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Pediatric and Congenital Heart Disease (G Singh, Section Editor)

An Update on Pediatric Cardiomyopathy

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Abbreviations *ACTA* Skeletal α-actin · *ACTC* Cardiac actin · *ACTN2* α-actinin · *DES* Desmin · *DMD* Dystrophin · *DSC-2* Desmocollin · *DSG-2* Desmoglein · *DSP* Desmoplakin · *JUP* Plakoglobin · *LMNA* Nuclear type A lamins · *MYH6* α-myosin heavy chain · *MYH7* β-myosin heavy chain · *MYHC7* β-myosin heavy chain · *MYBPC3* Cardiac myosin binding protein · *MYL3* Myosin cardiac ventricular essential light chain · *MYOZ2* Myozenin · *PKP-2* Plakophilin 2 · *RYR2* Ryanodine receptor · *SCN5A* Sodium channels · *TAZ* Tafazzin · *TGFβ-3* Transforming growth factor β · *TMEM43* Response element for PPAR gamma · *TNNT2* Cardiac troponin T · *TNNI3* Cardiac troponin I · *TNNC1* Cardiac troponin C · *TPM1* Tropomyosin · *TTN* Titin

Abstract

Purpose of review This review summarizes the clinical characteristics and updated outcomes of primary pediatric cardiomyopathies including dilated (DCM), hypertrophic (HCM), and restrictive cardiomyopathy (RCM), and briefly discusses left ventricular non-compaction (LVNC) and arrhythmogenic cardiomyopathy (ACM), primarily arrythmogenic right ventricular cardiomyopathy (ARVC).
Recent findings Pediatric cardiomyopathies are diseases of the heart muscle with an estimated annual incidence of 1.1–1.5 cases per 100,000. They are progressive in nature and are frequently caused by a genetic mutation causing a structural abnormality in the myocyte. Dilated cardiomyopathy, characterized by left ventricular dilation and systolic dysfunction with normal left ventricular wall thickness, accounts for about 50–60% of all pediatric cardiomyopathy cases. This is followed by hypertrophic cardiomyopathy accounting for about 40%, characterized by abnormally thickened myocardium in the absence of another cause of hypertrophy with non-dilated left ventricle. Left ventricular non-compaction and restrictive cardiomyopathy each account for about 5% of the cases. Genetic mutations play a dominant role in the development of pediatric cardiomyopathies. While treatment for congestive

heart failure and arrhythmias alleviates symptoms, it has not been shown to reduce the risk of sudden death. The 5-year transplant-free survival of DCM, HCM, RCM, and LVNC are 50%, 90%, 30%, and 60% respectively.

Summary Pediatric cardiomyopathies while not common they are a significant cause of morbidity and mortality in afflicted children. Dilated forms are the most common followed by hypertrophic, left ventricular non-compaction, and restrictive cardiomyopathies. Arrhythmogenic cardiomyopathies tend to be diagnosed later in the teenage years. Treatment typically follows adult recommendations for which there is significantly more data on treatment benefits, although the indications for ICD placement in children remain even less clear, other than for secondary prevention.

Introduction

Pediatric cardiomyopathies are diseases of the heart muscle with an estimated annual incidence of 1.1–1.5 cases per 100,000 patients from birth to 18 years of age [1, 2•, 3–5, 6•]. Cardiomyopathies can cause progressive systolic or diastolic heart failure or a combination of both leading to right, left, or biventricular dysfunction culminating in symptomatic congestive heart failure [2•, 5, 6•]. Although rare, they constitute a significant cause of morbidity and mortality in children. Cardiomyopathies are classified into two groups: (1) Primary cardiomyopathies in which the clinical disease process arises in the absence of other systemic comorbidities. These include dilated, hypertrophic, restrictive, left ventricular non-compaction, arrhythmogenic right ventricular cardiomyopathy, and mixed phenotype cardiomyopathies. (2) Secondary cardiomyopathies have pathological myocardial involvement as part of valvular, congenital heart disease, and generalized systemic disorders [1, 2•]. This review focuses on clinical characteristics and outcomes of primary pediatric cardiomyopathies including dilated, hypertrophic, and restrictive cardiomyopathy, and briefly discusses left ventricular non-compaction and arrhythmogenic right ventricular cardiomyopathy.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a progressive muscle disorder characterized by left ventricular dilation and systolic dysfunction with normal or reduced left ventricular wall thickness [7–9]. This accounts for about 50–60% of pediatric cardiomyopathy cases, with an annual incidence of 0.57 per 100,000 children [5, 6•,7, 8]. The presentation of children with DCM may range in severity from asymptomatic (as seen in echocardiographic family screening studies, wherein asymptomatic or mildly symptomatic family members may be identified) to acute congestive heart failure (CHF), which is more common, to frank cardiogenic shock due to poor systemic perfusion and a low cardiac output state. It is also the leading cause of heart transplantation (HTx) in children older than 1 year of age. Right ventricular dysfunction when present adds to the clinical severity of the disease.

