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# Clinical Characteristics and Treatment of Cardiomyopathies in Children

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**Abstract:** Cardiomyopathies are diseases of the heart muscle, a term introduced in 1957 to identify a group of myocardial diseases not attributable to coronary artery disease. The definition has since been modified to refer to structural and or functional abnormalities of the myocardium where other known causes of myocardial dysfunction, such as systemic hypertension, valvular disease and ischemic heart disease, have been excluded. In this review, we discuss the pathophysiology, clinical assessment and therapeutic strategies for hypertrophic, dilated and hypertrophic cardiomyopathies, with a particular focus on aspects unique to children.

**Keywords:** Children, cardiomyopathy, heart failure.

## DILATED CARDIOMYOPATHY

### Introduction

The dilated form of cardiomyopathy is typically characterized by ventricular chamber enlargement with systolic dysfunction. The wall thicknesses of the myocardium are usually normal and mitral regurgitation is common [1]. This pathology usually leads to the development of signs and symptoms of congestive heart failure. The disease frequently progresses to end-stage heart failure and death unless cardiac transplantation is performed.

### Etiology and Epidemiology

In the United States, the annual incidence of dilated cardiomyopathy (DCM) in children is 0.57 cases per 100,000 per year [2]. This is much lower than what has been reported in adults. Boys have a greater incidence of DCM than girls (0.66 vs 0.47 per 100,000) due to X-linked causes and neuromuscular disorders [1]. Black children are also more likely to be affected than white children (0.98 vs 0.46 cases per 100,000). Most cases of DCM in children are idiopathic but various inherited and acquired factors are causative (Table 1). Approximately 20-50% of children have a familial form of DCM. These patients have a genetic mutation that results in a disease of the myocardium. Mutations that result in DCM are usually inherited in an autosomal dominant fashion but may be inherited in an X-linked or autosomal recessive pattern. Frequently, the mutation occurs spontaneously in a family with no history of cardiomyopathy. The most common cause of acquired DCM is myocarditis. In children, myocarditis usually results from a virus or other infectious agent. Viruses such as enterovirus, parvovirus and adenovirus are frequently implicated. Non-infectious agents, such as drugs or toxins, can also cause myocarditis and result in a dilated form of cardiomyopathy.

### Pathophysiology

In DCM, an injury or insult to the myocardium causes diminished ventricular function, chamber enlargement and mitral regurgitation, all of which contribute to ventricular remodeling [3]. Altered hemodynamics lead to an upregulation of neurohormonal systems. Stimulation of the sympathetic nervous system and the renin-angiotensin-aldosterone system as well as the non-osmotic release of arginine vasopressin serve as adaptive mechanisms for restoring adequate vascular volume and blood pressure. While activation of counter regulatory systems occurs, including the release of natriuretic peptides, alterations in ventricular loading conditions that are beneficial in the short term contribute over time to ventricular remodeling and further decrements in ventricular function. The constellation of changes leads to the onset of symptoms recognized as the clinical syndrome of heart failure.

### Clinical Presentation

Heart failure in children with DCM may manifest as other common diseases of childhood such as asthma and gastroenteritis [4]. The majority of verbal pediatric patients with heart failure complain of dyspnea (either at rest or with exertion), fatigue or general malaise, and nausea or vomiting. Other common complaints include cough, abdominal pain and chest pain. The signs of heart failure observed on physical examination may be subtle. Vital signs are commonly abnormal and include tachycardia and tachypnea. Blood pressure, however, is usually preserved. Children typically

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present with features of congestion, such as hepatomegaly and a gallop rhythm. Peripheral edema, crackles, ascites and jugular venous distention are less common. Signs of compromised end-organ perfusion may be present, such as delayed capillary refill and cool distal extremities. An incompetent mitral valve can cause a blowing holosystolic murmur heard best at the apex and clavicular line.

### Diagnostic Studies

Traditional diagnostic studies such as chest radiograph and electrocardiogram (ECG) can help establish a diagnosis of DCM. On chest radiograph, the cardiac silhouette is usually enlarged and a lateral film may demonstrate left atrial enlargement. Some patients with DCM and heart failure have abnormal lung fields characterized by increased pulmonary vascular markings, alveolar edema and pleural effusions. If the onset of ventricular dysfunction was gradual enough there may not be appreciable pulmonary edema despite markedly elevated left-sided pressures. The ECG is non-specific for DCM but can sometimes reveal cardiac rhythm disturbances, especially in patients with advanced disease. It is not unusual to find supraventricular tachycardia, atrial flutter, ventricular tachycardia or high-degree AV block on ECG.

The echocardiogram is the most important test for establishing a diagnosis of DCM. It will provide important information regarding ventricular size and function. Most patients with DCM will have an ejection fraction of less than 50% (or shortening fraction of less than 25%). In infants with a new diagnosis of heart failure, it is absolutely necessary to evaluate the coronary arteries to rule out anomalous left coronary artery arising from the pulmonary artery. In patients with left ventricular noncompaction, excessive trabeculations and recesses in the myocardium of the left ventricular apex and free wall will be seen on echocardiogram. Significant ventricular dilation can lead to mitral valve annulus dilation, causing mitral regurgitation and left atrial enlargement.

## Medical Management of Dilated Cardiomyopathy

Management strategies should focus on amelioration of symptoms, when present, and prevention of hemodynamic perturbations that may cause an exacerbation of heart failure symptoms. Frequent follow up, good patient and parent education, compliance with medications and the prescription of standard of care pharmacologic therapies are of paramount importance for maintaining the patient in optimal condition prior to transplantation.

