before the onset of regurgitation, then functional mitral regurgitation is more obvious.

DCM Secondary to Valve Dysfunction

Mitral Valve. Chronic mitral valve regurgitation is associated with the development of DCM. However, mitral stenosis by itself does not cause DCM and is not discussed.

The proper timing of mitral valve repair to prevent the postoperative development of DCM in children is unclear. However, guidelines established for adults[255] can be helpful, given the paucity of data about diagnosing irreversible, preexisting, or progressive injuries in the myocardium in the presence of mitral regurgitation. In severe mitral regurgitation, echocardiographic measures of LV systolic function will be increased, given afterload reduction and volume loading. In this case, whether dilation and dysfunction will persist after the regurgitation is repaired is difficult to predict. However, if the LV is not only dilated but also markedly dysfunctional, LV function will not likely improve immediately after surgery to reduce preload and afterload. In this case, a cardiomyopathy secondary to mitral valve regurgitation can be diagnosed. Nevertheless, function and dilation can still improve later.[259]

In addition to data from adults, small studies in children have attempted to predict postoperative LV dilation and dysfunction, phenotypic features of DCM, if they persist.[260,261] In 46 children, preoperative global circumferential strain rate and global circumferential strain were more accurate (area under the curve, 0.80 and 0.74, respectively) than other measures in predicting LV dysfunction, defined as an ejection <50% soon after mitral valve repair or replacement.[260] In another study of 53 children, mean preoperative ejection fraction differed between long-term survivors and nonsurvivors (68% versus 54%, respectively; P=0.04).[261] However, other studies have found that preoperative echocardiographic measurements did not predict postoperative dysfunction or long-term outcomes.[259] These conflicting results underscore the difficulty in diagnosing LV dysfunction masked by loading conditions in small studies in the setting of mitral valve disease. Given the lack of data, members of the multidisciplinary cardiovascular team must integrate all available clinical information and use their judgment to determine the proper timing of mitral valve intervention to prevent future DCM.

Aortic Valve. In children, the association of DCM with aortic valve disease has been studied more often than with any other valvular diseases. As in mitral valve disease, reliably predicting whether myocardial structural injury is irreversible is not feasible before treating the stenosis or regurgitation. Therefore, DCM is typically diagnosed after adequate treatment such as surgical valve replacement or a catheter-based intervention. Even with palliative intervention, residual hemodynamic perturbation, particularly stenosis, is associated with LV

dilation or dysfunction. As in mitral valve regurgitation, given that relieving the anatomic substrate can lessen the risk of cardiomyopathy, studies examining preintervention predictors of residual remodeling are needed to better assist the clinician in determining the proper timing of intervention. Although studies in children are usually too small to generate accurate sensitivity, specificity, and cutoff values on a receiver-operating characteristics curve, the clinical characteristics that seem to predict ventricular dysfunction and remodeling are similar to those found in adults.[255,256,258] In small studies of children, these characteristics include preoperative LVEDD, LVESD, and ejection fraction or shortening fraction.[262–270] Aortic insufficiency accompanied by aortic stenosis and concomitant mitral valve disease is common in children. Most of these studies enrolled and analyzed children with both stenosis and regurgitation. The high afterload in isolated aortic valve stenosis means that systolic dysfunction, hypertrophy, and even proportional dilation may not necessarily indicate cardiomyopathy. Given the added preload in aortic valve regurgitation, increased LVEDD, increased wall mass, hypertrophy, and increased or preserved systolic function would also be expected. Although not studied adequately and certainly not an established criterion for repair, overt changes in diastolic function may manifest before systolic dysfunction and can add to serial monitoring by echocardiography. If systolic function is diminished or LVESD is increased, noncompensatory remodeling would be a concern. There are no established or recommended cutoff values for these LV parameters, so changes in the values of these parameters over time, the age and size of the child, and signs and symptoms of HF should dictate the intervention and its timing for each individual patient, especially those with complex congenital heart disease.

Pulmonary and Tricuspid Valve: Dilated Pulmonic Valve and Tricuspid Valve Disease. RV DCM is less common in tricuspid or pulmonary valvular diseases such as tetralogy of Fallot, pulmonary atresia, truncus arteriosus, and Ebstein anomaly, to name a few. For example, RV dysfunction caused by chronic pulmonic insufficiency after tetralogy of Fallot repair is well described. Although likely to be a prominent problem in adults,[271] it also occurs in children. Most patients will have RV dilation, and several studies describe the use of cMRI to evaluate RV dysfunction in this setting.[272–275] As in congenital mitral valve and aortic valve disease in children, the timing of pulmonary valve replacement is the critical issue in terms of preventing the development of RV DCM.

DCM of the RV secondary to congenital heart disease can also occur with marked tricuspid valve regurgitation. The most common congenital pathogenesis is Ebstein anomaly.[276] This lesion is also reparable, but the anatomic variety and clinical presentation can be quite variable, so the type and timing of repair are also variable. Whether earlier repair preserves RV function is unclear. More germane in the setting of severe regurgitation is whether the RV is adequate for either a 1.5 or biventricular repair with atrial septal defect closure. The amount of atrialization of the RV and its systolic function are important considerations in a successful repair.[277,278] In addition, LVNC has been associated with Ebstein anomaly.[279]

In the differential diagnosis of Ebstein anomaly is Uhl anomaly, an exceedingly rare condition in which the RV is thin, dilated, and dysfunctional. However, the defining feature of this anomaly is the partial or complete absence of the RV myocardium. The tricuspid valve may be dysplastic, and pulmonary valve regurgitation, stenosis, or atresia can be present.[280,281] Although the prognosis is grave in neonates diagnosed with this condition, there are reports of its incidental diagnosis in adults. Recognizing that Uhl anomaly is in the differential diagnosis of RV DCM may help practitioners who encounter a patient with the constellations of features described above.

DCM Secondary to Congenital Heart Disease

Any congenital heart disease can be associated with DCM if the hemodynamics are sufficient and the defect is not repaired. Other than valvular dysfunction, the 1 category of congenital heart defect that increases the risk for cardiomyopathy is single-ventricle circulation. Even without valvular disease or shunting, the single-ventricle circulation is not hemodynamically normal. In natural history studies of patients with single-ventricle circulation, the systemic ventricle was indeed found to be at risk for DCM.[282] Failed single-ventricle circulation is a well-known indication for heart transplantation.[283] Many infants listed for heart transplantation have irreparable or palliated congenital heart disease such as hypoplastic left-sided heart syndrome.[284,285] Despite a complete cavopulmonary connection, some will require transplantation.[286] Not all studies indicate the reason for transplantation. Because patients with complex congenital heart disease can have end-stage heart disease with or without ventricular dysfunction, attributing the true frequency of DCM is difficult in these patients. Nevertheless, patients with single-ventricle circulation are a high-risk population, with a constellation of factors such as valvular and ventricular dysfunction that can contribute to end-stage heart disease.

Congenital and Acquired DCM Secondary to Ischemic Heart Disease

DCM secondary to an ischemic pathogenesis is common in adults in the form of acquired atherosclerosis. Coronary perfusion insufficiency can be indolent, leading to chronic ischemia, or it can be caused by sudden complete occlusion such as in acute coronary syndrome.

Table 4. Conditions That Can Lead to DCM From an Ischemic Cause*

Congenital heart disease
Complication of the arterial switch procedure for D-transposition of the great arteries, Ross procedure, or other procedures requiring translocation of the coronary arteries
Long-term sequela of the atrial switch procedure
RV-dependent coronary circulation in pulmonary atresia with an intact ventricular septum
Anomalous origin of the left coronary artery from the pulmonary artery
William syndrome, with or without supra-aortic valvular stenosis
Isolated coronary ostium stenosis or atresia
Isolated atresia of the coronary artery
Abnormalities of coronary origin and fistulas in hypoplastic left-sided heart syndrome
Acquired conditions
Generalized arterial calcification of infancy
Kawasaki disease with coronary aneurysm or stenosis
Familial homozygous hypercholesterolemia
Hyperbetalipoproteinemia, familial combined hyperlipidemia, and hypoalphalipoproteinemia
Homocystinuria
Cardiac allograft vasculopathy from heart transplantation
Irradiation therapy to the chest
Chronic kidney disease
Chronic inflammation from autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis†
HIV infection†
Myocarditis†

DCM indicates dilated cardiomyopathy; and RV, right ventricle.

*In many of the conditions, DCM occurs only as a sequela of myocardial infarction.

†DCM can develop from other mechanisms besides ischemia from coronary artery disease.

When the myocardium is not sufficiently revascularized, infarction may occur. Regional myocardial infarction can lead to global myocardial injury and remodeling.[287] The terminology used in these well-characterized conditions is *ischemic cardiomyopathy*, but the morphofunctional phenotype is also dilated and hypokinetic. Additional features include mitral insufficiency, ventricular arrhythmia, and wall motion abnormalities.

Ischemic cardiomyopathy is clearly not as common in children as it is in adults. The causes are quite heterogeneous, and because it is rare, the clinician must be aware of the potential causes both to prevent ischemia and cardiomyopathy and to prevent sudden acute coronary insufficiency events (Table 4).

Although the diagnosis and presentation of the conditions listed in Table 4 have some common aspects, many are also unique. However, describing every cause and every unique presentation is beyond the scope of this statement. Instead, we use anomalous origin of the left coronary artery from the pulmonary artery to illustrate the presentation of ischemia and its diagnosis in children.

Anomalous origin of the left coronary artery from the pulmonary artery has features of ongoing ischemia, including angina, and the injury to the myocardium. Children can present with active or even subacute HF without caretakers being aware that something is amiss because many children present during infancy. In older children, even in the presence of LV dysfunction and coronary insufficiency, if the blood supply matches a limited demand, the patient can adapt and be conditioned to the limitations. Indeed, if the diagnosis has been missed during infancy, the child may not have angina. In addition to the signs and symptoms of active or chronic HF, the notable signs and symptoms suggesting angina are mitral valve regurgitation, ST/Q-wave changes suggesting ischemia or infarction, and angina in its various forms. Angina can be classic chest pain with exertion in older children or unexplained irritability in infants.

Inevitably, echocardiography can rule the diagnosis in but not necessarily rule it out.[288,289] Specifically, the myopathic criteria are a dilated and thin ventricle with systolic dysfunction that is typically global, sonographic brightness of the LV endocardium and mitral valve papillary muscle, and mitral regurgitation. Although no large studies have determined the utility of troponin concentrations in the diagnosis, elevated concentrations can support an ischemic or active myocardial injury process, as they do in adults. If an anatomic diagnosis by 2D echocardiography is uncertain, CT angiography or catheterization with angiography should be used to make the diagnosis.

Most patients with DCM from anomalous origin of the left coronary artery from the pulmonary artery, particularly infants, improve if they survive corrective repair and if mitral regurgitation lessens.[290–293] This improvement is an important difference in the natural history of cardiomyopathies because most adults with true ischemic cardiomyopathy (not just isolated wall motion abnormality from acute, regional stunning of the myocardium from an infarction) do not recover fully. This lack of recovery is also observed in many patients with DCM associated with valvular disease (see DCM Secondary to Structural Cardiac Disease). If severe mitral valve regurgitation persists, and certainly if symptoms and PH exist, these patients will need mitral valve repair.

The basic stress testing and advanced myocardial perfusion diagnostics used in adults may also be applied to children with suspected myocardial ischemia.[294–301] This application is true for patients who may be at risk for coronary insufficiency with an associated heart defect (before or after a surgical repair) or for those at risk for premature isolated atherosclerosis such as that accompanying familial homozygous hypercholesterolemia. Although isolated epicardial coronary artery disease is rare in young children, despite the number of conditions listed in Table 4, ischemic DCM can still develop

in children after an extensive myocardial infarction. For DCM secondary to anomalous left coronary artery from pulmonary artery and most other DCMs from an ischemic cause in children, the diagnostic criteria will be identifying an ischemic event or condition and ruling out other causes of DCM.

Cardiomyopathy Associated With Pulmonary Conditions

Causal Classification

RV dysfunction, and ultimately failure, caused by pulmonary disease most commonly occurs from factors causing PH. PH is defined as a mean pulmonary artery pressure of >20 mm Hg at rest, measured by cardiac catheterization.[302] The current World Symposium on Pulmonary Hypertension categorizes at total of 5 groups of PH (Table 5).[302] Each form of PH may ultimately cause RV stress, cardiomyopathy, and failure. It is notable that the term *cor pulmonale*[303] was initially defined by the World Health Organization as impairment of the RV resulting from abnormal structure or function of the lungs independently of left-sided heart disease (left-sided heart disease–associated PH is currently classified as group 2 PH).[304]

Group 1 PH represents those pulmonary vascular diseases that occur independently of airway or parenchymal lung abnormalities. It is defined by a mean pulmonary artery pressure of >20 mm Hg at rest in conjunction with pulmonary vascular resistance ≥3 Wood Units and a pulmonary capillary wedge pressure or LV end-diastolic pressure of ≤15 mm Hg measured by cardiac catheterization.[302] Subtypes of group 1 PH include, but are not limited to, idiopathic PAH, heritable PAH, congenital heart disease–associated PAH, connective tissue disease–related PAH, and HIV-associated PAH. In addition, rarer primary pulmonary vascular lesions may contribute to RV dysfunction and, in certain settings, RV failure such as pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis (categorized as group 1 PH).[302] Group 3 PH represents pulmonary conditions associated with airway or parenchymal lung diseases, particularly those that result in hypoxic or restrictive conditions. Although a variety of conditions may cause lung disease severe enough to result in PH, a common feature is the presence of profound lung disease that results in chronic hypoxia (eg, interstitial lung disease) or intermittent hypoxia (eg, sleep-disordered breathing).[302] Group 4 PH, known as chronic thromboembolic PH, is a progressive pulmonary vascular disease condition that typically occurs as a consequence of prior pulmonary embolic events after venous thromboembolism (recently reviewed by Simonneau et al[305]). Group 5 PH represents an array of additional conditions, each of which may cause PH, such as hemolytic disease, sarcoidosis, and metabolic disorders.