Genetics and etiologies

In the late 1990s, Bowles and Towbin first suggested the concept of a "final common pathway" wherein cytoskeletal disruption and abnormalities in the linkage of the sarcomere were the underlying issue in the pathogenesis of various cardiomyopathies, including dilated cardiomyopathy [8, 10]. Approximately 30 to 35% of patients with a genetic form of DCM are described to have sarcomere gene mutations, and disease-causing genetic mutations are identified in about 35% of patients with DCM [11, 12, 13•, 14, 15]. The most common mutations implicated are LMNA, MYH7, TNNT2, SCN5A, and MYH6, all of which demonstrate autosomal dominant inheritance. Duchenne muscular dystrophy (DMD) and Barth syndrome are inherited in X-linked recessive fashion, due to mutations in the dystrophin and tafazzin (TAZ) gene, respectively. Acquired causes include idiopathic, myocarditis, exposure to alcohol, drugs like anthracyclines, toxins, metabolic storage diseases, autoimmune diseases, peripartum, and endocrine disorders such as hypothyroidism [2•, 7–9]. While myocarditis is considered a distinct disease process from idiopathic DCM, it is the second most common diagnosis associated with a new-onset DCM after the idiopathic variety.

Diagnosis

The diagnosis of CHF is based on symptoms of tachypnea, dyspnea, easy fatigability, nausea, vomiting, abdominal pain, decreased appetite, chest pain, palpitations, diaphoresis, and syncope [16]. Infants may present with failure to thrive, and a history of frequent respiratory illnesses and recurrent "pneumonia," with chest X-ray revealing cardiomegaly and pulmonary edema [2•, 8]. On physical examination, tachypnea with rales (less common in pediatric patients), tachycardia, S3 gallop, hepatomegaly, and a systolic murmur of mitral regurgitation are classic features. Brain-type natriuretic peptide (BNP) and its N-terminal fragment (NT-proBNP) are serum biomarkers that are usually elevated in proportion to the severity of heart failure.

Once CHF is identified, an echocardiogram helps make the diagnosis DCM. Echocardiographic parameters defining DCM include (1) ejection fraction < 45% or (> 2 SD below normal), or fractional shortening < 25% or (> 2 SD below normal) and (2) left ventricular end-diastolic diameter > 117% (> 2 SD above normal) of the predicted value of 112% corrected for age and body surface area [1, 2•, 8, 9]. Electrocardiogram (EKG) may demonstrate left ventricular or biventricular hypertrophy, left atrial enlargement, and sometimes, a prolongation of the QRS interval. Holter is commonly performed to evaluate for the presence of arrhythmias. Cardiac magnetic resonance (CMR) is commonly utilized for diagnosing myocarditis, using the Lake Louise criteria, classifying myocarditis as two out of the following three (1) edema, (2) hyperemia or increased capillary leak, and (3) late gadolinium enhancement [17]. Endomyocardial biopsy is now less frequently performed. Histologically in DCM, there are varying grades of focal disruption in myofibrils with the replacement of healthy tissue by fibrotic tissue, and muscle hypertrophy, eventually leading to disruption of cellular architecture [8, 9].