Few prospective trials have been performed assessing the safety and efficacy of medications for the treatment of congestive heart failure in children. The International Society for Heart and Lung Transplantation established treatment guidelines for pediatric heart failure in 2014, relying heavily on adult trial data [5].

## Medical Management of Chronic Heart Failure

### Antagonism of the Renin-Angiotensin System

Inhibition of the angiotensin-converting enzyme (ACE) is considered a mainstay of therapy for both symptomatic and asymptomatic adult patients. Numerous studies have demonstrated improved functional status, decreased hospitalization and reduced mortality rates in patients with systolic heart failure, offering strong evidence for the use of ACE inhibitors as standard care [6-11]. The ACC/AHA executive summary recommends that ACE inhibitors be used in all patients with a reduced ejection fraction, with or without symptomatic heart failure.

Little is known about the effect of ACE inhibition in children with ventricular dysfunction. Enalapril may reduce left ventricular wall stress and improve function in children with ventricular dysfunction resulting from chemotherapy [12, 13]. Captopril acutely increases cardiac output in children with dilated cardiomyopathy, but long-term hemodynamic benefits have not been reported [14]. Mortality may be reduced in infants and children with cardiomyopathy treated with ACE inhibitors. Lewis *et al.* reported a significant improvement in survival up to 2 years after initiation of therapy among 27 patients treated with ACE inhibitors compared to children who received conventional medical therapy [15].

### β-Adrenergic Receptor Blockers

Although viewed with skepticism several years ago, β-blocker therapy in patients with left ventricular dysfunction has become standard of care and probably the most important addition to the current armamentarium of medical therapy for heart failure. During the 1970s and 1980s, several small trials demonstrated the clinical benefits of β-blocker therapy [16-19]. Subsequent prospective randomized trials have since demonstrated the safety and efficacy of β blockade and their overall beneficial impact on symptoms and outcomes [20-31]. Carvedilol is the most studied and widely used β-blocker for the treatment of heart failure in adults. It is a "third generation" β-adrenergic blocker with vasodilatory and anti-oxidant properties. Parker and colleagues conducted one of the landmark studies evaluating the efficacy of carvedilol on morbidity and mortality in patients with congestive heart failure [32]. In this randomized, double-blind trial carvedilol was found to lower the risk of mortality by 65% compared to placebo and its use was associated with a 27% reduction in the risk of hospitalization for cardiovascular causes.

Unlike the adult literature, few data have been published demonstrating the safety or efficacy of β-blocker therapy in children with heart failure [33-43]. The only relatively large randomized controlled of β-blockers in children was performed by the Pediatric Carvedilol Study Group [44]. In this study, 161 children age 3 months to 17 years with symptomatic ventricular dysfunction were randomized to receive either carvedilol or placebo. Changes in clinical status were determined by such measures as death, hospitalization for symptomatic exacerbation, functional class, and global-assessment scores. Carvedilol did not significantly improve outcomes in children and adolescents although there were significant limitations to the study, including limited enrollment and the inclusion of patients with a history of congenital heart disease [45].

### Digoxin

Historically, digoxin has been used as a first-line therapy in children with ventricular dysfunction with or without symptoms of heart failure. This treatment approach seems rational given the purported benefits of digoxin, including enhanced inotropy, possible neurohormonal attenuation and rate control in adults with atrial fibrillation. However, there are no data showing decreased mortality with digoxin in the treatment of chronic heart failure. In children, data are lacking for any type of benefit from digoxin when used in patients with ventricular dysfunction. Based on adult studies, the ISHLT has recommended that digoxin be employed in pediatric patients with ventricular dysfunction and symptomatic heart failure.

The HFSA guidelines for adults recommends that "digoxin should be considered for patients with LV systolic dysfunction (LVEF <40%) who have signs or symptoms of heart failure while receiving standard therapy, including ACE inhibitors and β-blockers". The strength of this recommendation rests almost entirely upon one trial, the Digitalis Investigation Group (DIG) study [46]. In the DIG study, 6,800 patients with chronic heart failure who were treated with ACE inhibitors and diuretics were randomized to receive either digoxin or placebo. The primary endpoint of the study was all-cause mortality, assessed over an average follow-up of 3 years. Digoxin did not reduce all-cause mortality, but did significantly reduce the number of patient hospitalizations and co-interventions, such as an escalation in therapies with diuretics or ACE inhibitors or the addition of new therapies, from 35% in the placebo group to 27% in the treatment group. However, upon further analysis of patients evaluating the health-related quality of life revealed that at 12 months, there was no statistically significant difference in perceived health, physical functioning, depression, anxiety or the 6-minute walk between the digoxin and placebo groups [47]. Other studies have also shown clinical improvement in patients treated with digoxin [48, 49].

Recent evidence has suggested that the dose of digoxin should be lower than what has traditionally been prescribed [50]. Adams *et al.* examined the relationship between serum digoxin concentrations (SDC) and clinical efficacy in patients with symptomatic left ventricular dysfunction [51]. Multiple regression analysis failed to find a relationship between serum digoxin concentration and primary end-points such as worsening heart failure, change in left ventricular ejection fraction and exercise tolerance.