Pathology and Phenotypic Expression

RV hypertrophy or dilation secondary to non–group 2 PH is also known as cor pulmonale.[303] Cor pulmonale does not necessarily insinuate an overt failure of the RV, although a component of chronic dysfunction is typically present. Under physiological conditions, the right atrium and RV are low-pressure chambers, with a diastolic RV filling pressure typically being 8 to 12 mm Hg. However, in chronic hypertensive pulmonary vascular disease, the RV will hypertrophy in response to increased pressure load and subsequently dilate as well. Systolic and diastolic dysfunction typically accompanies

Table 5. Classification of PH, as defined by the Sixth World Symposium on Pulmonary Hypertension

1 PAH
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
2 PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH
3 PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4 PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5 PH with unclear and/or multifactorial mechanisms
5.1 Hematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

PAH indicates pulmonary arterial hypertension; PVOD, pulmonary veno-occlusive disease; PCH, pulmonary capillary hemangiomatosis; PH, pulmonary hypertension; and LVEF, left ventricular ejection fraction.

these changes, increasing the stroke work of the RV and increasing the pressure of the right atrium.[306] The added stress on the RV, in concert with its altered morphology, jeopardizes coronary artery blood flow so that RV ischemia may further impair its health and performance. RV dysfunction may also impair LV function for several reasons, including a leftward shift of the interventricular septum that alters septal geometry, reducing LV volume and efficiency of contraction because the RV and LV share the pericardial sac and limiting LV adaptation to this leftward shift. Furthermore, the underlying lung disease may alter thoracic dynamics, altering venous return to the right side of the heart, which may further dilate the RV and stiffen the LV.[307,308]

Approach

PH in the presence of marked lung disease is a major risk factor for reduced cardiac performance and death and should be comprehensively evaluated and treated. The standard workup should be used, including evaluating the possible causes of PH in addition to lung disease and subsequent right-sided heart catheterization to confirm the presence of PH and to determine its hemodynamic implications. Determining whether the condition is entirely a precapillary condition of the pulmonary vasculature, is postcapillary, or is mixed is important for determining the clinical classification and guiding treatment.[302] Although pulmonary vasodilator therapies are routinely used for precapillary PH conditions (eg, group 1 PH [pulmonary arterial hypertension (PAH)]), group 3 PH requires primarily treating the underlying lung disease and reducing comorbidities.[309] For example, hypoxemia must be addressed with oxygen delivery and other approaches such as controlling sleep-disordered breathing. Group 4 PH, or chronic thromboembolic PH, is treated in a variety of ways, including pulmonary vasodilators, anticoagulation, and surgical approaches as necessary, including intravascular angioplasty and pulmonary endarterectomy.[310]

After, or concurrent with, attempts to address the underlying lung disease, pulmonary vasodilators may be appropriate if a precapillary PH condition is present. However, none of the current pulmonary vasodilators have been comprehensively evaluated in children or adults with lung disease, nor are they approved for use in children with group 3 PH. Thus, pulmonary vasodilators should ideally be considered in collaboration with specialists trained in their use (eg, specialists at a PH comprehensive care center). A comprehensive discussion of the evaluation and management of RV failure was recently published.[311]

Clinical Outcomes in Primary DCM

With death or cardiac transplantation used as the clinical end point, 5-year event-free survival in all children with primary DCM is 50% to 60% (Table 6).[7,8,312]

Table 6. Cumulative Event Rates for Death and Cardiac Transplantation in Children With DCM

Cause	End Point	Time From Diagnosis of DCM to End Point		
		0.5 y	1 y	5 y
IDCM (n=1192)	Death	0.08	0.11	0.16
	Transplantation	0.18	0.24	0.33
	Neither	0.74	0.66	0.51
Neuromuscular disorder (n=139)	Death	0.05	0.08	0.38
	Transplantation	0.03	0.06	0.07
	Neither	0.92	0.87	0.55
FDCM (n=79)	Death	0.07	0.08	0.10
	Transplantation	0.20	0.23	0.37
	Neither	0.74	0.68	0.53
Myocarditis (n=272)	Death	0.087	0.087	0.087
	Transplantation	0.127	0.146	0.215
	Neither	0.79	0.77	0.70

DCM indicates dilated cardiomyopathy; FDCM, familial dilated cardiomyopathy; and IDCM, idiopathic dilated cardiomyopathy.

Death and transplantation rates vary by patient characteristics and pathogeneses. Generally, children with HF at presentation, presentation after 1 year of age, greater LV dilation, and poorer function are at increased risk of death or transplantation.[8] Children with DCM and NMD have the greatest mortality and the lowest transplantation rate 5 years after DCM diagnosis.[8]

Children with IDCM have worse outcomes than those with acute myocarditis or FDCM (Figure 1). Up to 20% of children with DCM may recover normal echocardiographic dimensions over the first 2 years after diagnosis, although up to 10% of these children may die or undergo transplantation beyond 2 years after diagnosis (Figure 2).[313]

The estimated cumulative incidence rates for echo normalization in the presence of the competing risk for death/transplantation are shown in Figure 2. At 2 years, 22% of patients had normal echocardiographic values, 51% had died or undergone transplantation, and 27% remained abnormal with respect to LV size and function.

Children with acute myocarditis have better 5-year survival than those with idiopathic disease.[7,8] Children with myocarditis who had the most severely decreased LV function and the greatest LV dilation and septal thickness at presentation had the highest rate of recovering normal echocardiographic dimensions.[35]

Survival was the same in children with myocarditis diagnosed clinically or by myocardial biopsy.[35] SCD is uncommon (<3%) in children with IDCM.[314] With the use of survival curves, the death rate for all children with DCM is highest in those presenting at <1 year of age except for those with DCM and NMD.[7]

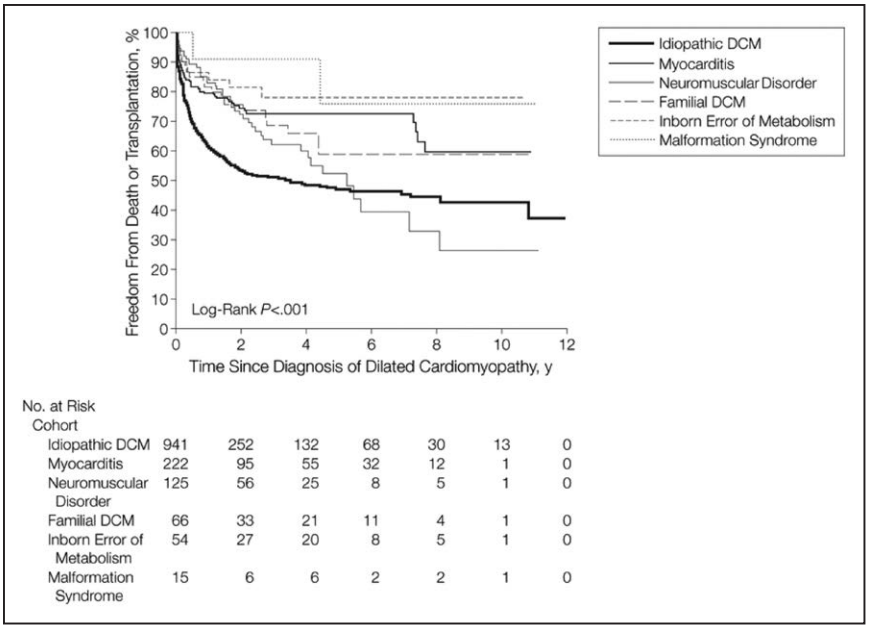

Figure 1. Time to death or heart transplantation in children with dilated cardiomyopathy (DCM).
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HYPERTROPHIC CARDIOMYOPATHY

Definition

HCM is the presence of a hypertrophied, nondilated ventricle in the absence of a hemodynamic cause that is capable of producing the existent magnitude of wall thickening, excluding both physiological hypertrophy (ie, secondary to physical activity) and pathological hypertrophy (ie, secondary to hypertension, aortic valvular stenosis, and other disorders).

Diagnostic Criteria

The primary diagnostic criterion for HCM is the maximum diastolic septal or LV free wall thickness. Published criteria in adults use 15 mm as the definitive threshold and 13 to 14 mm as constituting probable disease. In those who meet the probable threshold, causal predisposition (genetic or metabolic) or additional phenotypic characteristics (as described in this paragraph and the next) are used to evaluate the net probability of disease. The criteria for adults do not adjust for body size, which creates a risk for both underdiagnosis and overdiagnosis and presents a dilemma in large athletes. Adjusting for body size is mandatory in children; therefore, the diagnostic criteria are based on wall thickness *z* scores computed as the number of SDs from the mean value relative to body surface area in a normative population. Specific *z*-score thresholds in children have not been independently verified; therefore, *z* scores equivalent to the adult wall thickness criteria are recommended. The normal wall thickness in adults is 8±2 mm, so 15 mm represents a *z* score of 6 to 7 in adults, and 13 to 14 mm represents a *z* score of 4 to 6.

Structural and Functional Phenotype

The excess wall thickness characteristic of HCM is generally regional, and the anterior septum is the area most often involved, but any pattern of regional or global involvement can be encountered, including RV involvement, which is more common in infancy. No specific criteria for the diagnosis of RV-dominant HCM have been determined, but generally, the interventricular septum is involved, and septal thickness is used to

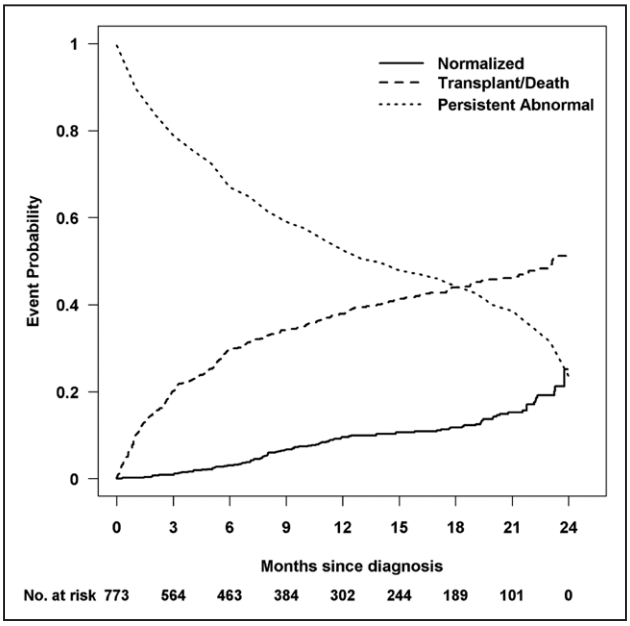

Figure 2. Cumulative incidence of echocardiographic normalization in children with idiopathic dilated cardiomyopathy (n=741) in the presence of the competing risks of persistently abnormal or death/transplantation.
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confirm the diagnosis. Various other structural abnormalities are often associated with the disease, including mitral valvular anatomic abnormalities (leaflet elongation, septal chordal insertions, anterior displacement of papillary muscle insertions) and myocardial crypts (localized invaginations communicating with the endocardium). Crypts are distinguished from trabeculations by the presence of a well-defined endocardial surface interrupted by an invagination that extends a variable distance into the myocardium, whereas trabeculations extend a variable distance into the cavity from a more uniformly compacted layer. Regional myocardial disarray is seen at the tissue level and leads to regional hypertrophy related to localized isometric force generation. The mixed phenotype of noncompaction HCM has also been described.

Ventricular systolic function is generally normal or hyperkinetic in HCM, although mixed phenotypes with hypokinetic HCM are late outcomes in patients with HCM and a primary characteristic of certain pathogeneses (eg, mitochondriopathies). When the phenotype evolves from hypertrophic to dilated or the function changes from hyperkinetic to hypokinetic or in the presence of mixed morphofunctional phenotype, such as hypertrophy with systolic dysfunction or restrictive phenotype with systolic dysfunction, the disease may be more advanced, and the patient has more significant HF. Ventricular diastolic function is usually abnormal in adults with HCM because of the mechanical effect of increased ratio of myocardial thickness to dimension, impaired diastolic tissue properties related to disturbed myocyte relaxation, and possibly the frequent finding of myocardial fibrosis. Although the relaxation abnormalities are usually present in children, restrictive physiology is usually absent, and left atrial dilation is far less common than in adults. LV outflow obstruction and mitral regurgitation are functional consequences of both the abnormal flow dynamics caused by the distorted ventricular shape and the structural abnormalities of the mitral valve.

Causes of Pediatric HCM

A wide variety of causes and associations have been described for HCM (Table 7). For many, including sarcomeric HCM, the association is variable, and not all individuals with the potential pathogenetic substrate manifest the phenotype. Pathogenetic categories include sarcomeric, syndromic, disorders of glycogen and fatty acid metabolism, lysosomal storage, mitochondrial defects, and infants of mothers with diabetes mellitus. These causes are discussed individually below. A large number of other disease associations have been reported, primarily as case reports. Given the absence of sufficient experience to know whether these associations coexist with HCM by chance or as the result of a causal relationship, they are not included here.

Table 7. Causes of HCM

Primary HCM
Sarcomeric
Secondary HCM
GSD
GSD type II (Pompe disease)
GSD type IIb (Danon disease)
PRKAG2
GSD type III (Cori or Forbes disease)
Lysosomal storage disorders
Mucopolysaccharidoses types I and II
Anderson-Fabry disease
Mucolipidoses (I cell)
Syndromic
Noonan syndrome
Noonan syndrome with multiple lentigines
Costello syndrome
Others: Donohue, Dwyer, Beckwith-Widemann
Fatty acid oxidation disorders
Very long-chain acyl-CoA dehydrogenase deficiency
Multiple acyl-CoA dehydrogenase (glutaric academia type II)
Long-chain hydroxyacyl-CoA dehydrogenase
Carnitine acylcarnitine translocase
Carnitine palmitoyltransferase II
Carnitine-acylcarnitine translocase deficiency
Mitochondrial diseases
Friedreich ataxia
Endocrine disorders
Primary hyperinsulinism
Infant of a mother with diabetes mellitus
Acromegaly

CoA indicates coenzyme A; GSD, glycogen storage disease; HCM, hypertrophic cardiomyopathy; and PRKAG2, γ-2 subunit of AMP-activated protein kinase.

Coexistence of HCM and Congenital Heart Disease

Congenital heart disease is sometimes a feature of some syndromes associated with HCM, such as Noonan syndrome, in which valvular pulmonary stenosis and the HCM phenotype are commonly seen independently or together. Therefore, the extreme hypertrophy is attributed to cardiomyopathy, not to the hemodynamic abnormality related to the pulmonary stenosis. Several case reports describe the HCM phenotype in association with complete atrioventricular septal defect and occasionally with other forms of congenital heart disease. In these cases, the association has not been

sufficiently common to exclude a chance association; therefore, they are considered causally unrelated.

Sarcomeric HCM

Sarcomeric HCM is the presence of a morphofunctional phenotype meeting the criteria for HCM in the presence of a pathogenic (causative) or likely pathogenic sarcomeric mutation. Strictly speaking, the presence of both a pathogenic sarcomeric mutation and the morphofunctional characteristics of HCM based on imaging and functional assessment (as described above for HCM) is required to meet the definition of sarcomeric HCM, despite the common practice of classifying patients without extracardiac manifestations as having sarcomeric HCM, even in the absence of a defined pathogenic mutation. Idiopathic HCM is classified as no known genetic or other cause after a careful evaluation of a list of the relevant differential diagnoses. Those patients initially classified as having idiopathic HCM should be considered for retesting at a future time when more pathological gene mutations are added to the HCM panel and evaluative causal tests become available. The term *familial HCM* is also commonly used as a synonym for sarcomeric HCM because of the typically autosomal-dominant mode of transmission of this disease. Nevertheless, currently, 40% to 50% of individuals who meet phenotypic diagnostic criteria test negative for a genetic cause, so a nonsarcomeric cause remains possible. Outcomes and therapy for the genotype-negative individuals remain largely the same as for those with a defined genetic cause, as would be expected for a disease in which the phenotype is the most important determinant of outcome. Therefore, they are commonly grouped together.

