# Chapter 44
# Acute Myocarditis and Cardiomyopathies

Brian Feingold and Steven A. Webber

**Abstract** The definition and classification of cardiomyopathies were recently revised by an expert panel of the American Heart Association (Maron et al., Circulation 113:1807–1816, 2006) following the initial classification by the World Health Organization in 1995 (Richardson et al., Circulation 93:841–842, 1996). Cardiomyopathies are considered "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic" (Maron et al., Circulation 113:1807–1816, 2006). Cardiomyopathies are generally considered as primary (disease solely or predominantly confined to heart muscle) or secondary, showing pathological myocardial involvement secondary to a systemic or multiorgan disease process. Both forms are commonly seen in children, although primary forms predominate.

The definition and classification of cardiomyopathies was recently revised by an expert panel of the American Heart Association [1] following the initial classification by the World Health Organization in 1995 [2]. Cardiomyopathies are considered "a heterogeneous group of diseases of the myocardium associated with mechanical and/or electrical dysfunction that usually (but not invariably) exhibit inappropriate ventricular hypertrophy or dilatation and are due to a variety of causes that frequently are genetic" [1]. Cardiomyopathies are generally considered as primary (disease solely or predominantly confined to heart muscle) or secondary, showing pathological myocardial involvement secondary to a systemic or multiorgan disease process. Both forms are commonly seen in children, although primary forms predominate.

Cardiomyopathies and myocarditis are significant contributors to end-stage heart failure in children, accounting for over 50% of all pediatric heart transplants [3]. They are also the commonest indication for ventricular assist device (VAD) support in childhood [4]. Pediatric cardiomyopathies have a reported incidence of 1.13–1.24 cases per 100,000 population in two recent large population-based studies [5, 6], though this is likely an underestimate. The true incidence of pediatric myocarditis is unknown. Many cases may be unrecognized and go on to experience clinical recovery. Some may be misdiagnosed as SIDS [7]. Others may present years later as chronic dilated cardiomyopathy with viral genome demonstrated in the myocardium but in the absence of active inflammation [8–10].

This chapter focuses on the role of the intensive care unit (ICU) in the management of the child with new-onset or established cardiomyopathy presenting with shock, heart failure, or arrhythmia. Management in the ICU comprises:

1. Determination of the form of cardiomyopathy and of the most likely etiology (most commonly discerning between acute myocarditis and an acute presentation of dilated cardiomyopathy (DCM))
2. Management of acute heart failure and / or arrhythmias
3. Estimation of prognosis and selection of patients for mechanical circulatory support and transplantation

B. Feingold (✉)
Pediatrics, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA
e-mail: brian.feingold@chp.edu

S. A. Webber
Department of Pediatrics, Vanderbilt University School of Medicine, Nashville, TN, USA

Monroe Carell Jr. Children's Hospital at Vanderbilt, Nashville, TN, USA
e-mail: steve.a.webber@vanderbilt.edu

## 44.1 Dilated Cardiomyopathy and Myocarditis

### *44.1.1 Anatomy*

DCM is characterized by dilation of one or both ventricles (most commonly the left ventricle) often with thinning of


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the left ventricle free walls. Varying degrees of hypertrophy may also be seen and left ventricular mass tends to be increased, even when the ventricular walls are thin. The left ventricle often takes on a globular shape and mitral regurgitation with annular dilation is frequently seen along with left atrial dilatation (Figs. 44.1a and 44.2a). Left ventricular systolic function is usually globally depressed, though varying degrees of ventricular dyssynchrony may be observed, even in the absence of bundle branch block. In contrast, right systolic ventricular function is often only minimally decreased or normal. Right ventricular dilation, when present, may be due to myocardial involvement from the primary disease process or secondary to tricuspid regurgitation and pulmonary hypertension.

In contrast, patients with acute myocarditis often show only a poorly functioning left ventricle with minimal dilation with, or without, regional wall motion abnormalities. There may be ventricular thickening secondary to myocardial edema, and left atrial enlargement may not be prominent, even when mitral regurgitation is present. These findings likely reflect the short duration of the disease process.