### Diuretics

Although no large trials have been performed assessing the efficacy of diuretic therapy on mortality, it remains a fundamental part of the outpatient management of heart failure [52]. Certainly, diuretics can effectively reduce circulatory congestion in patients with heart failure, but not all patients, especially children, develop symptomatic fluid retention as outpatients. The ISHLT guideline for the treatment of heart failure in children recommends that "patients with fluid retention associated with ventricular dysfunction should be treated with diuretics to achieve a euvolemic state using clinical criteria of fluid status and cardiac output [5]". An attempt should be made to discontinue diuretic therapy once the patient has adequate diuresis and shows no signs or symptoms of heart failure. Electrolyte disturbances are common in patients treated with diuretics, including hyponatremia, hypokalemia, hypocalcemia and hypomagnesemia. Metabolic abnormalities such as metabolic alkalosis, dehydration and nephrocalcinosis may also occur. In addition, diuretic therapy may lead to further activation of the renin-angiotensin-aldosterone axis, possibly further potentiating the adverse impact of neurohormonal activation on the progression of heart failure [53, 54].

A landmark study by Pitt *et al.* demonstrated the beneficial effects of potassium-sparing diuretic spironolactone in patients with severe congestive heart failure [55]. The Randomized Aldactone Evaluation Study (RALES) enrolled 1,663 symptomatic patients with left ventricular systolic dysfunction and an ejection fraction <35%. The investigators found a 30 percent risk reduction in death among patients treated with spironolactone compared to patients receiving placebo. In addition, patients who received spironolactone had a significant improvement in the symptoms of heart failure (NYHA class). The exact reason that chronic antagonism of aldosterone provides such beneficial effects is not fully understood, but it is likely not due to the diuretic effect alone. Attenuation of myocardial interstitial fibrosis, treatment of hypertension and inhibition of cytokine production may also play a role in reducing mortality.

### Arrhythmia Management

Arrhythmias are common in adult patients with heart failure and it is thought that the majority of sudden deaths in this population are due to ventricular tachyarrhythmias. Myocardial fibrosis, scar, ischemia and electrolyte disturbances provide ample opportunity for abnormal electrical conduction. Children with heart failure are also at risk for tachyarrhythmias [56-60]. Anti-arrhythmic therapies, however, have not shown efficacy in reducing mortality in patients with heart failure [61-64]. Though amiodarone has potentially serious side effects, including pulmonary fibrosis, thyroid abnormalities, hepatotoxicity and ophthalmic changes, it remains one of the safest and most effective antiarrhythmic agents for the prevention of recurrent atrial or ventricular arrhythmias. Several studies have examined the role of implantable cardioverter-defibrillators (ICD) for the prevention of sudden death from ventricular arrhythmias in adults [65-67]. The ACC/AHA recommends an ICD in adult patients with symptoms of heart failure and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation or hemodynamically significant ventricular tachycardia. No prospective studies have been performed assessing the efficacy of ICD therapy for prevention of sudden death in children.

Cardiac resynchronization therapy (CRT) is a form of biventricular pacing which attempts to restore normal ventricular synchronous contraction in patients with intraventricular conduction delay, thereby increasing the efficiency of ventricular ejection and diastolic filling, and reducing atrioventricular regurgitation. Several studies have demonstrated an improvement in exercise capacity, functional classification, ejection fraction and mortality in adult patients with heart failure who undergo CRT while receiving stan-

dard medical therapy [68-72]. Data are lacking for CRT in children and no formal management recommendations have yet been made.

## MEDICAL MANAGEMENT OF DECOMPENSATED HEART FAILURE

The clinical spectrum of decompensated heart failure ranges from the outpatient who is seen in clinic with subtle signs such as worsening peripheral edema to the child presenting to the emergency department in life threatening cardiogenic shock. Once the condition is recognized, the fundamental therapeutic goals are the same when managing patients with this very challenging clinical syndrome: reverse hemodynamic derangements, correct metabolic abnormalities and provide symptomatic relief [73].

### Diuretics

Intravenous diuretics are considered standard of care therapy for the initial treatment of decompensated heart failure and should be given without delay to treat symptoms of congestion. Patients with pre-existing heart failure who have been treated with diuretics as outpatients may require higher doses than the patient with newly diagnosed heart failure. Diuretic "resistance" may be overcome by the addition of a thiazide diuretic and a spironolactone antagonist to provide "sequential nephron blockade" [74]. Another strategy that may be used to improve diuresis is the use of a continuous infusion of a loop diuretic [75]. During intravenous diuretic therapy frequent monitoring for a variety of side effects including electrolyte disturbances (hypokalemia, hypomagnesemia), a worsening of renal function and hypotension should take place.

### Vasodilating Agents

Intravenous vasodilators such as nitroglycerin and nitroprusside should be considered as adjunctive therapy with diuretics for rapid improvement of symptoms in patients without systemic hypotension. These medications are used frequently in adults with decompensated heart failure but less frequently in children. At lower doses, intravenous nitroglycerin acts primarily as a venodilator, reducing pulmonary congestion and left ventricular filling pressures [76]. When used at higher doses it lowers systemic vascular resistance, improving stroke volume and cardiac output. Nitroprusside increases venous capacitance and reduces systemic vascular resistance in a dose-dependent manner [77].