Clinical course and outcomes

Injured myocardium with diminished systolic function and cardiac output leads to the activation of compensatory neurohormonal mechanisms including the renin angiotensin aldosterone system, and the sympathetic nervous system. These mechanisms become maladaptive leading to adverse cardiac remodeling and are hence targets of medical management, in addition to decongestive therapies [8, 9]. Adult clinical trials have shown increased survival benefit with the use of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), βeta blockers (BB), aldosterone antagonists, and vasodilator/afterload reduction agents in patients with heart failure. Vasodilator therapy has shown to improve survival in patients with DCM which includes hydralazine and isosorbide dinitrate. Additionally, one should exclude secondary causes of dilated cardiomyopathy that warrant disease-specific therapies, for example, arrhythmia management in tachycardia-induced cardiomyopathy, and surgical treatment of the coronary artery anomaly in those with anomalous origin of left coronary artery from the pulmonary artery [2•].

Genetic testing for dilated cardiomyopathy should be offered to first degree relatives of the index case [18]. Of note, an index case with a negative genetic test result does not mean the patient does not have a genetic disease, as there remains the possibility that a mutation could be present in a non-tested gene [13•].

Pediatric patients with DCM have a 2–3% incidence of sudden cardiac death within 5 years of diagnosis, and up to 5% incidence at 15 years after diagnosis [19, 20]. Factors associated with sudden cardiac death include younger age at diagnosis, larger left ventricular end-diastolic dimension, and echocardiographic parameters of thinning and inadequate hypertrophy of the left ventricle including thin left ventricular posterior wall and low ratio of left ventricular posterior wall to left ventricular end-diastolic dimension. Implantable cardioverter-defibrillator (ICD) implantation for prevention of lethal arrhythmias and sudden cardiac death should be considered in select patients including patients with prior cardiac arrest or sustained ventricular tachycardia [19, 20].

Patients who are refractory to medical therapy may benefit from mechanical circulatory support and heart transplantation. Pediatric patients with DCM have a 5-year HTx-free survival of approximately 55–60% from time of diagnosis [21–24]. Predictors for these adverse outcomes include presentation in neonatal period or at age > 5 years, lower fractional shortening at presentation, and family history of DCM. However, patients with DCM can also exhibit normalization of left ventricular size and function. The Pediatric Cardiomyopathy Registry (PCMR), a multi-center national registry of children with cardiomyopathy, study reported normalization in 22% of the patients at 2 years from diagnosis over a 22-year study period [25]. Factors associated with normalization of left ventricular echocardiographic parameters include younger age at diagnosis and the diagnosis of myocarditis. Children with a new-onset DCM with a diagnosis of myocarditis also have a lower risk for HTx or death compared to those with idiopathic DCM [26]. Further, transplant-free survival of patients with DCM in the recent era is significantly improving, even with similar transplantation rates, likely due to multiple factors including earlier

recognition of heart failure, earlier medical management, and the growing scope and use of ventricular assist devices [27].

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is the second most common pediatric cardiomyopathy, accounting for about 40% of patients [2•, 28–31]. It is characterized by abnormally thickened myocardium with a non-dilated left ventricle in the absence of another cause capable of producing hypertrophy (e.g., aortic stenosis, or systemic hypertension), with a classic histologic finding of "myocardial disarray" [1, 30]. HCM may be further classified into inherited HCM (with gene mutation identified), idiopathic HCM, and HCM associated with inborn errors of metabolism, syndromes like Noonan syndrome, or neuromuscular disorders [30–32]. The former two types are the most common and comprise about 70–75% of the cases.

Genetics and etiologies

Pathogenic mutations are identified in about 50% (up to 75% in some series) of the cases of HCM, with almost all being in sarcomere or sarcomere-related protein producing regions [28, 29, 33]. The most common genes involved with the strongest pathogenicity include MYHC7, MYBPC3, MYL2, MYL 3, TNNT2, TNNI 3, TNNC1, TPM1, ACTC, ACTN2, and MYOZ2. Inheritance is typically autosomal dominant, with a notable exception of the LAMP2 mutation causing Danon Disease which is X-linked dominant and is typically fatal by young adulthood. The presence of sarcomeric mutation is an independent risk factor for adverse outcomes including clinical heart failure, admissions for heart failure, and transplant or death [29, 33–35].

Inborn errors of metabolism that lead to HCM include Pompe disease (acid maltase deficiency) and Fabry disease (alpha-galactosidase deficiency), which are autosomal recessive in inheritance [30, 32]. Syndromes associated with HCM include Noonan syndrome (and other RASopathy syndromes), which may present in infancy, often with biventricular hypertrophy, and Freidrich's ataxia, which has progressive hypertrophy throughout childhood with decreasing systolic function in adolescence [30, 32].