The genes grouped under the term *sarcomeric* have evolved over time, initially including only the genes encoding 8 of the myofilament proteins (MYH7, MYL2, MYL3, MYBPC3, TNNT2, TNNI3, TPM1, and ACTC1). However, when the same morphofunctional phenotype was found to be associated with defects in genes encoding other sarcomeric proteins, in Z-disc proteins (such as CSRP3 and ACTN2), and subsequently in calcium signaling proteins (such as PLN), the term *sarcomeric HCM* was broadened to include these domains also. A recent review of putative HCM-causing genes discusses the issues involved in assessing the pathogenicity of the many gene variants that have been found in association with sarcomeric HCM, noting that the cause of HCM is unknown in most patients.[19]

Despite the large number of genes and mutations identified as causing sarcomeric HCM, the molecular mechanisms leading to the phenotype remain uncertain. Much of the evidence for the cause of the disease supports gain-of-function mutations as the primary cause. Mutations in the same family of sarcomeric genes are associated with both (hypocontractile) DCM and HCM. One proposed mechanism is that mutations that impair calcium-dependent sarcomeric tension generation result in the DCM phenotype, whereas those that enhance tension development are associated with HCM.[315] This relationship has been documented through both in vivo[315] and in vitro[316] models. However, HCM has also been associated with diminished contractile force-generating capacity and both increased or decreased calcium sensitivity. This association led to the hypothesis that the HCM phenotype is secondary to a functional imbalance among individual myocytes as a result of random expression of mutant and wild-type alleles.[317] This hypothesis potentially explains the myocardial disarray commonly noted in sarcomeric HCM, which is more difficult to explain on the basis of purely gain-of-function behavior alone. At present, no explanation of how such a broad range in genetic mutations can result in a uniform phenotype is uniformly accepted.

The diagnosis of sarcomeric HCM relies on identifying a pathogenic or likely pathogenic sarcomeric mutation known to be associated with the HCM phenotype in an individual who meets the morphofunctional criteria for HCM, as specified in the Diagnostic Criteria subsection in the Hypertrophic Cardiomyopathy section. Without a genetic test confirming a sarcomeric cause, certain characteristics of sarcomeric HCM generally lead to the assumption that it is the diagnosis. The disease does not have extracardiac manifestations other than those that represent its physiological consequences such as findings associated with HF. Although many of the nonsarcomeric forms of HCM manifest extracardiac primary abnormalities, not all do. Hence, the absence of extracardiac manifestations cannot be used as a definitive diagnostic criterion. As described in detail in the imaging section (Morphological Evaluation of Pediatric Cardiomyopathies), the cardiac phenotype in sarcomeric HCM is similar to that in many other forms of HCM, including substantial regional variation in ventricular wall thickness, global ventricular function that is typically normal or hyperdynamic, and other structural cardiac abnormalities, including abnormal mitral valve attachments, mitral leaflet elongation, and myocardial crypts.

HCM Caused by Infiltrative and Other Nonsarcomeric Diseases

Beyond sarcomere gene mutations, many causes of HCM are often identified in children and young adults. Such secondary forms of HCM include storage disorders, infiltrative diseases, and other metabolic causes (Table 7). These disorders all share the common phenotype of a hypertrophied, nondilated ventricle without a hemodynamic cause, as well as the risk of clinical

progression to florid HF. Identifying these various origins is important for directing disease-specific treatment and prognosis. Many conditions can cause multiple distinct or mixed cardiomyopathy phenotypes. Those conditions that are most commonly associated with a hypertrophic phenotype are described here.

HCM Caused by GSDs

GSDs are inborn errors of metabolism with abnormal storage or use of glycogen. Those most commonly associated with an HCM phenotype include GSD type II (Pompe disease), Danon disease (formerly referred to as GSD type IIb), and *PRKAG2* cardiomyopathy. Glycogen storage disease type III (Cori or Forbes disease) can also present with HCM.

Pompe disease is an autosomal-recessive disorder caused by deficient α-1,4 glucosidase activity. Infantile, juvenile, and adult forms have been described, with the infantile form being the most likely to manifest with early, severe cardiac hypertrophy. A diagnosis of Pompe should be suspected in any infant who presents with massive cardiomegaly, characteristic electrocardiographic findings (short PR interval, prominent QRS voltages), and accompanying hypotonia.[318] Testing for GAA enzyme activity through newborn screening in many states may lead to earlier and presymptomatic identification of all forms of the disease, with subsequent confirmation by repeat enzymatic and genetic testing.[10] The clinical evaluation of infants with suspected Pompe disease should include urine hexose tetrasaccharide and creatine kinase concentrations, as well as an ECG and echocardiogram.

Danon disease is an X-linked–dominant muscle disorder caused by defects in the *LAMP2* gene.[319,320] The most prominent manifestations of Danon disease are HCM, skeletal myopathy, and mild intellectual difficulties. Also commonly seen in Danon disease is a Wolf-Parkinson-White pattern of pre-excitation on ECG.[321,322] Male patients tend to show earlier and more severe cardiac involvement than female patients, although female patients with Danon disease can certainly show early onset, with either dilated or hypertrophic phenotype.[323,324] Given the relatively rapid progression of disease and frequent involvement of treatment-refractory arrhythmias, early suspicion for Danon disease should be confirmed via *LAMP2* gene testing whenever possible.

Mutations in the gene for the *PRKAG2* cause glycogen accumulation and cardiac hypertrophy, as well as electrophysiological abnormalities.[320,325] *PRKAG2* cardiomyopathy should be suspected in anyone presenting with the classic triad of HCM, ventricular pre-excitation, and progressive conduction disease. Diagnosis is confirmed by genetic testing.

HCM Caused by Lysosomal Storage Disease

Lysosomal storage diseases are a heterogeneous group of inherited disorders characterized by the accumulation of undigested or partially digested macromolecules, leading to cellular dysfunction and organomegaly. The forms that most commonly cause HCM include mucopolysaccharidosis, mucolipidosis, and sphingolipidosis.

Mucopolysaccharidose I (Hurler syndrome or α-L-iduronidase deficiency) is an autosomal-recessive condition, whereas mucopolysaccharidose II (Hunter syndrome or iduronate sulfatase deficiency) is an X-linked–recessive condition.[326] Both are characterized by short stature, coarse facies, skeletal changes, and HCM. The cardiac abnormalities seen perhaps even more commonly than hypertrophy are valve abnormalities resulting from glycosaminoglycan deposition in the valve tissues.[225,327] The diagnosis is supported by elevated urine glycosaminoglycan concentrations and is confirmed by genetic testing.

The mucolipidosis that most commonly causes HCM is type II (I-cell disease). This autosomal-recessive disorder is caused by N-acetylglucosamine-1-phosphotransferase deficiency, resulting in acid hydrolase secretion into the plasma rather than lysosomal incorporation.[328] The disease is characterized histologically by the presence of I cells, which are fibroblasts with inclusion bodies. Clinical features other than HCM include coarse facies, thickened skin, orthopedic abnormalities (including dysostosis multiplex), and valve abnormalities (including mitral thickening with regurgitation). Diagnostic tests include urinary oligosaccharide and plasma lysosomal hydrolase concentrations, as well as molecular testing for *GNPTAB* gene variants.

Anderson-Fabry disease (also referred to as Fabry disease) is an X-linked–recessive sphingolipidosis caused by α-galactosidase-A deficiency. Accumulation of globotriaosylceramide in the lysosomes of various tissues and organs leads to manifestations that include neuropathy, renal insufficiency, and gastrointestinal complaints.[227,329,330] The signs and symptoms of this multiorgan disease may occur in adolescents, usually as angiokeratomas and gastrointestinal pain. Cardiac involvement includes concentric hypertrophy, most commonly identified in the fourth and fifth decades of life.[331] With the benefit of earlier disease identification, however, subtle cardiac abnormalities can be detected even in children.[332] Progressive ventricular hypertrophy is the classic cardiac manifestation of the disease, leading to diastolic dysfunction and HF with initially preserved systolic function and later to chamber dilation with systolic dysfunction.[227,330] Valvular involvement is less common but may lead to insufficiency or stenosis. Systemic hypertension may occur in adults with renal insufficiency. A diagnosis can be confirmed in male patients by testing for enzymatic activity of α-galactosidase-A. A mutational analysis of the GLA gene is necessary for confirmation in female patients.

Syndromic HCM

HCM occurs in a variety of disorders and clinical syndromes that present in the newborn period or infancy.

Additional cardiovascular abnormalities, such as pulmonary valve stenosis, mitral valve dysplasia, and atrial and ventricular septal defects, may occur in children with Noonan syndrome and similar disorders.[333] Noonan syndrome is an autosomal-dominant disorder manifested by characteristic dysmorphic features, including short stature, developmental delay, hypertelorism, webbed neck, down-slanting palpebral fissures, and ptosis.[334] Mutations in several genes are linked to Noonan syndrome and related disorders. Gene testing may be helpful in diagnosis when phenotypic features are present.[335] The prevalence of HCM in Noonan syndrome is ≈22%, and about half of those patients are diagnosed by 6 months of age, much earlier than children with nonsyndromic HCM.[73,333] Compared with children with nonsyndromic HCM, patients with Noonan syndrome and HCM are more likely to present in congestive HF (24% versus 9%), to have obstruction across the LV outflow tract (30% versus 9%), and to have a higher 3-year mortality rate (26% versus 11%).[73] Other syndromes such as Noonan syndrome with multiple lentigines (formerly called LEOPARD syndrome) are also associated with HCM. Multiple brown skin spots (café au lait) develop on the face, neck, and trunk of patients with this condition. In a small cohort, 73% of patients with this syndrome had ventricular hypertrophy.[336] HCM is also common in Costello syndrome, occurring in more than half of diagnosed patients. Similar to Noonan syndrome, asymmetric septal hypertrophy is the typical morphology, and LV outflow tract obstruction may occur.[337,338] Noonan and Costello syndromes have phenotypic overlap with cardiofaciocutaneous syndrome, another disorder with cardiovascular abnormalities, including HCM. This disorder occurs rarely, but the incidence of HCM is high (44%).[339] Other rare disorders and syndromes in which HCM occurs include Donohue syndrome, Sawyer syndrome, and Beckwith-Wiedemann syndrome.[340,341] Many genes linked to these syndromes have been identified (Table 8).

HCM Secondary to Friedreich Ataxia

Friedreich ataxia is an autosomal-recessive disease caused most commonly by GAA trinucleotide repeat expansions in the *FXN* gene.[103,342] This expansion causes a deficiency in frataxin, a protein involved in mitochondrial and cellular iron homeostasis.[343] Friedreich ataxia should be suspected in children presenting with progressive ataxia, absent reflexes, and HCM. Arrhythmias and DCM are sometimes seen, more commonly in adulthood (see also the DCM Related to Mitochondrial Diseases section).

HCM Secondary to Fatty Acid Oxidation Disorders

As discussed in the DCM Secondary to Fatty Acid Oxidation Disorders section, many of the conditions can present with DCM or HCM.[211,220,344,345] The 1 condition that seems to be related predominantly to HCM is very long-chain acyl-CoA dehydrogenase deficiency. Although not always clearly discriminated in the literature, the ventricular arrhythmias and sudden death described in disorders of fatty acid metabolism perhaps reside mainly in fatty acid oxidation, given its predominantly hypertrophic phenotype and the properly conducted studies on very long-chain acyl CoA dehydrogenase deficiency in which the genotype, phenotype, and identification of sudden death were clearly delineated.[209,210,346] The HCM can be completely reversible with adequate metabolic management.

Other disorders that also present with HCM (the predominant phenotype) and have been described often include multiple acyl-CoA dehydrogenase (glutaric academia type II), long-chain hydroxyacyl-CoA dehydrogenase, carnitine acylcarnitine translocase, carnitine palmitoyltransferase II, and carnitine-acylcarnitine translocase deficiency.

HCM Secondary to Hyperinsulinism

The cardiomyopathy that results from the overproduction of insulin occurs solely in neonates. Hyperinsulinism can be divided into primary and secondary. In either form, it is considered a congenital cardiomyopathy.

In primary hyperinsulinism, the β islet cells of the pancreas can take on a focal adenomatous transformation or diffuse hyperfunction, both resulting in overproduction of insulin.[347,348] Infants present with severe hypoglycemia and can develop seizures, hypothermia, hypotonia, and lethargy. These infants tend to be large for gestational age but are not necessarily macrosomic. Some respond to medical treatment, and many require partial or total pancreatectomy. Only 1 large, well-described study has been done on the cardiomyopathy associated with hyperinsulinism.[349] In this study of 68 infants <3 months of age with this condition, 25 had echocardiograms after findings of respiratory distress, abnormal chest radiographs, murmur, or arrhythmia. Of these 25, 10 were diagnosed as having HCM. All were treated for hyperinsulinism, and their HCM resolved.

In secondary hyperinsulinism, infants are not presumed to have histological abnormalities of the pancreas, but they overproduce insulin in response to hyperglycemia from maternal or gestational diabetes mellitus. These infants are very large for gestational age and present with hypoglycemia. However, their hypoglycemia can be controlled with dextrose infusion, and practitioners are usually aware of their condition, given the mother's prenatal care.