A relatively new medication in the armamentarium for treating heart failure is nesiritide, a recombinant form of human B-type natriuretic peptide. By increasing cyclic guanosine monophosphate, nesiritide acts as a vasodilator of venous capacitance and arterial resistance vessels with additional natriuretic properties. Studies in adults have demonstrated that nesiritide significantly reduces the pulmonary capillary wedge pressure, providing symptomatic relief, increases urine output and unlike other vasodilators decreases neurohormonal activation [78-80]. In the ASCEND-HF trial, nesiritide was not associated with a decrease in the rate of death or rehospitalization and had a small, nonsignificant effect on dyspnea when used in combination with other therapies [81]. Data in children suggest that nesiritide may be safe and efficacious when used to treat decompensated heart failure. Jefferies *et al.* demonstrated in an open label, non-randomized study, that nesiritide therapy was associated with improved diuresis, decreased filling pressures and improved functional class [82].

### Inotropic Agents

Patients with decompensated heart failure and reduced blood pressure with normal or low systemic vascular resistance may not benefit from vasodilators and should therefore be considered for inotropic therapy. In these patients, inotropic agents may be necessary to maintain circulatory function, relieve symptoms and improve end-organ function.

Milrinone, sometimes referred to as an inodilator, is a phosphodiesterase inhibitor that acts by increasing cyclic adenosine monophosphate, thereby providing inotropy while vasodilating venous capacitance and systemic arterial resistance vessels. Milrinone also reduces pulmonary vascular resistance and is less likely to cause tachycardia than other inotropic agents. Only a few studies have evaluated the safety and efficacy of milrinone for the treatment of decompensated heart failure in adults, and thus far they have failed to show any clinical benefit when used for this indication [83, 84]. In fact, the data suggest that milrinone may actually increase the risk of arrhythmias and mortality. In the OPTIME trial, 949 adults hospitalized with an exacerbation of chronic heart failure were randomized to receive either a 48-hour infusion of milrinone or placebo [85]. The primary outcome measure was hospitalization for cardiac cause within 60 days of enrollment. There was no difference in the median number of cardiac-related hospital days between the milrinone group (6 days) and the placebo group (7 days, $p=0.71$). Sustained hypotension and atrial arrhythmias occurred significantly more frequently in patients receiving milrinone. Further post-hoc analysis of this study revealed that patients with an ischemic etiology had a higher 60-day mortality rate (11.6 percent) than patients with a non-ischemic etiology (7.5 percent, $p=0.03$). Despite this difference in mortality based on the etiology of heart failure, there was no difference in 60-day mortality between the milrinone treated non-ischemic patients (7.1 percent) and the placebo treated patients (7.7 percent, $p=0.21$).

Dobutamine is a sympathomimetic that is commonly used in adults hospitalized with decompensated heart failure. Dobutamine stimulates β-receptors in the myocardium and peripheral vasculature causing increased myocardial contractility and decreased systemic and pulmonary vascular resistance [86]. In contrast to dopamine, ventricular filling pressures fall due to venodilation [87]. Improved inotropy coupled with afterload reduction seemed like a desirable combination for patients with symptomatic heart failure; however, subsequent controlled studies have demonstrated significant adverse effects when dobutamine is used for this indication [88]. Data from the Flolan International Randomized Survival Trial (FIRST) demonstrated a higher mortality rate among NYHA class III and IV heart failure patients who were treated with dobutamine compared to those who were not (70.5 percent vs. 37.1 percent, $p=0.0001$) [88]. Dobutamine is also known to increase heart rate, myocardial oxy-

gen consumption and the incidence of atrial and ventricular arrhythmias. No controlled studies have been performed in children assessing safety or efficacy of dobutamine for advanced heart failure.

Dopamine is a sympathomimetic that stimulates β-receptors, as well as α-receptors and dopaminergic receptors on the peripheral vasculature. It acts predominantly on β1 receptors in the myocardium causing increased contractility and heart rate at doses of 3mcg/kg/min and greater. The α-receptor response is seen at doses of 10 mcg/kg/min and higher, causing peripheral vasoconstriction and overwhelming any β2-induced vasodilation. Dopamine is a good choice for patients in low cardiac output when sustained pressor support is needed quickly.

In life-threatening situations or cardiogenic shock, an epinephrine infusion is indicated. Even low dose epinephrine boluses can sustain systemic pressure until a more reliable therapy can be initiated. Although epinephrine may increase blood pressure, heart rate and contractility it also may cause ischemia, atrial or ventricular arrhythmias and increased myocardial oxygen consumption.

**Table 1. Causes of Dilated Cardiomyopathy in Children.**

| Factor | Examples |
|---|---|
| Genetic mutations | Lamin A-C, Myosin binding protein-C, Titin, Desmin, Tropinin I, Taffazin, Dystrophin |
| Myocarditis | Enteroviruses, parvovirus, adenovirus, influenza, human immunodeficiency virus, rubella, varicella, mumps, Epstein-Barr virus, cytomegalovirus, measles, mycoplasma, Lyme disease |
| Ischemia | Anomalous left coronary artery, Kawasaki disease |
| Metabolic disorders | Fatty acid oxidation disorders, glycogen storage disorders, carnitine deficiency |
| Endocrine disorders | Hypothyroidism, pheochromocytoma |
| Hematologic disorders | Iron deficiency anemia, sickle cell anemia, thalassemia, hemochromacytosis |
| Collagen vascular diseases | Systemic lupus erythematosus, rheumatic heart disease, dermatomyositis |
| Drugs | Anthracycline, cyclophosphamide |

## HYPERTROPHIC CARDIOMYOPATHY

### Introduction

Hypertrophic cardiomyopathy (HCM) is best described as the abnormal hypertrophy of the ventricular myocardium in the absence of other secondary causes such as hypertension or valvular heart disease [89]. Previously, this form of cardiomyopathy had been referred to as "idiopathic hypertrophic subaortic stenosis" (IHSS) and "hypertrophic obstructive cardiomyopathy" but now it is referred to as HCM since this encompasses both obstructive and non-obstructive forms of HCM [90]. HCM can be divided into a familial type or primary form that is most often the result of a sarcomeric protein defect. Secondary forms of HCM can be seen in syndromes such as Noonan syndrome or Freidrich's ataxia, or other metabolic and mitochondrial disorders (30-40%) [91, 92].