Diagnosis

HCM is diagnosed on echocardiography, which may be performed due to abnormal screening EKG, chest pain or discomfort during exercise, murmur, or symptoms of heart failure [28–31, 36]. Screening echocardiograms should then be done in all first degree relatives of patients diagnosed with HCM, which may reveal abnormalities. Concerning features on echocardiography include pathologic ventricular hypertrophy (z-score $> +2.5$), systolic anterior motion of the mitral valve, dynamic left ventricular outflow tract obstruction, abnormal diastolic filling indices, and abnormally low left ventricular cavity size.

The proband should undergo genetic testing. If the proband has a pathogenic mutation, then the parents should be screened for the mutation with genetic counseling pursued, to determine whether or not the proband has a de

novo mutation, and the need for sibling genetic testing. If a genetic mutation is identified, the screening echocardiograms may be performed in first degree relatives positive for the mutation. If no genetic mutation is identified, screening echocardiograms should be performed in all first degree relatives of the proband. These echocardiograms may reveal pathology, but also may yield a normal result. Such normal echocardiograms in gene-positive patients have led to the designation of a new cohort of HCM patients, who are "genotype positive phenotype negative" [28]. These patients are at risk of converting to a hypertrophic phenotype and hence are followed every 2–3 years until the age of 30 years, barring the period of pubertal growth when they are followed at least annually. There are also recent studies showing gene positive/phenotype negative patients can have abnormal CMR findings even in the setting of normal echocardiograms, with increased transmural circumferential strain difference as well as impaired left atrial emptying reflecting abnormal diastology [37, 38].

There is a growing body of knowledge about the utility of CMR in HCM diagnosis and prognosis. Late gadolinium enhancement indicating fibrosis and scarring on CMR are present in nearly half of the patients with echocardiographic HCM, and lend weight to a higher risk of sudden cardiac death, prompting a sooner discussion about placement of an ICD [39, 40].

Patients with HCM are at risk for ventricular arrhythmias due to multiple factors, including the disorganized myocardial architecture, elevated left ventricular end-diastolic pressures, and compromised coronary perfusion especially during higher heart rates. Holter monitoring to assess burden of ventricular or atrial ectopy in their diagnostic process guides their prognosis as well as management [32, 36].

Clinical course and outcome

Patients with HCM can range from being asymptomatic to findings of CHF, aborted sudden cardiac arrest, or presenting as a sudden death. Additionally, left ventricular diastolic dysfunction can lead to progressive left atrial enlargement that can predispose the HCM patient to atrial arrhythmias and pulmonary hypertension. Older children with HCM may experience progressive left ventricular dysfunction and dilation also known as "burned out HCM" with a transition to dilated phenotype and chronic systolic heart failure over time [32, 36].

Reversible myocardial ischemia and perfusion defects occur commonly in HCM, especially during exercise or higher heart rates, leading to the symptoms of chest pain, dyspnea, light-headedness, or syncope [32, 36]. Management of HCM hinges on managing these symptoms, optimizing hemodynamics to minimize dynamic left ventricular outflow tract obstruction, and reducing risk of sudden cardiac death. Beta blockers are usually first-line for symptom management, and help by reducing the heart rate hence decreasing the myocardial oxygen demand as well as allowing better left ventricular filling and lesser dynamic outflow tract obstruction. Patients are also advised to avoid high-intensity exercise, which is commonly when they are most symptomatic. Diuretics are usually avoided, even though there is left atrial hypertension, as volume depletion will worsen ventricular filling, and the goal in HCM is to keep the heart "slow" and "full." Simple childhood illnesses of gastroenteritis or bronchiolitis with increased volume losses are thus higher risk for the pediatric HCM patient [32, 36]. However, later in the course of disease, judicious use of diuretics may be needed to manage the symptoms of left atrial hypertension and CHF.