The first description of HCM in secondary hyperinsulinism was made possible by M-mode echocardiography.[350–352] Systolic anterior motion of the mitral valve was also identified in these infants. Isolated reports of clinical

Table 8. Genes Commonly Associated With Pediatric Cardiomyopathies

Gene Symbol	Inheritance	Associated Cardiac Phenotype					Additional Phenotype
		HCM	DCM	RCM	LVNC	ARVC	
Sarcomere: thin filament							
ACTC1	AD	X	X	X	X		Atrial septal defect
TNNC1	AD	X	X				
TNNI3	AD, AR	X	X	X			
TNNT2	AD	X	X	X	X		
TPM1	AD	X	X		X		
Sarcomere: thick filament							
MYBPC3	AD	X	X	X	X		
MYH7	AD	X	X	X	X		Skeletal myopathies
MYL2	AD	X					
MYL3	AD, AR	X		X			
Z disc							
ACTN2	AD	X	X		X		
CSRP3	AD	X	X				
LDB3/ZASP	AD		X		X		Myofibrillar myopathy
MYOZ2	AD	X					
TCAP	AD, AR	X	X				Limb-girdle muscular dystrophy (AR)
TTN	AD	X	X			X	Hereditary myopathy with early respiratory failure
Desmosome							
DSC2	AD, AR					X	Palmoplantar keratoderma and woolly hair (AR)
DSG2	AD		X			X	
DSP	AD, AR		X			X	Carvajal syndrome (AR)
JUP	AD, AR					X	Naxos disease (AR)
PKP2	AD					X	
TMEM43	AD					X	
RYR2	AD					X	
Cytoskeletal							
VCL	AD	X	X				
Intermediate filament							
DES	AD, AR	X					Limb-girdle muscular dystrophy (AR), myofibrillar myopathy (AD, AR)
Nuclear membrane							
EMD	X-linked		X				Emery-Dreifuss muscular dystrophy
LMNA	AD, AR	X	X	X			Congenital muscular dystrophy (AD), Emery-Dreifuss muscular dystrophy (AD, AR)
SYNE1	AD		X				Emery-Dreifuss muscular dystrophy
SYNE2	AD		X				Emery-Dreifuss muscular dystrophy
Plasma membrane							
CAV3	AD, AR	X					Limb-girdle muscular dystrophy (AD, AR), long QT (AD)
SGCD	AD, AR		X				Limb-girdle muscular dystrophy (AR)
Other							
CRYAB	AD, AR		X				Myofibrillar myopathy (AD, AR)
MIB1	AD					X	
RMB20	AD		X				

(*Continued*)

Table 8. Continued

Gene Symbol	Inheritance	Associated Cardiac Phenotype					Additional Phenotype
		HCM	DCM	RCM	LVNC	ARVC	
Syndromic cardiomyopathies							
BRAF	AD	X					Noonan/Costello/CFC syndrome
HRAS	AD	X					Noonan/Costello/CFC syndrome
KRAS	AD	X					Noonan/Costello/CFC syndrome
PTPN11	AD	X					Noonan/Costello/CFC syndrome
SOS1	AD	X					Noonan/Costello/CFC syndrome
SPRED1	AD	X					Noonan/Costello/CFC syndrome
Metabolic disorders							
CPT2	AR		X				Carnitine palmitoyltransferase II deficiency
GAA	AR	X					Pompe disease (GSD type II)
HADHA	AR	X	X				Long-chain 3-hydroxyacyl-CoA dehydrogenase
LAMP2	X-linked	X	X				Danon disease (GSD type IIb)
MT-TL1	Mitochondrial		X				MELAS
PRKAG2	AD	X					Cardiac GSD, Wolff-Parkinson-White syndrome
SLC22A5	AR	X	X				Primary carnitine deficiency
TAZ	X-linked		X		X		Barth syndrome
NMDs/neurodegenerative disorders							
DMD	X-linked		X				Duchenne/Becker muscular dystrophy
FXN	AR	X					Friedreich ataxia

AD indicates autosomal dominant; AR, autosomal recessive; ARVC, arrhythmogenic right ventricular cardiomyopathy; CFC, cardiofaciocutaneous; CoA, coenzyme A; DCM, dilated cardiomyopathy; GSD, glycogen storage disease; HCM, hypertrophic cardiomyopathy; LVNC, left ventricular noncompaction; MELAS, mitochondrial encephalopathy, lactic acidosis, and stroke-like episode; NMD, neuromuscular disorder; and RCM, restrictive cardiomyopathy.

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cardiac deterioration with the use of digoxin and furosemide, as opposed to improvement with propranolol, were published in this early period.[350] Additional studies verified that many infants have "asymmetric" hypertrophy involving mainly the interventricular septum, RV hypertrophy, and LV or RV dynamic outflow tract obstruction.[353,354] Infants can also have signs and symptoms of HF, including low cardiac output. The severity of maternal diabetes mellitus and the presence of outflow tract obstruction were associated with the degree of LV hypertrophy and the presence of cardiac failure, respectively.[353,355,356] One study even performed cardiac catheterization and found using echocardiography that stroke volume was associated with septal thickness.[357] Later studies suggest that maternal type 1 or 2 diabetes mellitus may be associated with a higher risk of HCM than gestational diabetes mellitus.[358] Clearly, recognizing maternal diabetes mellitus and monitoring glycemic control are important and will assist in managing the newborn. Although these infants can present with HF, the HCM resolves in the first year of life, often much earlier.

HCM in Acromegaly

Acromegaly is a rare condition resulting from oversecretion of growth hormone from an adenoma in the pituitary gland. The metabolic derangement in carbohydrate metabolism with hyperinsulinism and glucose intolerance is the basis for the multisystem abnormalities that include the cardiovascular system.[194,359] Clinical manifestations include enlargement of the head, hands, feet, chest, thorax, and heart. In prolonged periods of growth hormone excess, hypertension, coronary artery disease, and cardiac hypertrophy can occur. Even in shorter periods of excess, LV hypertrophy can develop.[359] These changes are reversible when the endocrine condition is treated. Without acromegaly, whether recombinant growth hormone administration for short stature without growth hormone deficiency has clinically important cardiovascular effects is controversial. In the largest report of recombinant growth hormone therapy from the National Cooperative Growth Study, HCM developed in only a few patients with Noonan syndrome.[359] However, HCM and other cardiovascular abnormalities are well known in this syndrome.

Clinical Outcomes in HCM

The 5-year survival rate (free of death or transplantation) for children with HCM varies widely, from 42% in children with HCM with an inborn error of metabolism to

Table 9. Survival Rate From Time of Diagnosis of HCM by Pathogenesis

Pathogenesis	Survival Since Diagnosis of HCM, %*			
	1 y	2 y	5 y	10 y
Inborn error of metabolism	53.6	44.9	41.7	…
Malformation syndrome	82.4	76.6	74.4	74.4
Neuromuscular disorder	98.2	98.2	98.2	91.7
Idiopathic disease	94.4	92.8	89.8	85.3
Infantile idiopathic disease	85.8	84.3	82.2	82.2
Noninfantile idiopathic disease	99.2	97.6	93.9	85.9

HCM indicates hypertrophic cardiomyopathy.
*Maximum follow-up was only 9 years.
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94% in children with HCM presenting after 1 year of age (Table 9).[9]

The age distribution at death for all children with HCM, as well as the idiopathic subgroup, is bimodal, with the highest mortality in the first 2 years after diagnosis and a smaller peak during adolescence (Figure 3).[9]

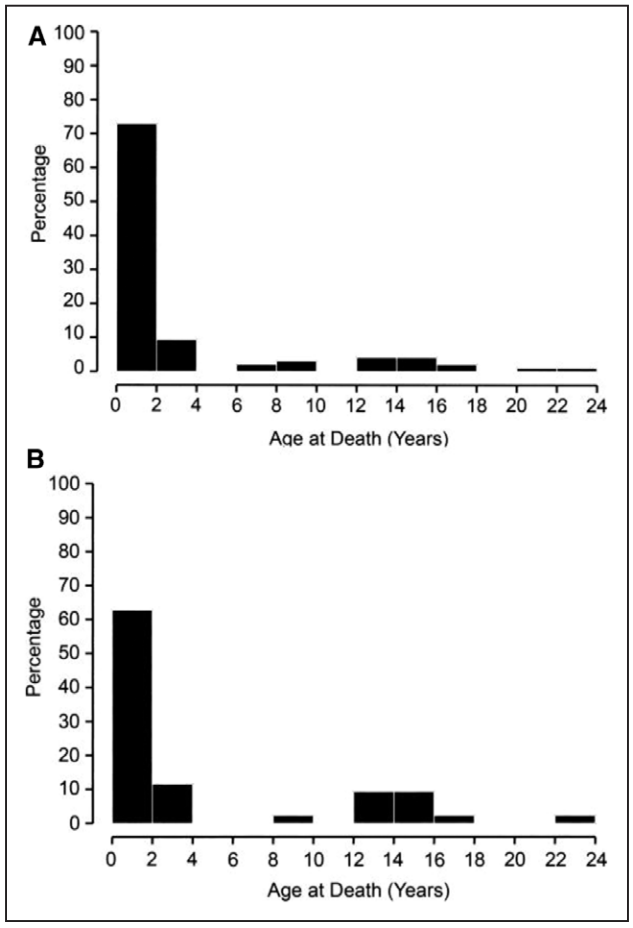

Figure 3. Age at death expressed as a percentage of deaths for all children with hypertrophic cardiomyopathy (HCM) (A; n=96) and for those with idiopathic HCM (B; n=43).
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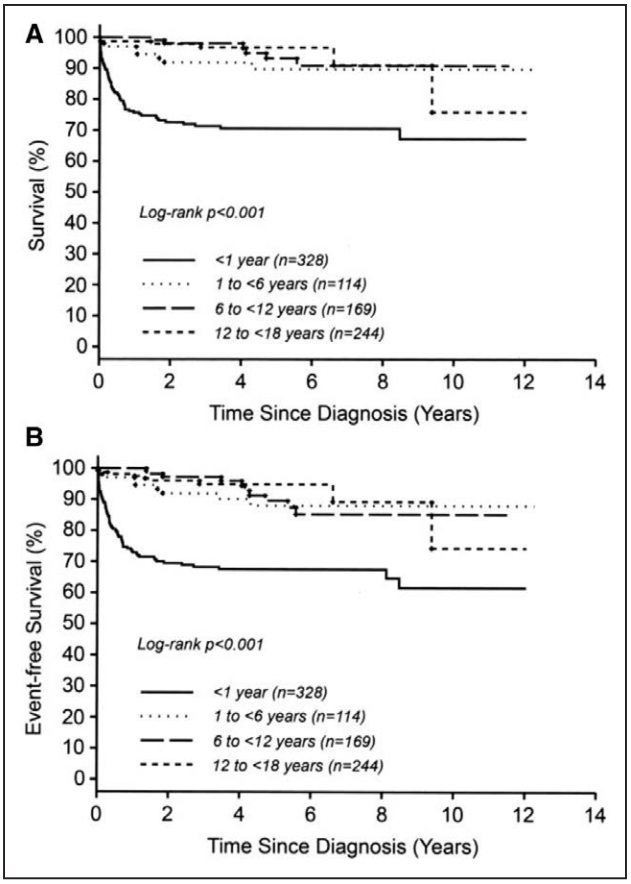

Figure 4. Survival rates from diagnosis to (A) death resulting from cardiomyopathy and to (B) death or transplantation by age at diagnosis.
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HCM presenting before 1 year of age generally has a much worse prognosis, particularly in children with idiopathic disease and in those presenting with inborn errors of metabolism or malformations syndromes (Figures 4 and 5).

In addition to age at diagnosis, HF and lower fractional shortening at presentation are generally associated with poor outcomes. For example, children with Noonan syndrome who are <6 months old and have congestive HF at presentation and those with a fractional shortening *z* score below the population median have much poorer outcomes, with nearly 20% of deaths occurring in the first year of life.[73] Children with HCM and >2 risk factors for poor outcomes identified at diagnosis have worse outcomes, although outcomes vary by pathogenetic group (Figure 6).[74]

For idiopathic HCM in children, the mortality rate for those who are alive after 1 year of age is about 1 per 100 patient-years, which is consistent with the rate in adults.[9,360] Although children with Friedrich ataxia make up 25% to 50% of children with HCM and an NMD, in a recent large series, all of these children lived at least to early adulthood.[9]

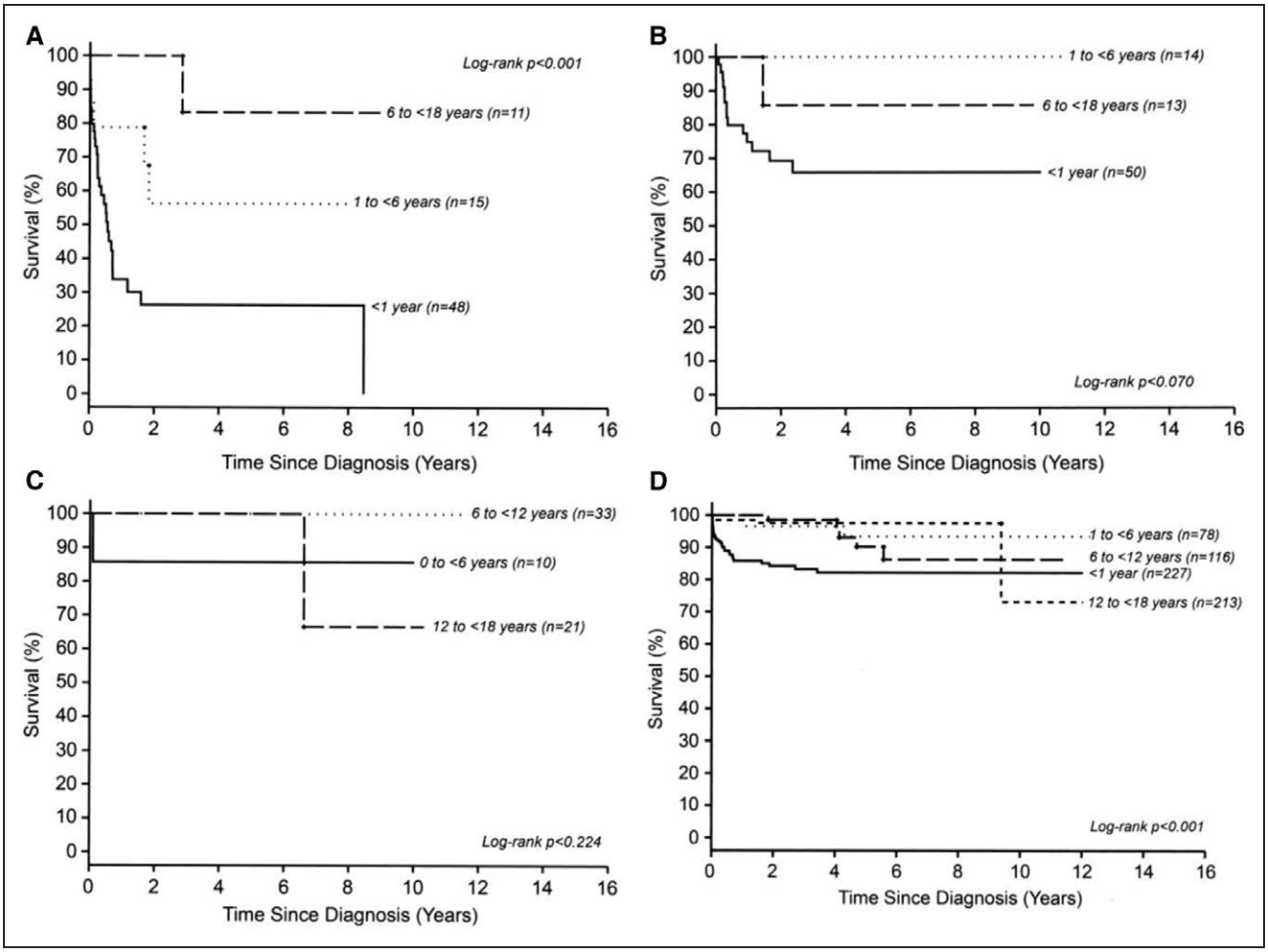

Figure 5. Survival since the diagnosis of cardiomyopathy caused by (A) inborn errors of metabolism, (B) malformation syndrome, (C) neuromuscular disorder, and (D) idiopathic hypertrophic cardiomyopathy.
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RESTRICTIVE CARDIOMYOPATHY

Definition

RCM is the presence of abnormal compliance without another predominant phenotype of RV or LV dilatation, hypertrophy, or systolic dysfunction. In some cases, mild hypertrophy or mild systolic dysfunction coexists with RCM.