### Etiology and Epidemiology

The inheritance pattern of familial or idiopathic HCM is autosomal dominant with the majority of mutations identified on the beta myosin heavy chain (30%), troponin T (15%), or myosin binding protein C genes (15%) [93]. In adults, primary HCM represents the most commonly seen form of cardiomyopathy with a population incidence of 1 in 500 [94]. The Pediatric Cardiomyopathy Registry (PCMR) data revealed that the annual incidence of idiopathic HCM was 3.6 per 1 million children. Of the 855 children included in this study, 8.7% had inborn errors of metabolism, 9% malformation syndromes, 7.5% neuromuscular disorders, and 74% were idiopathic HCM [95].

### Pathophysiology

Although there is significant morphologic heterogeneity in the pattern of left ventricular hypertrophy (LVH), most cases show diffuse myocardial hypertrophy that disproportionately involves the interventricular septum and anterolateral wall as opposed to the posterior segment of the free wall [96, 97]. One third of cases show mild left ventricular hypertrophy [98]. Few patients show a concentric pattern of left ventricular hypertrophy or isolated apical left ventricular hypertrophy. Histology of the myocytes shows that not only are they increased in size but also disorganized in arrangement with myofibrilar disarray [99]. The disorganized myocyte pattern may play a role in the abnormal dispersion of electrical depolarization and repolarization and serve as a substrate for arrhythmias [100]. The intramural coronary arteries are abnormal with intimae thickening, which may lead to inadequate coronary flow particularly in relation to the elevated oxygen demands of the hypertrophied myocardium. These factors may lead to myocardial ischemia, cell death, and scar formation that may form the substrate for congestive heart failure related death [101-103]. Although the ventricle hypertrophies, the ventricular cavity maintains a normal volume. Systolic function of the ventricle remains intact; however, there is impaired ventricular compliance and diastolic dysfunction, leading to elevated end diastolic pressures and left atrial enlargement. When systolic function becomes impaired this can represent a "burnt out" HCM that then results in ventricular dilation.

### Clinical Presentation

Most children with HCM are asymptomatic. If symptoms are present they most often result from the presence of left ventricular outflow tract obstruction. However, all patients with HCM are at risk for sudden death, which unfortunately may be the mode of presentation. The presence or severity of left ventricular outflow tract obstruction does not correlate with the risk of sudden death [104]. Risk factors for sudden death include age less than 30 years, family history of HCM and sudden death, abnormal blood pressure response to exercise, genetic abnormalities associated with an increased prevalence of sudden death, syncope or near syncope with

exertion, prior cardiac arrest or spontaneous sustained ventricular tachycardia, multiple or repetitive or prolonged bursts of nonsustained ventricular tachycardia, and extreme left ventricular hypertrophy with a wall thickness > 30mm [91]. Mechanical outflow tract obstruction may result from not only hypertrophy of the ventricular septum but also by the interaction of the mitral valve and ventricular septum during systole, which is referred to as systolic anterior motion (SAM) of the mitral valve. The obstruction may be estimated by assessing the flow velocity using continuous wave Doppler echocardiography [105]. According to the 2011 American Heart Association (AHA) guidelines, a peak instantaneous left ventricular outflow tract obstruction gradient of >50 mmHg at rest or with exercise and with symptoms that are poorly controlled with medications warrant a therapeutic intervention [106]. Physical exam findings in patients with HCM and left ventricular outflow tract obstruction include decreased pulse pressure after a premature ventricular contraction, increased murmur with the Valsalva maneuver or standing, and a jerky or bifid carotid pulse. In addition the presence of an S4 is common [107]. Approximately 3% of patients with HCM develop end-stage heart failure with a reduced ejection fraction (<50%) and present with a clinical picture not unlike those with a DCM. Patients with HCM and congestive heart failure may present with dyspnea, syncope, chest pain, palpitations, and orthopnea. The physical examination may also include jugular venous distension and a prominent "a" wave due to diminished right ventricular compliance. Systolic murmurs in HCM may be due to left ventricular outflow obstruction (crescendo-decrescendo) or mitral regurgitation (holosystolic). Due to the potential for scar formation and myofibrilar disarray, a nidus for arrhythmia can develop. In the pediatric patient this is most commonly ventricular tachycardia and it may be sustained or non-sustained. Sustained ventricular tachycardia is a significant risk factor for sudden death and should be addressed promptly [100]. Atrial fibrillation is more commonly seen in adults than in children with HCM and likely results from long-term diastolic dysfunction and atrial enlargement. The management of atrial fibrillation in HCM should be similar to those without HCM with respect to rhythm control and anticoagulation [106, 108].