### 44.1.2 Etiology and Pathophysiology

Both acute myocarditis and DCM are characterized primarily by systolic ventricular dysfunction with resultant clinical signs and symptoms of heart failure. Diastolic dysfunction

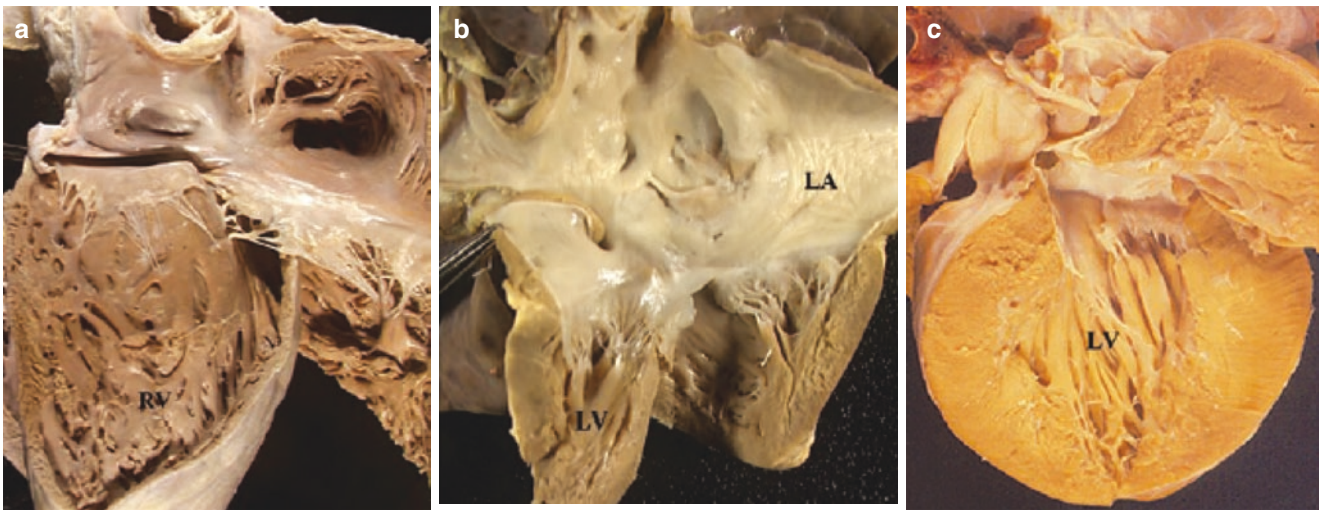


**Fig. 44.1** Spectrum of pediatric cardiomyopathies. (**a**) Dilated cardiomyopathy (DCM) with marked ventricular dilation and wall thinning (shown from RV side). (**b**) Severe hypertrophic cardiomyopathy (HCM) with concentric hypertrophy, in this case secondary to Pompe's disease (glycogen storage disease type II). (**c**) Restrictive cardiomyopathy (RCM) with small left ventricular cavity size and marked dilation of the left atrium. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh). LA left atrium, LV left ventricle, RV right ventricle