Diagnostic Criteria

The primary diagnostic criterion is impaired myocardial compliance. This abnormal compliance of the ventricles is caused by abnormalities in the myocyte or the intercellular matrix such as interstitial infiltration or fibrosis.[361] The diagnosis of RCM with impaired filling of the ventricles secondary to a stiff and noncompliant myocardium needs to be distinguished from impaired filling caused by constrictive pericarditis. In constrictive pericarditis, the pericardium impairs filling of the atria and ventricles. Typically, the pericardium is thickened and calcified, but normal ranges for pericardial thickness diagnostic of constrictive pericarditis have not been established for infants and small children. In addition, constrictive pericarditis has been reported in adults with histologically normal pericardial thickness. In these cases, symptoms of impaired cardiac filling resolved when the pericardium was removed. Microscopic examination of the tissue after pericardiectomy revealed fibrosis, inflammation, calcification, fibrin deposition, and focal noncaseating granulomas.[362] In RCM, the impaired ventricular compliance is caused by dysfunction of the active relaxation of the ventricle.[363] Although RCM can result from abnormalities of either myocytes or matrix, after pericarditis is excluded, active relaxation of the ventricle is attributed to ATP-dependent myocyte mechanisms, not abnormalities of matrix, which can be infiltrative and not active.[363]

Structural and Functional Phenotype

The abnormal compliance of the ventricles in RCM increases end-diastolic filling pressure, which is transmitted

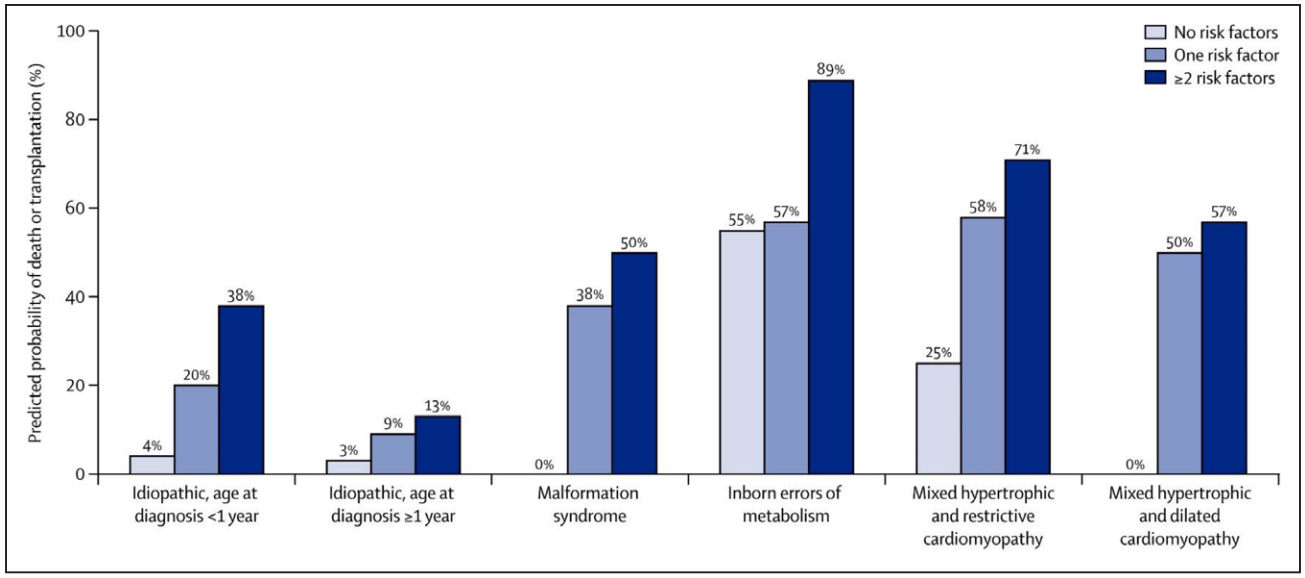

Figure 6. Probability of death or heart transplantation 2 years after diagnosis of hypertrophic cardiomyopathy (HCM) according to number of risk factors in 6 subgroups of children based on age at diagnosis, cause, or phenotype.

Probability of death or heart transplantation 2 years after diagnosis of HCM according to number of risk factors in 6 subgroups of children based on age at diagnosis, cause, or phenotype. Sample sizes and number of deaths or transplantations for each subgroup are as follows: idiopathic HCM, age <1 year at diagnosis (n=128; death or transplantation, n=23); idiopathic HCM, age ≥1 year at diagnosis (n=316; death or transplantation, n=23); HCM with malformation syndrome (n=42; death or transplantation, n=9); HCM with inborn errors of metabolism (n=34; death or transplantation, n=22); mixed HCM and restrictive cardiomyopathy (RCM; n=39; death or transplantation, n=17); and mixed hypertrophic and dilated cardiomyopathy (n=36; death or transplantation n=18). Threshold values for scoring a point in the risk scores by subgroup were as follows: idiopathic HCM, age <1 year at diagnosis (weight *z* score less than −1.4; age at diagnosis, <0.01 years; end-diastolic posterior wall thickness [EDPT] *z* score >4.42); idiopathic HCM, age ≥1 year at diagnosis (age at diagnosis >14.4 years; fractional shortening [FS] *z* score <1.85); HCM with malformation syndrome (age at diagnosis <0.2 years; FS *z* score <3.45); HCM with inborn errors of metabolism (weight *z* score less than −1.8; age at diagnosis <0.2 years; EDPT *z* score >6.7); mixed HCM with RCM (age at diagnosis <0.6 years; EDPT *z* score >3.9); and mixed HCM and dilated cardiomyopathy (weight *z* score less than −1.8; end-diastolic septal thickness *z* score >3.1). Binomial risk factors (sex, congestive heart failure status) did not have threshold values. Reprinted from *The Lancet*, Lipshultz et al,[74] with permission from Elsevier. Copyright © 2013, Elsevier.

to the atria during diastole. Because the atria are thin walled and distensible, the notable result is marked atrial enlargement. Although mitral and tricuspid regurgitation can develop in patients with advanced RCM, the atrial enlargement in RCM is not caused by atrioventricular regurgitation or by inlet obstruction such as mitral stenosis or a supramitral ring. Inlet anatomic abnormalities must be excluded when atrial enlargement is the predominant echocardiographic finding and a diagnosis of RCM is being considered. Atrial enlargement characteristic of RCM is generally recognized by marked biatrial enlargement, which indicates diastolic impairment or abnormal compliance of both the RV and LV. However, either the RV or LV can be predominantly involved.

The functional phenotype includes a variety of clinical presentations, from asymptomatic to overt right or left HF, syncope, arrhythmias, thromboembolic complications, and sudden death. Conduction abnormalities and atrial or ventricular arrhythmias can also be the first feature of RCM.[364] PH may be mild and reversible or severe and irreversible at presentation. The other predominant cardiac phenotypes can have restrictive physiology but are generally classified in terms of their other features such as restrictive HCM, restrictive LVNC, or DCM with restrictive physiology, as are seen commonly in oncological cardiomyopathy, including cardiomyopathy from anthracycline or radiation exposure. The oncological cardiomyopathies are discussed in the Oncological Cardiomyopathy section.

Clinical Testing for Characterizing RCM Phenotypes

Echocardiography, ECG, cMRI, and cardiac catheterization are all useful in identifying RCM, distinguishing RCM from constrictive pericarditis, and determining the functional severity of the disease. Serum biomarkers, such as NT-proBNP, may provide supportive evidence for RCM versus constrictive pericarditis. Moreover, cMRI and cardiac biopsy can aid in establishing a cause. Marked biatrial enlargement is the pathognomonic finding on echocardiography and surface ECG.

In addition, 2D echocardiography, Doppler echocardiography, and 2D speckle tracking are important tools for characterizing the phenotypic and functional aspects of RCM (Table 10).[365]

Diastolic filling patterns have been described in detail for adults with RCM and constrictive pericarditis. However, in children, the performance and interpretation of diastolic measurements are challenging, given the higher heart rates, potential need for sedation, and limited data on the relationships among the diastolic variables and the degree of dysfunction in children.

Table 10. Echocardiographic Differences Between Constrictive Pericarditis and RCM

	Constrictive Pericarditis	RCM
2-Dimensional echocardiography		
LV ejection fraction	Normal	Normal or slightly decreased
Pericardium appearance	Thickened/bright	Normal
Interventricular septum movement	Abnormal	Normal
Interventricular septum position	Varies with respiration	Normal
Doppler echocardiography		
E/a ratio	Increased (≥2)	Increased (≥2)
E/a ratio response to Valsalva maneuver	Variation >25%	Minimal variation
E-wave decelerating time, ms	Decreased (≤160)	Decreased (≤160)
E′ septal, cm/s	≥8	<8
E′ septal/lateral	Septal>lateral	Lateral>septal
S′, cm/s	>5	<5
Mitral valve inflow propagation, cm/s	Normal or increased (≥100)	<55
Hepatic vein flow	Diastolic flow reversion during expiration	Diastolic flow reversion during inspiration
2-Dimensional speckle tracking echocardiography		
Circumferential strain	Decreased	Normal
Radial strain		
Basal	Decreased	Normal
Apical	Normal	Normal
Longitudinal strain		
Septal	Normal	Decreased
Lateral	Decreased	Decreased
Basal segments	Normal	Decreased
Apical segments	Decreased	Decreased
Global	Decreased	Decreased
Twist motion	Decreased	Normal
Apical rotation	Decreased	Normal
Left atrial reservoir strain		
Lateral	Decreased	Decreased
Septal	Increased	Decreased

Doppler values are based on adult normative data, as discussed in the text. LV indicates left ventricular; and RCM, restrictive cardiomyopathy.

The strain patterns and tissue Doppler imaging cutoffs are based primarily on adult data and may not apply to children, particularly younger children or those with disease processes that differ from those in adults. It is well known that ventricular compliance worsens with age for a variety of reasons; thus, compliance may be abnormal in children with RCM before it is identified by adult normative data. In fact, in the assessment of diastolic dysfunction among 175 children with cardiomyopathy, the percentage of normal diastolic variables was high in children with overt cardiac dysfunction.[40] Mitral E deceleration time was most helpful in identifying children with RCM, abnormal in 75% of patients. Another study to determine whether guidelines for assessing LV diastolic function in adults could be applied to children with RCM found overlapping echocardiographic measures of diastolic function between healthy children and those with RCM. Left atrial size indexed to body surface area was the most useful measurement for distinguishing healthy children from children with RCM.[366] When the disease process advances and PH is present, the interventricular septal motion and position by echocardiogram may become flattened as a result of elevated pressures during systole in the RV in RCM. This is typically not seen in constrictive pericarditis and may aid in distinguishing the entities.

Cardiac catheterization can distinguish between restrictive and constrictive physiology, determine the severity of the diastolic dysfunction by directly measuring the filling pressures of the both ventricles, and assess the presence and reversibility of PH in children with RCM. cMRI is important for diagnosing RCM. Fibrosis or abnormal deposits in the interstitium can be seen with special cMRI techniques. Findings from cMRI for specific pathogeneses are discussed in the Cardiomyopathy Associated With Arrhythmia Substrate section (Genetic Testing, Diagnostic Criteria, and Cardiac MRI subsections).

In terms of the utility of biomarkers to distinguish between RCM and constrictive pericarditis, natriuretic peptides have been shown to be elevated significantly in adults with RCM. A study of 49 adults (20 with RCM and 29 with constrictive pericarditis) showed that median plasma NT-proBNP was 1775 (208–7500) pg/mL in those with RCM versus 124 (68–718) pg/mL in those with constrictive pericarditis (P=0.001).[367] A smaller study in 5 adults with RCM and 6 with constrictive pericarditis found similar results for B-type natriuretic peptide, with patients with RCM having significantly higher BNP levels than patients with constrictive pericarditis despite similar elevations in intracardiac pressures.[368] These same results have not been validated in children.

Pathogenetic Classification

The PCMR investigators recently published the preliminary results of whole-exome sequencing of 36 genes involved in the development of cardiomyopathy. Pathogenic or likely pathogenic variants that affect protein function were found in 50% of children with RCM, the highest diagnostic yield of the cardiomyopathy phenotypes in this cohort.[369]

Mutations in both sarcomeric and nonsarcomeric genes have been associated with RCM (see details in

Table 11. Causes of RCM

Primary RCM
Genetic
Sarcomeric
Desmin
Filamin-C
Secondary RCM
Infiltrative
Amyloidosis
Lysosomal storage disorder
Anderson-Fabry disease
Iron overload
Endomyocardial fibrosis
Parasitic infection
Autoimmune disorders
Malignancy with hypereosinophilia
Possible dietary deficiencies or ingested toxins in certain areas of endemic disease[370]

RCM indicates restrictive cardiomyopathy.

the Genetics of Pediatric Cardiomyopathies section and Table 8).[78] Inheritance is autosomal dominant with variable penetrance and expressivity. The nonfamilial or secondary causes of RCM are varied and include infiltrative diseases, storage disorders, and fibrotic processes (Table 11).

RCM Caused by Sarcomeric Mutations

Sarcomeric mutations associated with RCM have been found in patients presenting from infancy to adulthood. Mutations in myosin-binding protein (*MYBPC3*), β-myosin heavy chain (*MYH7*), myosin light chain genes (*MYL3*), troponin I (*TNNI3*), and troponin T (*TNNT2*) have been associated with RCM.[66,78,371] This disruption in the binding of domains within the contractile apparatus of the myocyte is believed to increase calcium sensitivity of contraction and to impair relaxation. In 12 children with isolated, nonsyndromic RCM, those with sarcomeric mutations did not differ significantly in any clinical, echocardiographic, histopathological, or hemodynamic variable from those without sarcomeric mutations.[67]

Other mutations in sarcomeric genes may be associated with pediatric RCM. These include mutations in α-cardiac actin (*ACTC*)[67] and an autosomal-recessive mutation involving troponin C (*TNNC1*).[372] Both have been reported in families with mixed phenotypes of DCM and HCM, respectively. Other reports of mutations in sarcomeric genes include abnormalities of tropomyosin 1 (*TPM1*) and myosin light chain (*MYL3* and *MYL2*) in isolated RCM.[373] Additional segregation and function data are required to establish the pathogenicity of these variants.

RCM Caused by Nonsarcomeric Mutations

Nonsarcomeric mutations have been identified in pediatric RCM, albeit less commonly than sarcomeric mutations. Mutations described have included those found in desmin, an intermediate filament that forms an intracytoplasmic network connecting myofibrils to each other, other organelles, and the plasma membrane. Desmin is important in cardiac, skeletal, and smooth muscle structure and function. It is also present in Purkinje fibers. Mutations in desmin that cause RCM generally have features of skeletal myopathy, particularly the distal myopathies, and of conduction abnormalities such as advanced atrioventricular block requiring a pacemaker or ventricular arrhythmias.[374] However, in 4 generations of 1 family with desmin-associated RCM, desmin did not accumulate in the skeletal muscle, despite accumulating in the heart in severe RCM. In this family, the onset of RCM was as early as 5 years of age and as late as the fifth decade of life, and the onset appeared to be earlier in successive generations.[375] This familial RCM has been linked to an abnormality in chromosome 10.[376]

Mutations in filamin-C (*FLNC*) have also been described in RCM. Like desmin, *FLNC* is important for cross-linking to membrane proteins. Filamin-C is expressed predominantly in the heart and skeletal muscle, where it cross-links actin to the membrane and supports several signaling proteins. Despite its expression in skeletal muscle, no clinically detectable skeletal involvement has been reported in families with RCM. Filamin-C can cause early onset of RCM, with the youngest member of a 4-generation family with RCM diagnosed before 2 years of age.[377] There may be a wide array of different mutations identified with this clinical morphofunctional phenotype, and as a result, broad manifestations may be implied across different families.