## Diagnostic Studies

Diagnostic studies include a chest film, which may be normal or demonstrate cardiomegaly with left atrial enlargement due to mitral regurgitation or diastolic dysfunction. An echocardiogram may demonstrate asymmetric hypertrophic myocardium where the ventricular septum is relatively thicker than the posterior wall. The left ventricular diameter may be at the lower limit of normal or smaller than normal. The left atrium may be enlarged due to diastolic dysfunction and left atrial hypertension. Doppler echocardiography may be used to evaluate the presence of a left ventricular outflow tract obstruction that is usually dynamic in nature. Systolic anterior motion of the anterior mitral valve leaflet is one of the hallmarks of obstructive HCM. Systolic function is typically normal and may be hyperdynamic. Diastolic dysfunction may be present and is demonstrated with abnormalities in mitral inflow patterns and or tissue Doppler tracings [106]. There is an evolving role for exercise echocardiograms at eliciting dynamic outflow tract gradients that are not seen at rest. Cardiac MRI is useful for evaluating the anatomy and outflow tract obstruction in patients with poor echocardiographic windows. MRI can also visualize the apical form of HCM better then echocardiogram [106, 109]. Areas of late gadolinium enhancement on cardiac MRI correlate with areas of fibrosis, which may be associated with an increased risk for ventricular tachycardia [100, 109].

Exercise treadmill testing may be useful by demonstrating a blunted heart rate and blood pressure response to exercise, which is a risk factor for sudden death. In addition, exercise testing may elicit ST segment changes heralding myocardial ischemia with exertion and or arrhythmia [106, 110]. Caution should be taken for exercise testing in those with significant left ventricular outflow obstruction or prior history of arrhythmia. Electrocardiograms and 24 hour ambulatory Holter monitoring may be useful for the detection of electrocardiographic abnormalities. ST and T wave abnormalities and evidence of left ventricular hypertrophy are the most commonly seen findings. Other findings observed on ECG include ventricular pre-excitation, left atrial enlargement, deep and narrow Q waves, and diminished R waves in lateral precordial leads [106, 111, 112]. A cardiac catheterization may be indicated to assess hemodynamics and to determine the degree of outflow tract obstruction that is not well demonstrated by echocardiography, diastolic characteristics of the left ventricle, and ventricular as well as coronary arterial anatomy [113]. One of the potential causes of chest pain in patients with HCM is myocardial bridging, in which the coronary artery is compressed by the hypertrophied myocardium during systole [91]. Finally, genetic testing is recommended of the proband and in all first-degree relatives if a mutation is identified. A genetic mutation is found in approximately 50-60% of individuals with HCM [114]. Genetic counselling is recommended for all individuals who are positive for a genetic mutation and especially for those first-degree relatives who are phenotype negative. With regards to infants less than one year of age presenting with HCM, it is important to determine underlying metabolic and/or mitochondrial disorders that may also be present as many of these may be lethal conditions. The overall mortality of children with HCM is highest before one year of age. Infants with an inborn error of metabolism or malformation syndrome have the lowest 5 year survival (26.3% and 65.8% respectively). However, in those with idiopathic HCM who survive beyond one year of age, there annual mortality is 1.0 per 100 patient-years [95].

## Medical and Surgical Management

Preventative measures to reduce the incidence of sudden cardiac death include pharmacotherapy and restriction from strenuous physical activity and competitive sports [115]. Calcium channel blockers such as verapamil and disopyramide have been used for patients with left ventricular outflow obstruction because of their negative inotropic effects [116]. Beta blockers are negative chronotropes that allow for better ventricular filling in the setting of diastolic dysfunction and can ameliorate the left ventricular outflow track obstruction in conjunction with calcium channel blockers and may potentially reduce the incidence of arrhythmia

[117]. However, it must be noted that no pharmacologic therapy has been shown to reduce the incidence of sudden death [118]. The Implantable Cardiac Defibrillators (ICD) has been shown in a number of studies to be a lifesaving intervention for arrhythmias in the patients with HCM [119-121]. Planning of an ICD implant must be done thoroughly as there may no longer be an opportunity to perform cardiac MRI thereafter. Left ventricular septal myectomy can be successful in reducing the left ventricular outflow tract obstruction (gradient > 50 mmHg) with low recurrence and complication rate in symptomatic patients [90, 91, 122]. This surgery is usually well tolerated in older children and young adults with a very low incidence of postoperative complications or death [123, 124] Alcohol septal ablation has been performed although it is associated with a higher incidence of residual gradient and bundle branch block [105]. In the setting of symptomatic myocardial bridging, coronary artery unroofing has been described as a therapeutic option, however the overall success of this procedure to alleviate symptoms is controversial [125, 126]. HCM is the least common form of cardiomyopathy requiring cardiac transplantation [127]. However, it may be considered as a palliative option in those children with HCM and restrictive physiology or poor systolic function. Children with HCM and restrictive physiology have a higher incidence of death or transplant (29%) at ten years than those without restrictive physiology (1.5%) [128]. In those with end-stage HCM with either severe LV dysfunction or restrictive physiology not amenable to medical management, mechanical circulatory support may be considered, however to date the experience in patients with the HCM is limited [129].

## RESTRICTIVE CARDIOMYOPATHY

### Introduction

Of the four types of cardiomyopathy categorized by the WHO, restrictive cardiomyopathy (RCM) is the least common [130]. In children, RCM accounts for 2.5-5% of diagnosed cardiomyopathies [131-136]. Restrictive cardiomyopathy is characterized by normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular wall thickness and atrioventricular valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function [131].