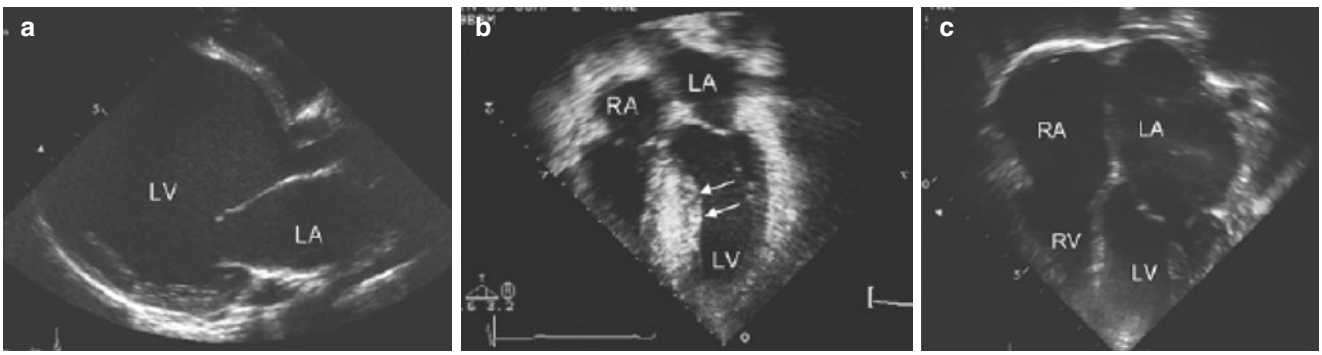


**Fig. 44.2** Echocardiographic findings of pediatric cardiomyopathies. (**a**) Parasternal long-axis view demonstrates severe left ventricular dilation in a child with idiopathic DCM. (**b**) Asymmetric septal hypertrophy (arrows) in a child with HCM. (**c**) Apical four-chamber view demonstrates small ventricular chamber sizes and biatrial enlargement typical of RCM. LA left atrium, LV left ventricle, RA right atrium, RV right ventricle. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

may also contribute to reduced myocardial performance in both settings, but particularly in acute myocarditis. In the latter, cardiac dysfunction may result from both direct viral invasion and myocyte lysis, as well as from the effects of myocardial inflammation. In clinical practice (beyond the neonatal period), symptoms are most often associated with (presumed) postviral lymphocytic infiltrates and autoimmunity. Adenovirus and enteroviruses (particularly Coxsackie B) are most frequent in children [11], although many other infectious and noninfectious causes have been identified, including viral, bacterial, fungal, and protozoal infections, as well as drug toxicities and various systemic disorders. The latter include Kawasaki disease and rheumatic fever.

Pediatric DCM encompasses a final common phenotype for a wide variety of etiologies. While the causes of most pediatric DCM are unknown, it is estimated that 30–40% of DCMs are inherited [12, 13], mostly in an autosomal-dominant fashion. Mutations in genes encoding myocyte cytoskeletal proteins as well as genes encoding sarcomere proteins have recently been identified as etiologies for DCMs [14]. Other genetic causes include inborn errors of metabolism (e.g., mitochondrial transport chain defects) [15] and neuromuscular syndromes (e.g., muscular dystrophies). Also, the finding of viral genome in patients with DCM suggests that at least some DCMs may result from prior myocarditis (either apparent or clinically unapparent) [9]. Other acquired forms of DCM include medication-related (e.g., anthracycline toxicity) and arrhythmia-induced (e.g., chronic, incessant supraventricular tachycardia).

### 44.1.3 Clinical Presentation

Heart failure in children from any cause often presents somewhat insidiously, after repeated evaluation and medical testing for other, more common conditions. Neonates and infants often present acutely unwell; yet, the diagnosis of a primary cardiac disorder may not be made on initial evaluation. It is not uncommon for cardiac disease to be considered only after ancillary studies fail to corroborate the presumed diagnosis or initial resuscitative attempts fail to improve the child's condition (e.g., shock due to sepsis). While much of the diagnostic difficulty results from the relative infrequency of primary cardiac disease in children, the inability of an infant or young child to verbally convey their symptoms also contributes. Also the frequency with which young children experience nasal, respiratory, or gastrointestinal symptoms, particularly during the winter and spring, often results in the initial symptoms of heart failure being attributed to these much more common maladies.

Infants with heart failure may present with a history of poor feeding, respiratory distress, listlessness, poor weight gain, or irritability. Common adult symptoms of paroxysmal nocturnal dyspnea and orthopnea are uncommon in pediatric patients. In older children, abdominal pain, anorexia, nausea, and vomiting are often observed and are likely due to liver capsule distention from hepatomegaly and/or intestinal venous congestion.

On physical examination, the child may appear anxious, and sinus tachycardia is usually present. Sweating is common in infants. Elevation of the jugular venous pulse may be present but is difficult to identify in the infant and toddler. Pallor and cool extremities may be present and are often associated with poor peripheral pulses and prolonged capillary refill. Resting tachypnea and retractions (suprasternal, intercostal, and subcostal) are common. Unlike adults, crackles are exceedingly rare in infants and young children with heart failure, even when pulmonary edema is present. Wheezes are more likely to be present. While hepatomegaly is a common finding, it is often overlooked or underappreciated by the inexperienced practitioner. Periorbital edema (infants and young children) with or without ascites (older children) is more common than peripheral edema in children. Failure to thrive may also be evident, particularly with chronic heart failure.