RCM Caused by Infiltrate

In infiltrative RCM, the disease is characterized by abnormal deposits of protein such as amyloid in the interstitium. Cardiac amyloidosis is caused by the deposition of amyloid, an insoluble fibrillar protein, in the interstitium. Amyloidosis is an uncommon cause of cardiomyopathy, and most forms occur late in life. Hereditary transthyretin amyloidosis has the earliest age at onset, averaging 30 years. Patients also have extracardiac manifestations of sensory neuropathy, autonomic dysfunction, and carpal tunnel syndrome.[378] Early detection and treatment can improve cardiac function and survival.[379] Echocardiography may reveal a thickened or speckled myocardium, and ECGs tend to have low voltage. The diagnosis can be made by endomyocardial biopsy and staining of the myocardium with Congo red.

In amyloidosis, the excess amyloid protein is deposited globally in the myocardium, but the deposits occur first and, to a greater extent, in the subendocardium.

This intramyocardial gradient is seen by MRI T1 imaging and has prognostic value in amyloidosis.[380]

Although amyloidosis is notable as a classic form of infiltrative RCM with distinctive features on echocardiography, MRI, and biopsy, it is extremely rare in childhood.

RCM Caused by Storage Disorders

In storage disorders, abnormal deposits in the cardiac myocyte cause diastolic dysfunction. RCM caused by storage disorders may first be recognized by diastolic dysfunction, but the cardiac phenotype progresses to include LV hypertrophy.

Anderson-Fabry disease is the most common lysosomal storage disorder. Children with this disorder have absent or decreased activity of the enzyme α-galactosidase and are unable to break down glycosphingolipids, which accumulate in the heart, kidneys, and nerves. Measuring serum concentrations of α-galactoside is necessary for a definitive diagnosis. Echocardiographic findings include diastolic dysfunction with or without LV hypertrophy. cMRI shows midmyocardial delayed enhancement and prolonged myocardial T2 relaxation.[381]

In iron-overload cardiomyopathy, the excess, non–transferrin-bound iron is taken up rapidly by certain cells, notably cardiac myocytes. Iron overload can occur in the heart, liver, pancreas, and gonads of children with hemochromatosis, as well as those receiving multiple blood transfusions. Children with transfusion-dependent Diamond-Blackfan anemia and sideroblastic anemia are especially at risk for cardiac iron deposition and toxicity.[382]

In the early stages of iron overload, the children display an RCM phenotype. However, as the iron deposition progresses, systolic dysfunction ensues, and the patient's phenotype may be characterized as DCM with restrictive physiology. cMRI accurately diagnoses myocardial iron overload by showing lower T2 times. These times correlate with the severity of deposition and can be measured serially to determine response to therapy.[382] Pathological findings of cardiac biopsies obtained from patients with iron overload include positive staining for iron with Prussian blue and the presence of granular, yellow-gray deposits in the sarcoplasm of the myocytes.[381]

RCM Caused by Fibrotic Processes

Endomyocardial fibrosis is an important cause of RCM worldwide, particularly in Africa, Asia, and South America, where it is caused by parasites that live in tropical regions. Parasitic infections, autoimmune disorders, certain dietary deficiencies, ingested toxins, and malignancy can cause hypereosinophilia. In severe cases, hypereosinophilic syndrome is characterized by an initial acute inflammatory phase with pancarditis, then a thrombotic phase, and finally a fibrotic stage with irreversible endocardial fibrosis.[383] The fibrosis predominates in the atrioventricular valves and the ventricular apices. The RV tends to be more affected than the LV, although more than half of patients have biventricular involvement. The fibrotic stage can be prevented by treating the cause and reducing the eosinophilia and acute inflammation.

The diagnosis of endomyocardial fibrosis can be made with echocardiographic evidence of a thickened endocardium, severely dilated atria, and intracardiac thrombi.[384] Fibrosis can also be diagnosed by cMRI with the use of delayed enhanced inversion recovery imaging and contrast-enhanced T1 mapping to identify areas of hyperenhancement with contrast that indicate fibrosis. Although eosinophilia is present in the early stage of disease, it can be absent in the later stages when cardiac symptoms become apparent.[384]

Clinical Outcomes in RCM

Children with RCM have the worst outcomes of any pediatric cardiomyopathy group. About two-thirds of children with RCM have a pure phenotype, and the rest present with a mixed RCM-HCM phenotype.[385] Both groups have similar 5-year mortality rates of 20% to 28%, but children in the pure RCM group are more likely to undergo transplantation by 5 years after diagnosis than those in the RCM-HCM group (58% versus 30%, respectively; Figure 7).[385]

As with HCM, HF and lower LV fractional shortening at diagnosis are associated with worse outcomes. Higher LV posterior wall thickness was associated with worse outcomes only in the RCM-HCM group.

LVNC CARDIOMYOPATHY

Definition

LVNC in children has been described in association with complex congenital heart disease and coronary artery anomalies and as an isolated finding in the heart, with and without musculoskeletal and other system abnormalities.[386–388] Both the ESC and AHA use the distinctive appearance of prominent LV trabeculations and deep intratrabecular recesses detected on imaging studies or pathological examination to identify patients with LVNC.[18,19] The ESC considers LVNC to be an unclassified cardiomyopathy and emphasizes the fact that LVNC with normal cardiac function may not meet the criteria for cardiomyopathy because many patients do not have evidence of impaired cardiac function.[19,389,390] The AHA classification, which is based largely on molecular and genomic information, considers LVNC to be a congenital cardiomyopathy that can be profiled genetically.

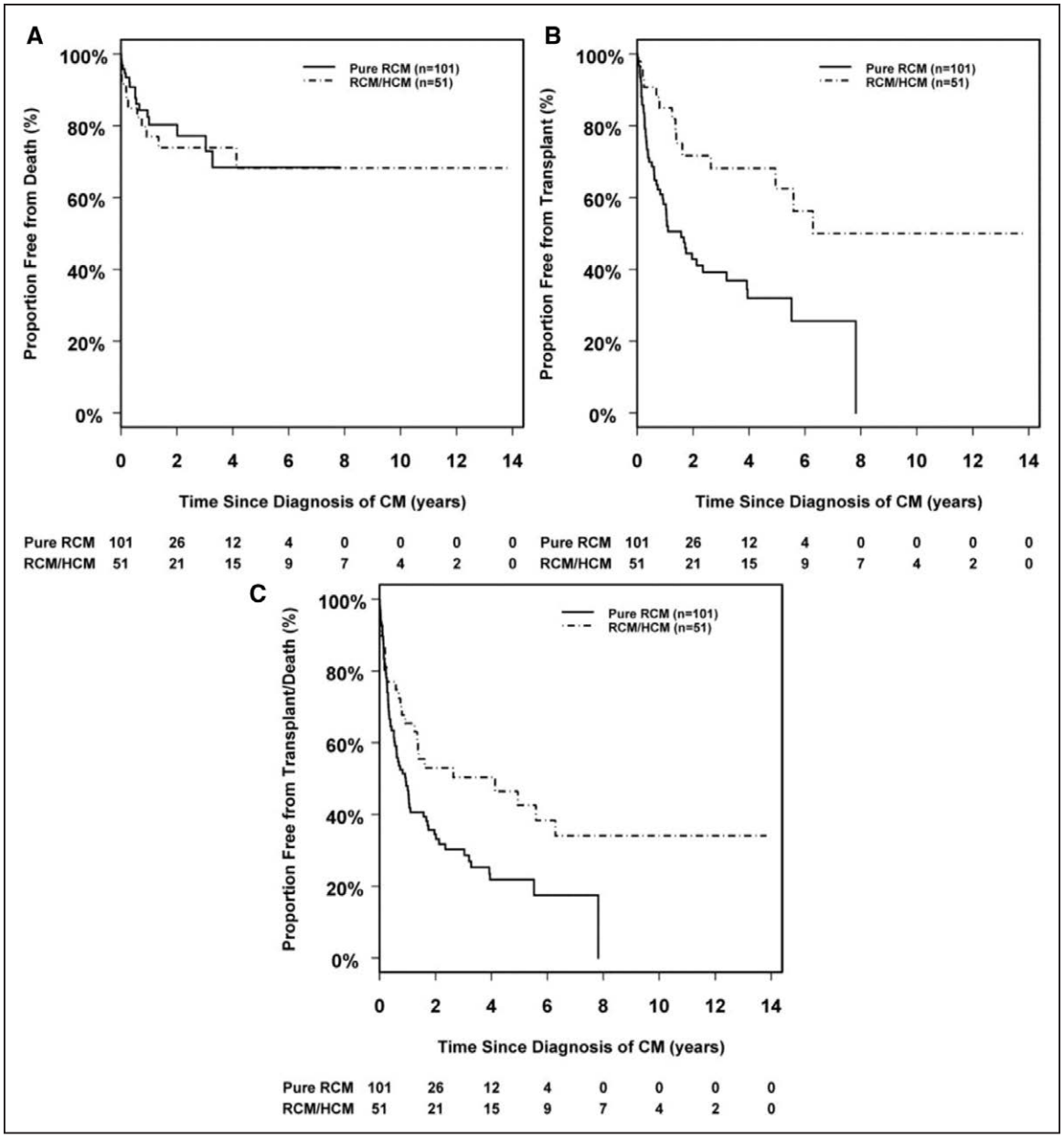

Figure 7. Probability of freedom from (A) death (censored at transplantation), (B) transplantation, and (C) death or transplantation among 152 children with restrictive cardiomyopathy (RCM) stratified by phenotype (pure RCM vs mixed or overlapping RCM and hypertrophic cardiomyopathy [HCM] phenotypes).

CM indicates cardiomyopathy. Reprinted from Webber et al.[385] Copyright © 2012, American Heart Association, Inc.

LVNC may represent a failure of maturation, and hypertrabeculation may represent a more primitive state of the myocardium. Several investigators argue against this hypothesis, however. Recent histological evidence indicates that the fetal myocardium with LVNC does not have the same immunohistochemical profile as normal embryonic myocardium.[391] Other evidence suggests that LVNC is nothing more than excessive trabeculations that, alone, are not disease causing.[392] For example, controversy remains as to whether the finding of trabeculations in the LV fulfilling imaging criteria for LVNC is cardiomyopathy (disease) or simply a morphological trait.[393]

Structural and Functional Phenotypes

LVNC can occur as an isolated finding or in association with a dilated, hypertrophic, or mixed phenotype. The majority of patients reported in the PCMR had an associated dilated phenotype. Prognosis in patients with LVNC is variable, and the clinical phenotype, not the morphological findings of hypertrabeculation, appears to be the main driver of outcomes.[10] An analysis of echocardiograms from adults in MESA (Multi-Ethnic Study of Atherosclerosis) found that hypertrabeculation was not associated with a decline in LV function over 10 years, indicating that this finding in isolation was not clinically relevant.[390]

Table 12. Causes of LVNC

Sarcomeric
Metabolic disorder
Barth syndrome
Other genetic
ZASP
HCN4
α-Actinin-2

LVNC indicates left ventricular noncompaction cardiomyopathy.

Causes of LVNC

Marked heterogeneity characterizes the genes controlling the sarcomeric, cytoskeleton, and mitochondrial functions in patients with LVNC[394,395] (Table 12). In 79 Japanese patients with familial LVNC, autosomal-dominant inheritance was the prominent mode of transmission, with X-linked and mitochondrial inheritance less commonly described.[396] Next-generation sequencing identified pathogenic variants in 38% of 102 unrelated patients with LVNC. Sarcomeric pathogenic variants, the most common variants, were found in 63% of patients, and genes associated with channelopathies were found in 12%. Pathogenic variants were more common in patients who were younger, had a lower ejection fraction, and presented with HF.[395] In another series of 190 nonconsanguineous patients, whole-exome sequencing identified variants of interest in LVNC or other known cardiomyopathy genes in 59% of patients. Variants of interest in the sarcomeric gene mutations were also found in 45% of patients. The number of variants of interests in a given patient strongly correlated with the ratio of noncompacted to compacted myocardium and with LV ejection fraction.[394] Several of the genetically identified LVNC cardiomyopathies have specific clinical phenotypes that can assist in identifying, managing, and predicting outcomes in affected patients.

Barth syndrome, an inborn error of metabolism caused by a mutation in the Tafazzin gene locus on the X chromosome, has been particularly well characterized clinically.[397] It is an X-linked–recessive disorder with the cardiac findings of LVNC and DCM. The underlying pathological abnormality results from impaired cardiolipin acetylation, changes in the cardiolipin content and composition that alter the inner mitochondrial membrane by disrupting sarcomere assembly, and contractile stress generation.[398]

The hallmark clinical findings of Barth syndrome, in addition to HF, include a skeletal myopathy, lactic acidosis, and neutropenia. In recent reports from the United Kingdom and France, 49% to 55% of infants presenting with Barth syndrome had undergone heart transplantation or died in infancy, with reports of stabilization and even recovery of normal cardiac function after 3 years of age in the transplantation-free survivors.[399,400]

LVNC has been associated with arrhythmias, including complete heart block, interventricular conduction defects, atrial fibrillation, sinus bradycardia, and VT. When associated with complete heart block, LVNC carries a poor prognosis, particularly in fetuses.[401] Interventricular conduction defects have been described in patients with LNVC and mutations in ZASP, one of the major components of the Z-disk proteins in the cardiac muscle.[402] A disease-causing variant in a-actinin-2 has been found in a family with LVNC and juvenile-onset atrial fibrillation.[403] *HCN4* mutations have been found in several series of patients with sinus node dysfunction and LVNC.[404,405] Ventricular arrhythmias have been reported primarily in adults with LVNC.[406]

Clinical Outcomes for LVNC

Children with LVNC may be classified by cardiac imaging as having isolated disease or LVNC with another cardiomyopathy phenotype (eg, DCM, HCM, or RCM), and this can be further stratified on the basis of normal ventricular function or dysfunction. Children with isolated LVNC have a 5-year survival of 94%, whereas those with a mixed LVNC phenotype have survival rates similar to those with the non-LVNC phenotype (Table 13).[10]

A recent single-institution report suggests that arrhythmias are associated with poor outcomes for children with LVNC.[407]

CARDIOMYOPATHY ASSOCIATED WITH ARRHYTHMIA SUBSTRATE

Table 14 has a list of cardiomyopathies belonging in this category.