### Epidemiology and etiology

In studies of RCM in children the average age at the time of diagnosis is 6 years with a median of 5 years and a range from 0.1-19 years [132-134, 137-162]. In RCM the distribution amongst sexes appears to be relatively even with about 54% being female [132-166]. Sporadic and familial cases of RCM are reported. And approximately 30% of patients have a positive family history [132-166]. Mutations in at least 10 genes have been associated with the restrictive cardiomyopathy phenotype and include sarcomeric (troponin I and T, actin, myosin and titin) and nonsarcomeric gene defects (desmin, RSK2, lamin A/C, transthyretin and BAG3) [167-182]. Modes of inheritance include autosomal dominant, autosomal recessive and X-linked. De novo mutations also occur.

RCM has multiple causes and may result from noninfiltrative or infiltrative processes of the myocardium, storage diseases, endomyocardial diseases, myocarditis, drugs/chemotherapy, radiation, and following cardiac transplantation [183-198]. The pathology and histology vary with the underlying disease process. The most common etiology of RCM worldwide is secondary to endomyocardial fibrosis, which is estimated to affect 10 million people world wide, occurring most often in children and adolescents [184-185]. In adults, outside the tropics, amyloidosis is the most common cause of RCM [186]. One case of cardiac amyloidosis has been reported in a pediatric patient [134]. In the pediatric population, outside the tropics, idiopathic RCM is probably the most common cause of RCM based on reported cases in the literature [132-166].

### Pathophysiology

Typically the left atrium dwarfs the left ventricle. The left ventricular cavity size is normal with no appreciable left ventricular hypertrophy. In the vast majority of cases the hearts are otherwise structurally normal, although rarely they may have an atrial septal defect or small hemodynamically insignificant ventricular septal defect [140, 159]. The histology in idiopathic RCM is nonspecific revealing varying degrees of fibrosis and myocyte hypertrophy [132, 163, 166]. The histology may vary with the underlying disease process. Restrictive physiology often results from increased myocardial stiffness with decreased compliance causing a marked ventricular pressure rise with small changes in volume. Restrictive hemodynamics can also be caused by dysfunction and delay of active relaxation of the ventricle rather than increased intrinsic stiffness of the ventricular wall [141].

### Clinical presentation

Signs and symptoms of heart failure in children are often confused with other diseases. Common presenting symptoms often appear to be pulmonary or gastrointestinal in origin. Referral to a cardiologist eventually occurs when cardiomegaly is noted on chest radiograph or abdominal scout films. Earlier referral to a cardiologist occurs when the presenting sign is an abnormal heart sound, such as a murmur, gallop or loud P2. Syncope accounts for approximately 10% of the presenting complaints and often related to ischemia, arrhythmias, or thromboembolism [140, 141]. Aborted sudden death or sudden death can be the first symptom [136, 143, 166].

### Diagnostic Studies

Approximately 98% of electrocardiograms are abnormal [132-141, 143-156, 159, 161, 166] Figure 1 is a representative electrocardiogram of a patient with RCM. The most common abnormalities are right and/or left atrial enlargement. ST segment depression and ST-T wave abnormalities are frequently present. Right and/or left ventricular hypertrophy can also be seen as well as conduction abnormalities. Holter evaluations can also be useful for the evaluation of disturbances in rhythm and conduction, and for ST segment analysis as well. Ischemic changes with ST segment depression may be most evident at higher heart rates [140, 199]. Of the pediatric studies reporting arrhythmias, approximately

15% of the patients had arrhythmias and/or conduction disturbances [132, 133, 138-140, 150, 154, 156, 159, 163, 166, 200]. Atrial flutter was the most commonly reported arrhythmia. Atrial fibrillation and atrial tachycardias, Wolff-Parkinson-White syndrome with supraventricular tachycardia, symptomatic sinus bradycardia and ventricular tachycardia and torsade have also been reported. High-grade second degree and third degree heart block were the next most commonly reported rhythm disturbances. Chest radiographs are abnormal in approximately 90% of cases and demonstrate cardiomegaly and pulmonary venous congestion [132-141, 143-153, 159, 166]. The echocardiogram is usually diagnostic (Figure **2**). On 2-D imaging classic cases demonstrate markedly dilated atria, often larger than the ventricles. Typically there is normal or nearly normal left ventricular systolic function, and an absence of significant hypertrophy or dilatation. During 2-D imaging an evaluation for thrombi should be conducted, as thrombotic and embolic events are not infrequent [132, 133, 138, 139, 141, 155, 159, 201-203]. Aside from the markedly enlarged atria that are typically seen, other parameters of diastolic dysfunction on echocardiogram are less consistent [138, 139, 141, 156, 204, 205]. Cardiac catheterization is not usually necessary to make the diagnosis of RCM. The endomyocardial biopsy is rarely diagnostic of a specific etiology and neither catheterization nor biopsy is risk-free in these hemodynamically fragile children [132, 134, 139, 141, 148, 163, 166] However, pulmonary hypertension and elevated pulmonary vascular resistance are common and testing for pulmonary vasculature reactivity may be deemed necessary [132, 139, 156, 1578-160, 163-165] Weller and colleagues found that 40% of patients with RCM were deemed not suitable for transplant due to an elevated and non-reactive pulmonary vascular resistance at the time they were evaluated for cardiac transplantation [159]. The differential diagnosis includes constrictive pericarditis, which is the disease process most commonly confused with RCM. It is important to distinguish the two diseases as they have different treatments and outcomes. Some of the mixed phenotype cardiomyopathies can also be difficult to distinguish from RCM [132, 139, 141, 159] Because some children with RCM may have some degree of left ventricular hypertrophy confusion may arise as to whether the patient has RCM versus HCM with restrictive physiology [132, 133, 139, 141, 159]. This distinction is important as children with HCM with restrictive physiology have a better prognosis than children with "pure" RCM [206, 207]. The prognosis of children with RCM remains poor. Approximately half of the children die or require transplantation within 2-3 years of diagnosis. Heart failure related deaths are the most common, but sudden cardiac death is also fairly common [132-134, 137, 138, 140, 141, 158, 163, 166, 200]. When comparing survival with RCM versus survival after transplant for RCM it is clear that transplant results in longer survival in most cases [159].