The clinical distinction between acute, fulminant myocarditis and acute presentation of chronic DCM is often difficult. At the time of presentation, many will have a history of an intercurrent or recent viral illness. In fact, viral syndromes are so common in early childhood that the etiologic relationship to the onset of acute heart failure is often not clear. However, the distinction between myocarditis and DCM is crucial. Many patients with fulminant myocarditis will recover completely if they are supported, whereas children with severely decompensated heart failure from DCM often will not recover without transplantation. Thus, the expectations from mechanical support (ECMO or VAD) and consideration for cardiac transplantation are directly impacted by the underlying diagnosis.

In many cases, clinical testing may help guide the diagnosis of acute myocarditis or acute presentation of DCM. The presence of marked cardiomegaly on *chest radiograph* and massive left-sided precordial forces on *ECG* suggest the underlying process occurred over time, favoring a diagnosis of chronic DCM over myocarditis. In contrast, absence of (or mild) cardiomegaly (Fig. 44.3a) and globally diminished voltages on electrocardiogram are more typical of acute myocarditis. Frank myocardial infarction may sometimes be observed on the 12 lead ECG of children with acute myocarditis. *Echocardiography* is very useful in the evaluation of infants and children suspected to have either myocarditis or cardiomyopathy and should be performed in all patients in whom these diagnoses are considered. *Endomyocardial biopsy* can generally be performed safely in children over the age of 1 year [16] and should be considered in the diagnostic

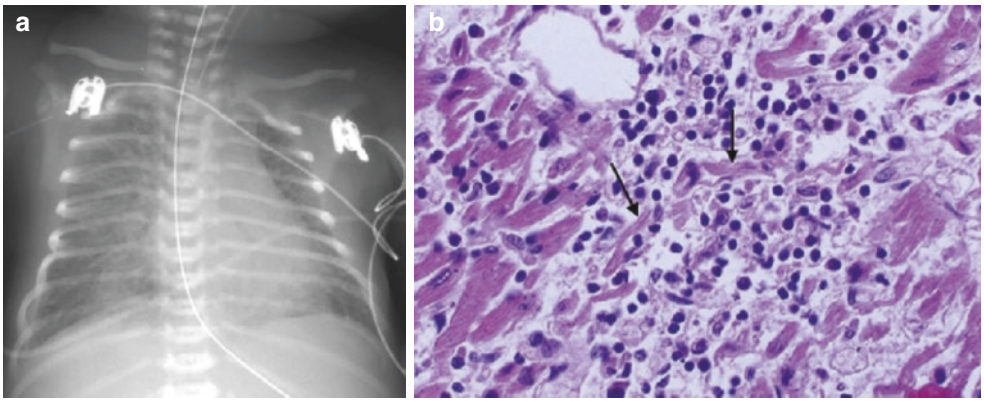


**Fig. 44.3** Acute myocarditis. (**a**) Chest radiograph shows a small heart with pronounced pulmonary edema. (**b**) Endomyocardial biopsy specimen showing lymphocytic infiltrate with myocyte destruction (arrows). (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

evaluation, particularly when trying to distinguish between myocarditis and DCM. Biopsy samples from the right ventricle can be analyzed by routine hematoxylin and eosin staining for lymphocytic infiltrates with myocyte necrosis (Fig. 44.3b), consistent with a diagnosis of acute myocarditis [17] or for evidence of myocyte hypertrophy and/or interstitial fibrosis, favoring a diagnosis of DCM. A fresh-frozen sample should also be obtained for *PCR* analysis of common viral causes of myocarditis. *Viral cultures* of stool, urine, and respiratory secretions may contribute to the diagnosis, as may *polymerase chain reaction analysis* of blood, pericardial effusion, or cerebral spinal fluid. *Viral titers* (at presentation and during convalescence) are often performed, but are generally noncontributory to the diagnosis of childhood myocarditis.

Diagnostic *evaluation for inborn errors of metabolism* is generally reserved for patients presenting with dilated or hypertrophic cardiomyopathies in the first year of life. The presence of severe acidosis, hypoglycemia, elevated lactic acid, deranged liver function tests, and hyperammonemia should all lead to rapid metabolic and genetic evaluation although all of these may also be observed in the setting of cardiogenic shock from nonmetabolic causes. A full description of the evaluation of infants suspected of having an inborn error of metabolism is outside the scope of this text, but readers may refer to some excellent recent reviews [15, 18, 19].