The risk of sudden death in pediatric HCM has been the topic of much discourse [28–32, 41–43]. The established risk factors from adult studies include septal thickness > 30 mm, history of aborted cardiac arrest with documented ventricular fibrillation or tachycardia, fall or less than 20 mmHg rise in blood pressure during exercise, history of syncope, history of non-sustained ventricular tachycardia, and family history of sudden cardiac death [36]. However, in the pediatric HCM population, these factors are still under investigation. In a recent study of 100 patients with pediatric-onset HCM, 24 patients had potentially lethal arrhythmic events, at a rate of 1.9% per year [41]. These events were associated with the presence of mutations in Troponin I or T genes, and with the presence of heart failure symptoms at diagnosis. Two patients had lethal arrhythmic events even in the presence of an ICD. The threshold for ICD implantation in pediatrics is also a matter of debate. In a large registry of 224 pediatric HCM patients who received ICD implantation from 1987 to 2001, a total of 19% experienced appropriate discharges, from time periods ranging from 1 day to 8.6 years after implantation [42]. There was one death during the follow-up period related to ventricular arrhythmia that could not be aborted by the device. Of note, 86% of the patients who received appropriate shocks were also on anti-arrhythmic therapy. Further, the hesitation towards ICD in pediatric HCM patients is due to the side effect profile with device-related as well as psychosocial complications. In this study, 28% received inappropriate shocks while another 12% suffered device-related complications including lead fracture/dislodgement, bleeding complications, or infection [42]. Thus, by general consensus, two or more risk factors are considered before placing an ICD in the pre-adolescent, while in an adolescent or young adult, a single factor may be enough to prompt strong consideration of an ICD [36, 42].

A gradient of more than or equal to 30 mmHg across the left ventricular outflow tract in a patient with HCM is associated with progressive heart failure symptoms and cardiovascular death [36]. Dynamic sub-aortic obstruction in HCM is associated with asymmetric septal hypertrophy with the anterior motion of the mitral valve. Left ventricular outflow tract obstruction may be addressed surgically or by a less invasive strategy, if the gradient is greater than 50–60 mmHg in a symptomatic patient [44–49]. Surgical septal myectomy helps in improving the gradient and subsequently symptoms; however, the obstruction may recur in children undergoing this procedure in infancy or early childhood, and there is persistent septal anterior motion of the mitral leaflet and/or moderate mitral regurgitation in 20–30% of the patients in various series [45–46]. Transcatheter infusion of absolute alcohol into the septal perforator coronary branches creates a deliberate local infarction leading to reduced septal thickness. Studies have shown good results from septal ablation in reducing outflow tract gradient in adults as well as pediatrics, with about 10% risk of needing a pacemaker, and a 95% survival at 5 years [47–48]. Two studies reported low sudden death rate following septal reduction therapies, with one reporting a reduced sudden death rate compared to conservative therapy [44, 49]. Finally, in HCM associated with inborn errors of metabolism (Pompe disease and other lysosomal storage disorders), treatment with enzyme replacement therapies has been shown to be beneficial in preventing progression of phenotype [50, 51].

Genetic screening is indicated in all first degree relatives of patients with HCM, to enable timely diagnostic testing and follow-up [13]. Overall

transplant-free survival in HCM patients is greater than 80% at 5 years from diagnosis; however, it varies significantly with the age at diagnosis [31, 52]. Infants diagnosed with HCM have a 5-year HTx-free survival of just under 80%, while those diagnosed older than 1 year of age have a 5-year HTx-free survival of over 95%. Survival also worsens with mixed phenotypes, with HCM patients with dilated or restrictive phenotypes having a 5-year HTx-free survival around 55%, while those with HCM associated with inborn errors of metabolism have a 5-year HTx-free survival of about 30% only [41, 52]. Across phenotypes, in addition to young age, other factors associated with transplant or death include lower weight, presence of congestive heart failure, lower fractional shortening, and increased end-diastolic left ventricular posterior wall thickness [31, 43, 52].

Restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a rare pediatric entity, accounting for 5% or less of pediatric cardiomyopathy cases [2, 5, 6, 53]. It is characterized by severely impaired ventricular diastolic function with increased atrial volumes and preserved systolic function, in the setting of normal or low ventricular volume and normal atrioventricular valves [1, 2•]. Patients have elevated left ventricular end-diastolic pressures (classically distinguished from constrictive physiology by left ventricular end-diastolic pressures being higher than the right ventricle, and the right ventricular systolic pressures being > 60 mmHg). Approximately a third of these patients may also have features of hypertrophic cardiomyopathy.