Arrhythmogenic Ventricular Cardiomyopathy

Definition

AVC is an autosomal-dominantly inherited heart disease characterized pathologically by fibrofatty replacement of the myocardium and clinically by ventricular arrhythmias, as well as by impaired ventricular systolic function. The disease was initially called arrhythmogenic RV dysplasia, but because biventricular involvement and, less often, isolated LV involvement may be present in a substantial proportion of patients,[408] a broader term such as *AVC* is preferred, as proposed by the Heart Rhythm Society and the European Heart Rhythm Association.[409]

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Table 13. Outcomes of 155 Children With LVNC by Phenotype

Outcome	Cardiomyopathy Phenotype			
	Isolated (n=35)	Dilated (n=91)	Hypertrophic* (n=17)	Indeterminate (n=12)
Median follow-up in event-free subjects, y	3.3	4.2	4.3	5.5
Total deaths, n	2	14	4	1
5-y death rate (95% CI)	6 (2–22)	22 (13–37)	25 (10–53)	9 (1–49)
Total transplantations, n	0	16	0	3
5-y transplantation rate (95% CI), %	0	27 (17–41)	0	27 (9–62)
Total transplantation listings, n†	0	23	0	5
5-y listing rate (95% CI), %	0	38 (25–55)	0	42 (20–73)
Total with death or transplantation, n	2	30	4	4
5-y death/transplantation rate (95% CI), %	6 (2–22)	43 (31–57)	25 (10–53)	33 (14–66)
Total with death or listing, n	2	33	4	5
5-y death/listing rate (95% CI), %	6 (2–22)	45 (34–59)	25 (10–53)	42 (20–73)

LVNC indicates left ventricular noncompaction cardiomyopathy.
*Idiopathic or familial isolated hypertrophic cardiomyopathy.
†Of 28 initial listings, 24 were status 1A. One of the remaining 4 was upgraded to status 1A.
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Phenotypic Correlation

AVC is an important cause of SCD in young adults, accounting for 11% of all cases and 22% of cases among athletes.[410] Affected patients may also present with ventricular tachyarrhythmias or HF. The incidence and severity of AVC are higher in male patients than in female patients, likely because of the influence of sex hormones and the amount and intensity of exercise performed by males. Genotype-phenotype correlation studies have shown that the disease can have a wide phenotypic spectrum, as well as features ranging from grossly normal hearts, in which only a careful histopathological investigation can reveal AVC features in 1 or both ventricles, to hearts with massive biventricular disease involvement.[408]

The disease is called right-dominant when RV involvement is the dominant disease. A left-dominant AVC also exists, usually as an isolated, nonischemic LV fibrofatty scar seen on postcontrast cMRI or at autopsy.[411,412] Left-dominant AVC has been reported as a cause of life-threatening ventricular arrhythmias and SCD in young people and athletes.[413] This condition has also been linked to a genetically defective desmosome, suggesting that it may be an additional phenotypic variant of AVC manifesting as an exclusive and segmental involvement of the LV.[413]

Genetic Testing

AVC is most commonly inherited as a mendelian autosomal-dominant trait with incomplete penetrance, although 2 autosomal-recessive forms have also been described.[414] Mutations of genes encoding for desmosomes or desmosome-interacting proteins are seen in 40% to 50% of cases. Several gene mutations have been described,[415] but the 7 gene panels commonly offered in most specialized laboratories are for *DSC2*, *DSG2*, *DSP*, *JUP*, *PKP2*, *RYR2*, and *TMEM43* (GeneTest).[416,417] Other gene mutations that have been associated but not included in the commercial panel are *MIB1* and *TTN* (Table 8). Defective cell-to-cell adhesion caused by mutations in genes encoding desmosomal proteins has been implicated in the pathogenesis of AVC. The result is disruption of the cardiac gap junction apparatus, which is thought to cause both functional impairment and the failure of impulse transmission with subsequent arrhythmogenesis.[418] Genetic testing is indicated for symptomatic patients with AVC and family members of a patient testing positive for a mutation.

Diagnostic Criteria

The diagnosis of AVC is established by a point score according to the revised Task Force 2010 criteria (Table 15) using imaging modalities, biopsy evidence of fibrofatty replacement, electrocardiographic abnormalities, ventricular arrhythmias, and a positive family history, including identified genetic mutations.[419,420] These criteria are modifications of those proposed by the original Task Force of the Working Group for Myocardial and Pericardial Disease of the ESC and of the

Table 14. Causes of Arrhythmogenic Cardiomyopathy

AVC
Cardiomyopathy caused by channelopathy
LQTS
Brugada syndrome
Catecholaminergic polymorphic VT
SQTS
Lenègre disease
Tachycardia- and pacing-induced cardiomyopathy

AVC indicates arrhythmogenic ventricular cardiomyopathy; LQTS, long-QT syndrome; SQTS, short-QT syndrome; and VT, ventricular tachycardia.

Table 15. Comparison of Original and Revised Task Force Criteria for the Diagnosis of AVC

Original Task Force Criteria	Revised Task Force Criteria
Global or regional dysfunction and structural alterations*	
Major	
Severe dilatation and reduction of RV ejection fraction with no (or only mild) LV impairment Localized RV aneurysms (akinetic or dyskinetic areas with diastolic bulging) Severe segmental dilatation of the RV	By 2-dimensional echocardiography: Regional RV akinesia, dyskinesia, or aneurysm And 1 of the following (end diastole): PLAX RVOT ≥32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m^2) PSAX RVOT ≥36 mm (corrected for body size [PSAX/BSA] ≥21 mm/m^2) Or fractional area change ≤33% By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction And 1 of the following: Ratio of RV end-diastolic volume to BSA ≥110 mL/m^2 (male patient) or ≥100 mL/m^2 (female patient) Or RV ejection fraction ≤40% By RV angiography: Regional RV akinesia, dyskinesia, or aneurysm
Minor	
Mild global RV dilatation or ejection fraction reduction with normal LV Mild segmental dilatation of the RV Regional RV hypokinesia	By 2-dimensional echocardiography: Regional RV akinesia or dyskinesia And 1 of the following (end diastole): PLAX RVOT ≥29–<32 mm (corrected for body size [PLAX/BSA] ≥16–<19 mm/m^2) PSAX RVOT ≥32–<36 mm (corrected for body size [PSAX/BSA] ≥18–<21 mm/m^2) Or fractional area change >33%–≤40% By MRI: Regional RV akinesia or dyskinesia or dyssynchronous RV contraction And 1 of the following: Ratio of RV end-diastolic volume to BSA ≥100–<110 mL/m^2 (male patient) or ≥90–<100 mL/m^2 (female patient) Or RV ejection fraction >40%–≤45%
Tissue characterization of wall	
Major	
Fibrofatty replacement of myocardium on endomyocardial biopsy	Residual myocytes <60% by morphometric analysis (or <50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor	
	Residual myocytes 60%–75% by morphometric analysis (or 50%–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	
Major	
	Inverted T waves in right precordial leads (V_1, V_2, and V_3) or beyond in individuals >14 y of age (in the absence of complete RBBB, QRS ≥120 ms)
Minor	
Inverted T waves in right precordial leads (V_2 and V_3) (people >12 y of age in the absence of RBBB)	Inverted T waves in leads V_1 and V_2 in individuals >14 y of age (in the absence of complete RBBB) or in V_4, V_5, or V_6
	Inverted T waves in leads V_1–V_4 in individuals >14 y of age in the presence of complete RBBB
Depolarization/conduction abnormalities	
Major	
Epsilon waves or localized prolongation (>110 ms) of the QRS complex in right precordial leads (V_1–V_3)	Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V_1–V_3)
Minor	
Late potentials (SAECG)	Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS duration of ≥110 ms on standard ECG
	Filtered QRS duration ≥114 ms
	Duration of terminal QRS <40 μV (low-amplitude signal duration) ≥38 ms
	Root-mean-square voltage of terminal 40 ms ≤20 μV
	Terminal activation duration of QRS ≥55 ms measured from the nadir of the S wave to the end of the QRS, including R′, in V_1, V_2, or V_3 in the absence of complete RBBB

(*Continued*)

Table 15. Continued

Original Task Force Criteria	Revised Task Force Criteria
Arrhythmias	
Major	
	Nonsustained or sustained VT of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)
Minor	
LBBB-type VT (sustained and nonsustained) (ECG, Holter, exercise)	Nonsustained or sustained VT of RV outflow configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis
Frequent ventricular extrasystoles (>1000 per 24 h) (Holter)	>500 ventricular extrasystoles per 24 h (Holter)
Family history	
Major	
Familial disease confirmed at necropsy or surgery	ARVC/D confirmed in a first-degree relative who meets current Task Force criteria
	ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative
	Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation
Minor	
Family history of premature sudden death (<35 y of age) resulting from suspected ARVC/D	History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria
Familial history (clinical diagnosis based on present criteria)	Premature sudden death (<35 y of age) resulting from suspected ARVC/D in a first-degree relative
	ARVC/D confirmed pathologically or by current Task Force criteria in second-degree relative

Diagnostic terminology for original criteria: This diagnosis is fulfilled by the presence of 2 major, 1 major plus 2 minor criteria, or 4 minor criteria from different groups. Diagnostic terminology for revised criteria: definite diagnosis, 2 major, 1 major and 2 minor criteria, or 4 minor from different categories; borderline, 1 major and 1 minor or 3 minor criteria from different categories; and possible, 1 major or 2 minor criteria from different categories. AVC indicates arrhythmogenic ventricular cardiomyopathy; aVF, augmented vector foot; aVL, augmented vector left shoulder; ARVC/D, arrhythmogenic right ventricular cardiomyopathy/dysplasia; BSA, body surface area; LBBB, left bundle-branch block; LV, left ventricular; MRI, magnetic resonance imaging; PLAX, parasternal long-axis view; PSAX, parasternal short-axis view; RBBB, right bundle-branch block; RV, right ventricular; RVOT, RV outflow tract; SAECG, signal-averaged electrocardiogram; and VT, ventricular tachycardia.

*Hypokinesis is not included in this or subsequent definitions of RV regional wall motion abnormalities for the proposed modified criteria.

†A pathogenic mutation is a DNA alteration associated with ARVC/D that alters or is expected to alter the encoded protein, is unobserved or rare in a large control population without ARVC/D, and either alters or is predicted to alter the structure or function of the protein or has demonstrated linkage to the disease phenotype in a conclusive pedigree.

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Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology, which were published in 1994.[420] A definite diagnosis of AVC requires the presence of 2 major criteria, 1 major and 2 minor criteria, or 4 minor criteria from different categories (Table 15).[419]

Although these criteria were based on adult data, a pediatric study by Etoom et al[421] in 2015 reaffirmed the role of cMRI in the diagnosis of AVC in children and adolescents. They concluded that, even with the revised Task Force 2010 criteria (Table 15), diagnosing AVC in pediatric patients remained quite challenging, especially because children who are gene positive may not exhibit all of the phenotypic features of the disease until adulthood. Their study showed that abnormal cMRI findings were frequent in children and adolescents with a suspicion for AVC. Of the cMRI parameters listed in the revised Task Force 2010 criteria, indexed RV end-diastolic volume and wall motion abnormalities were the 2 most important cMRI contributors to diagnosing AVC in children. Although widely measured, fatty infiltration and myocardial fibrosis rarely occurred in the children studied. On the other hand, LV enlargement and systolic dysfunction were common findings on cMRI. Surprisingly, there was very little correlation between cMRI findings and echocardiography for diagnosing AVC in the pediatric population studied. Echocardiography was found to be relatively insensitive to the early changes of AVC because of limitations in acoustic windows of the RV free wall compared with cMRI.[421]

Although the RV free wall is most commonly involved (right-dominant), the LV may be the only ventricle involved (left-dominant), and sometimes both ventricles are involved. cMRI is the best imaging modality for diagnosing AVC[422] and is used to evaluate RV size, function, wall motion abnormalities, intramyocardial fat (using a fat-suppression sequence), and late gadolinium enhancement to assess areas of fibrosis. RV wall thickening or thinning and prominent trabeculations are also seen in AVC.[421,423]

One of the largest studies of AVC in children consisted of 75 patients, of whom 55 were probands and 20 were family members who met the diagnostic criteria

on screening.[424] The primary outcome measures were spontaneous sustained VT, resuscitated SCD, SCD, appropriate implantable cardioverter-defibrillator interventions for ventricular arrhythmia, indications for cardiac transplantation, and cardiac death. Of the 75 children, 41 (55%) experienced at least 1 of the above primary outcomes. Most of the affected children in this study were male (55%), and AVC was associated with a gene mutation in 80%. One-fourth of the children presented with either SCD (15%) or resuscitated SCD (11%).[424]

Cardiac MRI

The RV is better visualized on cMRI than on echocardiography, making cMRI the modality of choice for evaluation.[423] In addition to evaluating RV size, cMRI is useful for evaluating RV function, wall motion abnormalities, intramyocardial fat (using fat suppression sequence), and late gadolinium enhancement to assess areas of fibrosis.[423] Besides determining the presence of morphofunctional ventricular abnormalities, cMRI can characterize myocardial tissue with late gadolinium enhancement, which provides information on the presence, morphology, and wall distribution of myocardial fibrofatty scar. RV wall thickening or thinning and prominent trabeculations are also seen in arrhythmogenic RV cardiomyopathy.[423]

Clinicopathological Correlation

Clinical Manifestations

The most common clinical presentation of AVC consists of ventricular arrhythmias and related symptoms or events, which include palpitations, syncopal episodes (mostly occurring during physical exercise), cardiac arrest dyspnea, and atypical chest pain or discomfort.[425] SCD may occur unexpectedly in previously asymptomatic individuals, mostly young people and competitive athletes. The prognosis of AVC is related to either ventricular electric instability, which may lead to arrhythmic SCD, or progression of ventricular muscle disease, resulting in RV or biventricular systolic dysfunction.

Endomyocardial Biopsy

Because the patchy distribution of abnormalities often results in a low diagnostic yield, endomyocardial biopsy is not routinely performed unless the patient is undergoing an electrophysiological study at the same time. The fact that the interventricular septum is rarely affected by fibrofatty infiltration is an important disadvantage of endomyocardial biopsies usually obtained from the septum, which may often yield false-negative results.[426] If biopsy is considered, either an echocardiography- or MRI-guided biopsy of the RV free wall is crucial to establish a diagnosis.

Major criteria include <60% residual myocytes by morphometric analysis, with fibrous replacement of the RV free wall myocardium in ≥1 samples, with or without fatty replacement of tissue. Minor criteria include 60% to 75% residual myocytes by morphometric analysis, with fibrous replacement of the RV free wall myocardium in ≥1 samples, with or without fatty replacement of tissue.[420]

Electrophysiology

Changes in electrocardiographic characteristics reflect areas of slow intraventricular conduction. Because the underlying substrate consists of regions of normal myocardium interspersed with fatty and fibrous tissue, an ECG typically shows right bundle-branch block (RBBB) with right precordial repolarization alterations characterized by negative T waves in leads V_1 through V_3.[426] The ventricular arrhythmias in AVC range from isolated premature ventricular beats to sustained VT or VF leading to cardiac arrest. VT with a left bundle-branch block and an inferior axis pattern is considered a minor diagnostic criterion because of its low specificity. VT with left bundle-branch block and a superior or indeterminate axis is more specific for AVC and is a major diagnostic criterion.[420] In left-dominant AVC, ventricular arrhythmias show an RBBB morphology, confirming their origin from the LV.[412] During an electrophysiological study, a sustained monomorphic VT can be induced by programmed ventricular stimulation.