### 44.1.4 Management

The critically ill patient, who presents on the verge of hemodynamic collapse, requires aggressive therapy to augment oxygen delivery while minimizing consumption. Intubation with mechanical ventilation and sedation (± paralysis) is useful to eliminate the work of breathing while improving pulmonary edema as a result of positive pressure ventilation. Placement of central venous and arterial monitoring lines is also facilitated by these maneuvers. In addition to being able to administer medications and monitoring hemodynamics, these lines serve to limit the need for repeated phlebotomy in infants and young children, in whom fear, agitation, and site availability are complicating issues. The use of pulmonary arterial catheters is less common in the pediatric age group than in adults and rarely improves management when it is apparent that pulmonary edema is of cardiac origin.

Intravenous diuretics are used to augment diuresis and improve congestive symptoms. Continuous infusions of furosemide have been used with success in pediatric patients when intermittent dosing has failed to result in adequate diuresis. Inotropes are used to augment cardiac function and output. Therapy often consists of low-to-moderate doses (2–5 μg/kg/min) of dopamine for renal perfusion and blood pressure support and milrinone (0.125–1 μg/kg/min) to diminish afterload and augment cardiac output. Augmented inotropy can be achieved with dobutamine (1–10 μg/kg/min), while further afterload reduction may be achieved with sodium nitroprusside (0.3–4 μg/kg/min), if blood pressure tolerates. Rarely do patients require support with infusions of high doses of epinephrine or norepinephrine. In these cases (except when pathology is believed to be rapidly reversible), serious consideration should be given to early institution of mechanical circulatory support (see below). Caution must also be taken with regard to the arrhythmogenic potential of all inotropes, particularly with escalating doses. Appropriate monitoring is essential and care must be taken to aggressively correct all electrolyte disturbances, particularly hypo or hyperkalemia and hypomagnesemia.

Only limited data exists regarding the use of nesiritide for the treatment of acute heart failure in the pediatric population. Our experience has primarily involved its use in children who were otherwise recalcitrant to diuretics [20]. With appropriate monitoring of blood pressure and serum sodium, no complications were noted and some success was achieved in inducing diuresis. Others have reported use of nesiritide immediately after cardiac surgery, reporting no adverse hemodynamic effects or arrhythmias [21].

With stabilization and improvement in end-organ perfusion, gradual weaning of therapies is indicated. When oral medications can be safely tolerated and adequately absorbed, digoxin is often initiated, though of unproven benefit in pediatric patients. Intravenous diuretics are changed to oral forms and angiotensin-converting enzyme (ACE) inhibitors are begun for afterload reduction while weaning milrinone. Beta-blockers (other than as antiarrhythmic agents) only play a limited role in the ICU care of the child with DCM. Indeed, during acute deterioration requiring use of intravenous inotropes, beta-blockers will generally need to be withdrawn. Institution of beta-blockers for new-onset DCM is generally not performed in the ICU, since benefits (if they exist) are long-term and patients in the ICU are often hypotensive or being aggressively diuresed and vasodilated. Introduction of beta-blockers is part of the long-term management of chronic heart failure and is of unproven benefit (though widely performed) at this time [22]. Usually, beta-blockers are commenced after transition to oral diuretic therapy and once ACE inhibitor dosing is optimized. This generally occurs on the medical floors or in the outpatient setting.

When acute heart failure is unresponsive to aggressive medical management, institution of mechanical circulatory support must be considered. This is discussed in detail in Chap. 6. In general, ventricular assist devices are most appropriate when used as a bridge to transplantation, since prolonged periods of support may be required. Recovery from acute (including fulminant) myocarditis is often rapid, so ECMO or short-term use of VADs is more appropriate.