Genetics and etiologies

Several genes have been implicated in RCM, with genetic causes identified in 10–60% of patients [10, 13•]. Leading mutations include MYH7, TNNI3, TNNT2, MYL2, and DES. RCM may also be associated with systemic diseases including post radiation and chemotherapy and/or bone marrow transplantation.

Diagnosis

The diagnosis of RCM is suspected based on the finding of usually marked biatrial enlargement and restrictive physiology features on echocardiogram in patients typically presenting with congestive heart failure symptoms (due to left atrial hypertension from the impaired diastolic function) or syncope/cardiac arrest [2•, 53]. Cardiac catheterization may be needed to help distinguish from constrictive physiology and assess for pulmonary hypertension. A key feature is pulmonary hypertension with elevated pulmonary vascular resistance in these patients, which has been reported to be more severe in those with isolated RCM features compared to those with combined HCM and RCM features [53].

Clinical course and outcome

Historically, the prognosis assigned to patients with RCM has been grim due to the risk of sudden death and progression of pulmonary vascular disease, leading to early listing for HTx [5, 6•, 53, 54]. Initial medical management strategies include judicious use of diuretics for decongestion, anti-arrhythmic management

including medication and devices, and anti-thrombotic agents. ACEi and/or ARBs may be adjuvants in cases in which systolic function is also impaired, but these patients can be more susceptible to their blood pressure lowering effects without benefit of increased cardiac output. Patients with elevated pulmonary vascular resistance are sometimes started on pulmonary vasodilators (phosphodiesterase inhibitors) in combination with diuretics, but again caution is advised as pulmonary edema may ensue due to persisting left atrial hypertension and increased pulmonary blood flow resulting in worsening of symptoms.

While the 5-year overall survival ranges from 70 to 86%, the 5-year transplant-free survival is ~ 30% [5, 6•, 53, 54]. Features of CHF, depressed systolic function at presentation, and higher left ventricular posterior wall thickness in patients with RCM/HCM combination phenotype have been found to be risk factors for death or HTx, while smaller studies have also shown younger age and isolated RCM phenotype as risk factors for death [53, 54]. Arrhythmias and embolic phenomenon are a clinical concern in these patients in the setting of the dilated atria. Arrhythmias have been reported in up to 60% of these patients, with 7% receiving anti-arrhythmic therapy while 40% receive implantable cardioverter-defibrillator device implantations (although therapies by the device are rare) [54]. The true risk of embolic phenomenon in pediatric patients with RCM is difficult to assess, as ~ 50% of the patients in the reported series are already on anticoagulation and/or anti-platelet agents, and they typically undergo early listing and HTx due to poor transplant-free survival. Of note, neither arrhythmias or aborted sudden death events, nor stroke have been found to be risk factors for death or transplant in this cohort [2•, 53, 54]. This may be due to relatively small numbers. Post-transplant outcomes of pediatric RCM recipients are comparable to those transplanted for other indications [53].

Left ventricular non-compaction cardiomyopathy

Left ventricular non-compaction (LVNC) comprises approximately 5% of pediatric cardiomyopathies [1, 2•, 5, 6•, 55]. In a report from the Pediatric Heart Transplant Study Group (PHTS), about 4% of the patients listed for heart transplant between 2005 and 2013 had LVNC [56]. It is characterized by a non-compacted, "spongy" appearing myocardium on echocardiography, with prominent myocardial fronds or trabeculations, with deep recesses in between, and only a thin layer of compacted normal appearing myocardium on the epicardial side [55, 57].

Genetics and etiologies

Several genes have been implicated in LVNC, with the most common ones being MYH7, TTN, MYBP3, and TAZ [13•, 57, 58]. Having more than one pathogenic mutation is associated with worse clinical outcomes and greater risk of heart failure progression [57, 58]. LVNC may also be associated with systemic disorders including Barth syndrome (specifically with the TAZ mutation), other mitochondrial disorders, and neuromuscular dystrophies. Genetic testing for LVNC may also be guided by the secondary phenotype of the patient (for, e.g., mixed dilated or hypertrophied phenotype). In mixed phenotypes, testing for genes relevant to DCM or HCM phenotype should also be considered. Finally,

there is growing data on the co-existence of LVNC with congenital heart disease (CHD), with adult studies reporting CHD in 10–20% of LVNC cases, as well as evidence that non-compaction may be associated with worse clinical outcomes and progression to heart failure in palliated CHD patients [57, 59, 60].