Electroanatomic mapping is an emerging technique in the diagnosis of AVC. It is used to identify scar or delayed conduction on 3-dimensional electroanatomic mapping. The extent of reduced endocardial bipolar voltages in the diseased ventricle may predict arrhythmia outcome in AVC. If the bipolar endocardial voltage map is normal, then this may characterize a low-risk subgroup.[427,428] If endocardial surface mapping is unsuccessful, epicardial mapping with ablation can be performed successfully in children.[429]

Risk Stratification

Follow-up studies have identified several risk factors for AVC. A history of cardiac arrest caused by VF or sustained VT is generally agreed to confer the highest risk of SCD.[430] The prognostic value of unexplained syncope and nonsustained VT is controversial. Moderate to severe systolic dysfunction of the RV, LV, or both independently predicted poor outcomes in prospective studies.[431]

Studies predominantly in adults have shown that a greater extent of T-wave inversion across the 12 leads has also been associated with unfavorable arrhythmic prognosis during follow-up.[426] The inducibility of VT or VF was the most significant independent predictor of appropriate treatment with implantable cardioverter-defibrillators for VT but not for shocks on VT or VF.[432,433] Lifelong follow-up is warranted in symptomatic

patients and asymptomatic carriers of pathogenic mutations. Physical exercise promotes the phenotypic expression of the disease and is a major factor that triggers life-threatening ventricular arrhythmias in patients with AVC.[434,435] Affected individuals should not participate in competitive or endurance sports because the physical activity associated with sports promotes the development of the phenotypic expression and can trigger malignant ventricular arrhythmias.[436] However, there is still controversy as to whether phenotype-negative/genotype-positive individuals should have activity restrictions. More work is needed in this area to determine whether patients who have not manifested the disease but carry the gene should be restricted from sports.[76,77]

Cardiomyopathy Caused by Channelopathies

Definition

Channelopathies are nonstructural, inherited arrhythmic conditions resulting from abnormal cardiomyocytes, although the heart appears structurally intact. This appearance supports the fact that an arrhythmia in this subgroup is a sign of cardiac dysfunction and distinguishes channelopathies from diseases of the cardiac cytoskeleton, desmosomes, and sarcomeres.[437] Channelopathies are a result of mutations of cardiac ion channel genes and include long-QT syndromes (LQTS), short-QT syndromes (SQTS), Brugada syndrome, Lenègre disease, and catecholaminergic polymorphic VT (Table 14).[437]

Although debate continues as to whether channelopathies are true cardiomyopathies, there is considerable overlap between cardiac ion channel genes and the gene locus for several cardiomyopathies. For example, chromosome 3p22-p25 contains the *SCN5A* gene, which has been associated with AVC, LQTS, Brugada syndrome, and Lenègre disease. Having discussed this extensively, the writing group decided that it is prudent to include this subgroup of cardiac disease in this document.

Corrado et al[437] eloquently argued that channelopathies should be regarded as cardiomyopathies:

> Heart muscle diseases are traditionally classified according to their peculiar pathophysiologic features such as "dilated," "hypertrophic," "restrictive," and "arrhythmogenic ventricular" cardiomyopathy. The extraordinary advances in molecular genetics have allowed the identification of the genetic etiology of most of these conditions. The World Health Organization (1995) defines cardiomyopathies as "diseases of the myocardium associated with cardiac dysfunction," and should include not only forms with hemodynamic dysfunction, but also conduction and rhythm disturbances. Arrhythmias are a sign of cardiac dysfunction and may reflect an underlying myocardial electrical disease with or without structural abnormalities as features.
>
> These nonstructural inherited arrhythmic conditions should be regarded as cardiomyopathies because the myocyte is abnormal, although the heart is apparently intact. It is therefore time for a new classification of cardiomyopathies taking into account the underlying gene mutations and the cellular level of expression of encoded proteins, thus distinguishing cytoskeleton (cytoskeletalopathies), desmosomal (desmosomalopathies), sarcomeric (sarcomyopathies), and ion channel (channelopathies) cardiomyopathies.[437]

Pathogenic Classification

Molecular genetics has helped to identify genetic defects associated with syncopal episodes, rapid polymorphic VT, and cardiac arrest precipitated by VF. Genotype-phenotype correlations have helped to identify asymptomatic healthy gene carriers at risk for sudden lethal cardiac events.[438]

In a large family affected by an autosomal-dominant cardiac conduction defect associated with sinus node dysfunction, arrhythmias, RV and LV dilatation, and dysfunction, the phenotype was mapped to a region on chromosome 3p22-p25, which contains the *SCN5A* gene. Mutations of this gene have been associated with AVC, LQTS, Brugada syndrome, and Lenègre disease (Table 14).[439]

Long-QT Syndrome

LQTS, the first channelopathy discovered, is characterized by a prolonged ventricular repolarization–QT interval. The corrected QT (QTc; Bazett formula) in LQTS is usually >440 milliseconds, although some patients may have a normal QTc at rest. LQTS can lead to lethal ventricular arrhythmias such as torsade de pointes and VF, resulting in sudden death. Seven different variants, LQT1 through LQT7, have been described. Variants LQT1, LQT2, LQT5, and LQT6 are associated with mutations of genes encoding for potassium channels. The LQT3 variant is caused by mutations of sodium channel genes; LQT4 is linked with calcium signaling genes; and LQT7 is caused by a defect in a structural protein, ankyrin B, which reduces the current amplitude.[437]

The most common variant of LQTS, LQT1, is caused by autosomal-dominant loss-of-function mutations on the *KCNQ1* gene. They cause many Romano-Ward (autosomal-dominant) syndromes and account for ≈45% of all genotyped families with LQTS.[440]

Jervell and Lange-Nielsen syndrome is an autosomal-recessively inherited form of LQTS characterized by profound sensorineural deafness and a prolonged QT interval, usually >500 milliseconds. The syndrome is usually caused by homozygous or compound heterozygous

pathogenic variants in *KCNQ1* or *KCNE1*, but additional mutations in other genetic loci should also be considered.[441]

Phenotypic Manifestations. Patients with LQT1 are more prone to syncope or cardiac arrest when engaging in strenuous sports, physical activity, or exercise. Patients with LQT2 are prone to arrhythmias when experiencing strong emotions or exposed to loud noises. Patients with LQT3 show a bradycardia-dependent QT prolongation and SCD at rest or during sleep. This finding underscores why patients with LQT1 respond to β-blockers, whereas patients with the other LQTS variants have only a variable response to β-blockers.[441]

Brugada Syndrome

Brugada syndrome has some genetic and phenotypic similarities to LQT3, but the QT interval is normal. It commonly presents in adults but can also occur in children. The classic electrocardiographic pattern is RV conduction delay and a cove-like ST-segment elevation of >2 mm in the anterior chest leads (V_1–V_3), followed by a negative or flattened T wave. Although RBBB may be present, it is not required for the diagnosis.[442]

The electrocardiographic characteristics can fluctuate in some patients and may at times be normal. Provocative use of sodium channel–blocking medications, such as procainamide or flecainide, may be necessary to uncover the electrocardiographic diagnosis.[443]

Brugada syndrome has an autosomal-dominant inheritance with variable penetrance, and most patients have a family history of sudden death or malignant arrhythmias. The syndrome has been linked to several genes, but the most common is the *SCN5A* gene.[444] Mutations in this gene have been detected in up to 30% of patients with Brugada syndrome.[437]

Other mutations decrease L-type calcium current and transient outward potassium current. These electrolyte abnormalities lead to RV conduction disturbances and the associated Brugada syndrome electrocardiographic pattern.[445] Whether the exact mechanism is an abnormal depolarization or repolarization pattern, or possibly both, is unknown.

Phenotypic Manifestations. The clinical presentation of Brugada syndrome varies from asymptomatic to a history of syncope, seizures, palpitations, nocturnal agonal respirations, and aborted sudden death.[446] It may also present as sudden and unexpected nocturnal death and has been linked to sudden infant death syndrome.[446]

Catecholaminergic Polymorphic VT

Catecholaminergic polymorphic VT is characterized by exercise-induced polymorphic VT that can degenerate into VF and sudden death. It is responsible for syncope and sudden death in young patients with no structural heart disease and a normal QT interval.[447] Ventricular tachyarrhythmias are easily induced by any form of sympathetic stimulation and should be looked for systematically in children presenting with convulsive seizures or faintness triggered by exercise or emotion. The diagnosis is commonly made in the stress laboratory during exercise electrocardiographic testing.[437] In the electrophysiology laboratory, the characteristic VT can be induced with a small dose of isoproterenol.

The condition has been linked to mutations of the ryanodine receptor gene and the calsequestrin gene, both of which encode for proteins regulating intracellular calcium homeostasis.[448] As the name implies, it commonly presents as a polymorphic bidirectional VT, although it can sometimes be monomorphic with RBBB morphology.[447]

Short-QT Syndrome

SQTS is the newest channelopathy to be added to the inherited arrhythmias associated with SCD.[449] It is rare, but its prevalence is believed to be underestimated. In SQTS, the QTc is <300 milliseconds. The normal QTc according to population studies is 340 to 360 milliseconds.[450] The underlying pathophysiological features involve shortening of myocardial repolarization, which creates the electrical substrate for atrial and ventricular tachyarrhythmias.[451]

Genetic studies have shown that SQTS is associated with gain-of-function mutations in 3 different potassium channels[452] and with 3 loss-of-function mutations in the L-type cardiac calcium channel.[453] Patients with SQTS associated with calcium channelopathies and patients with Brugada syndrome with calcium channelopathies have overlapping phenotypes.[454] In contrast, the presence of a short QT interval in isolation may not always indicate SQTS.[451]

Lenègre Disease or Lenègre-Lev Syndrome

Lenègre disease is an autosomal-dominant inherited conduction disorder caused by mutation of the *SCN5A* gene. It has an important familial aggregation.[439] Pathophysiologically, extensive fibrosis of the conduction system often includes lesions involving multiple sites of the conduction system. An initial RBBB may be followed by a left anterior hemiblock and eventually by a high-grade or complete atrioventricular block. Patients with unilateral or bilateral bundle-branch block are usually asymptomatic and do not require any specific treatment, but symptomatic patients, who tend to have high-grade, third-degree atrioventricular block, may experience palpitations, dizzy spells, syncope, or Stokes Adams attacks.[454]

Tachycardia- and Pacing-Induced Cardiomyopathy

Tachycardia-induced cardiomyopathy occurs when atrial or ventricular tachyarrhythmias (or frequent ectopy) result in ventricular dysfunction.[455] Atrial ectopic tachycardia

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and permanent junctional reciprocating tachycardia are the most common rhythm disturbances leading to this disorder in children.[456] On ECG, atrial ectopic tachycardia is a narrow complex rhythm with p-wave morphology that does not appear to be sinus in origin. Abrupt onset or termination may help distinguish it from sinus tachycardia. VT is an uncommon cause. The initial presentation is often characterized by HF signs or symptoms in the presence of a tachyarrhythmia and ventricular dysfunction. Echocardiographic findings at presentation usually reveal a dilated LV with severely depressed systolic function.[456] Neonates or infants may present in cardiogenic shock and require intensive care. Because tachyarrhythmias may be secondary to myocardial dysfunction, other causes of cardiomyopathy must be ruled out. The tachyarrhythmias may be controlled with antiarrhythmic monotherapy or dual therapy in neonates and infants. However, ablation is usually necessary to successfully manage the arrhythmia in older patients. Complete or partial recovery of function with reverse remodeling is the norm. Median time to functional recovery after the tachycardia is controlled is 2 months.[456]

When LV systolic dysfunction occurs in the setting of chronic RV pacing and no other cause of ventricular dysfunction is identified, the condition is called pacing-induced cardiomyopathy. In children, this cardiomyopathy is diagnosed in only 5% to 10% of patients who require RV pacing and is most often reported in those with congenital complete atrioventricular block.[457–459] LV dysfunction usually develops late after pacemaker implantation. The typical time to the development of cardiomyopathy may be ≥15 years. During ventricular pacing, the electric impulse is thought to be transmitted through non-Purkinje fibers, disrupting normal systolic fiber shortening, perfusion, and oxygen consumption.[460] An asynchronous and abnormal sequence of activation leads to abnormal LV systolic and diastolic function. When pacing-induced cardiomyopathy develops, changing to single-site pacing of the LV or upgrading to a biventricular system may promote ventricular remodeling and functional improvement.[461] In severe cases with advanced HF, cardiac transplantation may be necessary.

SUMMARY

The following summarizes key points from this scientific statement and provides general suggestions for clinical practice:

1. Given the lack of evidence and consensus in the classification and diagnostic evaluation of children with cardiomyopathy, the current work takes the form of a scientific statement instead of a clinical practice guideline. Thus, suggestions instead of recommendations are provided when indicated.
2. We suggest that the classification of cardiomyopathy in children should follow a morphofunctional approach with a hierarchy that starts at the top with the structural and functional phenotype familiar to the practicing cardiologist. Genetic and nongenetic causes are subcategorized.
3. The variety of causes of the different cardiomyopathies in children is large, and their frequency during childhood is not well delineated.
4. A comprehensive discussion of pathogeneses reported in the literature, even for conditions that are rarely seen, adhering to the hierarchical categorization under a morphofunctional classification system, is provided.
5. Because finding a cause is often elusive and may require the participation of multiple subspecialists such as electrophysiologists, geneticists, biochemical geneticists, mitochondria-metabolism experts, and endocrinologists, a step-by-step approach or decision-making algorithm to the diagnostic evaluation is not within the scope of this statement. It is the writing group's hope that the current statement will provide an impetus for such an effort in the future.
6. Nevertheless, the pathogenesis should be considered in children. A thorough history, a physical examination, detailed cardiac imaging, and attention to possible extracardiovascular abnormalities can aid the diagnostic evaluation. This is particularly relevant to infants in whom the early manifestation of cardiomyopathy and the lack of chronology to allow the underlying disease to evolve and declare itself may necessitate more comprehensive evaluation.

CONCLUSIONS

This scientific statement has addressed the classification and pathogenesis of pediatric cardiomyopathies. The classification and causes of cardiomyopathies presenting during the neonatal period and in infancy, childhood, and adolescence have some overlap with adult-onset cardiomyopathies but, in many cases, have very different pathogeneses, risk factors, and course, making the classification different from that in adult-onset cardiomyopathy. In this statement, we have not provided evidence-based guidelines for diagnostic strategies or treatment because of limited data. Rather, we have given a current perspective of the state of this field to illustrate what is known and where knowledge gaps exist for future discovery.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

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