## Management

A variety of combinations of drugs have been used to treat RCM including diuretics, digoxin, afterload reducing agents, calcium channel blockers and beta-blockers with no clear benefit. In adults with diastolic dysfunction tachycardia is poorly tolerated, therefore beta-blockers or calcium channel blockers have been suggested, but they have no survival benefit [208]. Their use is not currently recommended in children unless there is an additional indication [209]. The risks and benefits of ACE inhibitors in RCM remain to be determined and are not currently recommended unless there are additional factors such as hypertension [209]. Medical therapy is primarily supportive and is in large part limited to diuretics in patients with signs and symptoms of systemic or pulmonary venous congestion. Over-diuresis should be avoided because these patients are sensitive to alterations in preload. In pediatric RCM the incidence of thrombosis ranges from 0 to 40%, while the incidence of embolism ranges from 12-33% with approximately 50% being cerebrovascular events [132, 133, 138, 139, 141, 155, 159, 201-203]. Therefore some form of antithrombotic/anticoagulation therapy is recommended at the time of diagnosis. There have been no studies thus far that have compared the efficacy of aspirin versus warfarin or enoxaparin in patients with RCM. The development of pulmonary hypertension due to diastolic dysfunction is a significant problem in children with RCM. In adults, left sided heart disease is the most common cause of pulmonary hypertension [210]. In addition to the "fixed" degree of elevation in pulmonary artery pressure a reactive component may develop [209-211]. If pulmonary vasodilator therapies are used, careful monitoring for the development of pulmonary edema is necessary as the left atrial pressure may rise, negating the benefit of the fall in pulmonary artery pressures. None of the standard therapies for systolic heart failure in adults have been shown to improve survival in adults with predominantly diastolic heart failure. Thus it is not surprising that none of the pediatric studies have found any medical therapies to be efficacious given the much smaller number of patients with pure diastolic heart failure in children. The International Society of Heart and Lung Transplant issued a monograph on the ISHLT guidelines for the management of pediatric heart failure in 2014 [209]. The only Class 1 recommendations for medical treatment in pediatric diastolic heart failure were to use diuretics to establish euvolemia with close monitoring of renal function and blood pressure. Class III (not recommended) drugs included calcium channel blockers and digoxin unless needed for another indication, inotropes such as dopamine, dobutamine and epinephrine, and pulmonary vasodilators such as prostaglandins and endothelin receptor antagonists. However some positive inotropes such as milrinone also have lusitropic properties, but the afterload reducing effects of milrinone may outweigh whatever benefit is gained from the lusitropy, requiring very careful monitoring [209].

Cardiac transplantation remains the definitive therapy in children with RCM. Outcomes in children transplanted for RCM are comparable to children transplanted for other forms of heart disease [160, 164, 165, 212-214]. Most patients should be evaluated and listed for transplantation "early", however how early remains controversial in the literature [140, 163, 164, 212]. Periodic monitoring for developing or progressing pulmonary hypertension is needed. Orthotopic heart transplant is the preferred transplant since survival is better than heart-lung transplant and more feasible than heterotopic transplant in small children, although heterotopic heart transplantation has been performed in small children with RCM [164, 215]. Dipchand *et al.* reported that

children with RCM were less likely to be listed status 1, ventilated, receiving inotropes, and had fewer arrhythmias at listing than their counterparts with dilated cardiomyopathy [216]. However, their likelihood of death while waiting was similar [216]. Zangwill *et al.* reviewed the outcomes of children with RCM listed for heart transplantation, 44% of whom were listed UNOS status 1 [212]. They found children requiring mechanical support had a significantly higher risk of death while waiting than other children listed with RCM. Wait list mortality was shown to be higher for children with nondilated forms of cardiomyopathy (restrictive or hypertrophic) who were being ventilated at listing [213]. These studies underscore the importance of not waiting "too long" to list these patients for heart transplant. It is harder to support children with RCM with left ventricular assist devices (LVAD) due to smaller ventricular cavity sizes and because the right ventricle is usually affected as well. There are reports of successful bridging to cardiac transplantation with the Berlin EXCOR® LVAD [217, 218]. All had left atrial cannulation and one patient required bi-ventricular devices. Patients should have periodic ECG's and Holter monitoring performed routinely, and as symptoms dictate. Pacemakers are indicated for those with significant conduction disturbances. Implantable defibrillators should be considered for patients with evidence of ischemia and ventricular arrhythmias. Strenuous physical activity should be avoided.

## CONFLICT OF INTEREST

Jack Price, MD has no financial conflicts of interest.

Aamir Jeewa, MD has no financial conflicts of interest.

Susan Denfield, MD has no financial conflicts of interest.

## AUTHOR CONTRIBUTIONS AND ACKNOWLEDGEMENTS

Authors Jack Price, Aamir Jeewa, and Susan Denfield contributed equally to the research, preperation, revisions and completion of the Cardiomyopathies in Children Manuscript.

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