Diagnosis

The diagnosis of LVNC is made based on echocardiography or, more recently, cardiac MRI findings [55, 57]. The most common diagnostic criteria are the Jenni criteria, based on the ratio of non-compacted to compacted myocardium greater than 2:1, prominent trabeculations in the apical/mid-lateral/mid-inferior regions, and color flow evidenced in the intertrabecular recesses in connection with the true left ventricular cavity. These lines seem to have a different spacing or alignment than the rest of the document. Could you please help make this alignment/spacing the same as the rest of the text? all of which are measured at end-diastole [55, 57].

Clinical course and outcome

LVNC can have a waxing and waning clinical course [55, 61, 62]. While a cohort presenting in infancy can have a more aggressive course and may need heart transplantation, a majority presenting in childhood or adolescence may have no clinical findings other than abnormal strain pattern on echocardiography, although dysfunction may progress [55, 61, 62].

Medical management strategies include ACEi, ARB, and beta blocker in the cohort with depressed ventricular function and dilation, supported by diuretics for those with signs of volume overload. While there is evidence to show that reverse remodeling therapies improve the systolic function as measured on echocardiography in pediatric LVNC patients, their impact on admission rates, transplant-free survival, or mortality has not been reported [63]. Finally, there is a concern for stasis in the intertrabecular recesses being a nidus for thrombus formation, and Oeschlin et al. reported 24% of their series of 34 adult patients suffering from thromboembolic complications [64]. Although there are case reports describing the use of anticoagulants in patients with LVNC with a history of thromboembolic complications, guidelines for their use have not been established [65, 66].

The overall 5-year HTx-free survival for this cohort has been reported to be from ~ 60% up to 86% [61, 62]. Patients with younger age, dilated phenotype, and depressed systolic function have worse outcomes. Fortunately, patients with LVNC have comparable outcomes after HTx compared to their DCM counterparts, with similar waitlist mortality as well as post-HTx freedom from rejection [56]. Interestingly, there was no difference in the burden of arrhythmia or stroke at time of listing, even though there is concern about the high risk of both these comorbidities in the LVNC cohort [56, 67].

Arrhythmogenic cardiomyopathy

Diseases of the myocardium that are typically characterized by their arrhythmic substrate are now termed as arrhythmogenic cardiomyopathy

(ACM). ACM is a relatively rare inherited cardiomyopathy characterized by progressive infiltration and subsequent replacement of the myocardium with fibrous and fatty tissue. This was initially described in the right ventricular myocardium, leading to the terminology of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) [2•, 68]. However, now there is growing evidence of the involvement of the left ventricle as well [2•, 69]. Its prevalence is estimated at 1 in 5000 adults, and pediatric studies are limited to case series [68, 69, 70]. Although it is typically diagnosed in adulthood, with median age of presentation in the third decade of life, it may present in the pediatric population with ventricular arrhythmias or sudden death, leading to cardiac imaging which yields the diagnosis.

Genetics and etiologies

Several gene mutations involving cardiac desmosomal and non-desmosomal proteins have been implicated in the pathogenesis of ACM/ARVC including PKP-2, DSG-2, DSC-2, DSP, TGFb3, JUP, TMEM43, and RYR-2 [13•, 71]. These are most commonly inherited in autosomal dominant fashion, except for recessive variants of mutations in DSP (Carvajal syndrome), DSC2, and JUP (Naxos syndrome). Recently, Van Der Zwaag and colleagues published that phospholamban R14del mutation may account for the crossover clinical phenotypes seen in ACM/ARVC and DCM [72].

Diagnosis

In the adolescent and young adult population, ACM/ARVC is a differential diagnosis for premature ventricular contractions or ventricular tachycardia originating from the right ventricular outflow tract, sudden cardiac death, or for abnormal findings (e.g., prolonged QRS, epsilon wave, inverted T-waves in V2-V3) found on screening electrocardiograms [68, 69, 70, 73, 74]. The modifications to the original criteria defined by the Task Force of the Working Group Myocardial and Pericardial Disease of the European Society of Cardiology and of the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology in 2010 have streamlined the diagnostic criteria for ACM/ARVC, taking into consideration global as well as segmental dilation or hypokinesis/akinesis of the right ventricle, as well as features of the electrocardiogram and relevant family history [73, 74].

Symptoms of ACM/ARVC may overlap with the symptoms of DCM posing a challenge to distinguish these 2 clinical phenotypes [68, 70, 75]. Although heart failure is not a component of the 2010 modifications to the Task Force criteria, left ventricular involvement is being increasingly recognized in adults with ARVC/D, with estimated prevalence up to 20% [75–77].

Clinical course and outcomes

Initial management of ACM/ARVC is governed by the symptoms, primarily targeting arrhythmia management and reduction of risk of sudden cardiac

death [68, 70, 75]. Anti-arrhythmic medications have been shown to reduce arrhythmia burden, and there are emerging reports of ablation in the electrophysiology laboratory to temporize symptoms from foci of ectopy [70, 78]. However, due to the progressive nature of the disease and the inherent risk of sudden death, neither of these therapies eliminates the risk of sudden cardiac arrest. Implantation of an ICD is indicated in patients with aborted sudden cardiac death, syncope, or hemodynamically unstable ventricular tachycardia [68, 75]. In other cases, it is an individualized decision, depending on extent of ventricular myocardial involvement, ectopy burden, and family history.

Classically, findings of right ventricular failure and congestion are the culminating step in the evolution of ACM/ARVC, as increasing amounts of the myocardium are replaced with transmural fibrofatty tissue, and conduction as well as contractile functions cease to operate normally. Competitive exercise is contraindicated in all patients with ACM/ARVC, to minimize the stress on the intercellular connections in the myocardium which are already abnormal in these patients.

Left ventricular myocardium involvement in patients with ACM/ARVC has been reported from 20% up to 75% in various series [75–77]. The left ventricle is also suspected to be involved early in even asymptomatic patients, which makes it more relevant for the pediatric population. Chungsomprasong et al. reported their findings from a study with 142 pediatric patients who underwent CMR for ARVC evaluation, of whom about a third had cardiac symptoms or arrhythmias [77]. Overall 61% were diagnosed with possible, borderline, or definite ARVC, with left ventricular global circumferential strain being lower and end-diastolic volumes being higher in patients who had higher scores per the revised Task Force criteria. Furthermore, over serial CMR studies in 48 of these patients, the increase in left ventricular end-diastolic dimension correlated with the increase in right ventricular end-diastolic dimension, and the decrease in left ventricular ejection fraction correlated with the decrease in right ventricular ejection fraction. This may have bearing on a potential for early introduction of reverse remodeling agents in these patients. A subset of patients with ACM/ARVC will require HTx. They have similar post-HTx outcomes when compared to other cardiomyopathies [79].

Conclusion

In this review, we discussed salient features and emerging data about pediatric cardiomyopathy. While not common, they are a significant cause of morbidity and mortality in afflicted children. Dilated forms are the most common followed by hypertrophic, left ventricular non-compaction, and restrictive cardiomyopathies. Arrhythmogenic cardiomyopathies tend to be diagnosed later in the teenage years. Genetic mutations play a dominant role in the development of pediatric cardiomyopathies, and genetic counseling is an integral part of these patients' work-up and management. Treatment typically follows adult recommendations for which there is significantly more data on treatment benefits, although the indications for ICD placement in children remain even less

clear, other than for secondary prevention. While much has been learned, significant knowledge gaps persist requiring ongoing research to optimize outcomes for these children.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807–16.
2.• Lee TM, Hsu DT, Kantor P, Towbin JA, Ware SM, Colan SD, et al. Pediatric cardiomyopathies. Circ Res. 2017;121(7):855–73.

This is a recent article reviewing the four major categories of pediatric cardiomyopathy and their complications and outcomes.

3. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003;348(17):1647–55.
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This article review the results from the pediatric cardiomyopathy registry (PCMR), a multi-center registry including the USA and Canada founded in 1994. This includes the etiology of cardiomyopathy, clinical course, and outcomes of 3500 patients under 18years of age, and also describes the avenues for further investigation.

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