In acute myocarditis, therapy is primarily supportive. Only rarely is infection caused by a specific agent for which there is established antimicrobial therapy of proven efficacy. Intravenous immunoglobulin and corticosteroids have both been used [23], though there is no proof of their efficacy in randomized clinical trials. Steroids are contraindicated when there is evidence of active viral infection. More potent immunosuppressive agents, including T cell cytolytic agents and calcineurin inhibitors, have been used in some programs. There is no data to support a specific risk/benefit ratio and most programs do not use these agents.

Avoidance of dysrhythmias is a key component in the management of all patients with acute and chronic heart failure. In addition to careful attention to maintaining normal serum electrolyte concentrations, control of tachyarrhythmias (both supraventricular and ventricular) is important. Amiodarone is commonly used for treatment and prophylaxis of ventricular tachycardia, as well as for refractory atrial tachycardias.

The role of implanted cardioverter-defibrillators (ICDs) in the management of children and adolescents has not been as well defined as in adults. Evidence suggests children with DCM have a lower risk of sudden death as compared to adults with similar degrees of ventricular dysfunction [24]. Nonetheless, in children with DCM, particularly those with evidence of ventricular tachycardia, ICDs have been utilized and are likely indicated in patients with syncope and aborted sudden death. Factors that may complicate placement of ICDs in children include greater risk of complications such as lead fracture (possibly due to growth or greater levels of activity in children as compared to adults), greater risk of inappropriate discharge due to ability to achieve higher (sinus) heart rates, and the inability to use endovascular leads in smaller children (<15 kg), necessitating epicardial lead placement [25].

### 44.1.5 Long-Term Outlook

Traditionally, long-term outlook in children with DCM was said to follow the "rule of thirds" with 1/3 improving, 1/3 remaining the same, and 1/3 demonstrating progressive deterioration in cardiac function. Recent population data from several groups has improved our understanding of the natural history of DCM. The National Australian Childhood Cardiomyopathy Study showed 5-year freedom from death or transplantation of 63% for children with DCM [26, 27]. The Pediatric Cardiomyopathy Registry showed a 5-year survival of 54% for DCM in North America [28, 29]. These data include outcomes for those followed with a diagnosis of DCM that may never have required intensive care. It is, therefore, of interest to note a recent important publication that focused on epidemiology and outcomes for new-onset heart failure from myocardial (nonstructural) disease. In a population-based study for the United Kingdom and Ireland, 82% of children presenting with new-onset heart failure (most due to DCM) were in NYHA (or Ross) class III or IV and 41% required mechanical ventilation during first admission. One-year transplant-free survival was only 66% [30]. This is far worse than outcomes for new-onset heart failure in adults. Predictors of survival for DCM vary considerably between series. In a recent systematic review [31], it was noted that the most consistent findings associated with improved outcome were younger age at diagnosis, better fractional shortening and ejection fraction at diagnosis, and presence of myocarditis.

In general, the outcomes of acute myocarditis in children are good. A number of studies have shown survival rates of between 75% and 100% for acute myocarditis in childhood [23], including fulminant cases that may require mechanical circulatory support. This emphasizes the benefit of knowing the diagnosis of myocarditis, since acute transplantation should be avoided even if mechanical support is required. This will provide the opportunity for cardiac recovery, as well as minimize the risks of transplantation during recent or active viral infection.

## 44.2 Hypertrophic Cardiomyopathy

### 44.2.1 Anatomy

In hypertrophic cardiomyopathy (HCM), it is most common for patients to show asymmetric hypertrophy of the interventricular septum, with varying degrees of obstruction to left ventricular outflow due to prominence of the subaortic septum and/or systolic motion of the anterior leaflet of the mitral valve (Fig. 44.2b). Less commonly, children with HCM may demonstrate concentric left ventricular hypertrophy (Fig. 44.1b). In infant presentation, involvement of both the left and right ventricles is common, and biventricular obstruction may occasionally be observed. As ventricular hypertrophy may not be apparent until puberty, children with a family history of HCM in whom no genetic diagnosis/marker has been established should undergo serial evaluation with electrocardiography and echocardiography before, during, and after puberty to assess for development of abnormal cardiogram and ventricular hypertrophy.

### 44.2.2 Etiology and Pathophysiology

HCM is most commonly an inherited disorder (autosomal dominant) with marked variability in clinical expression. Nearly all mutations identified to date are in ten genes that encode cardiac sarcomere proteins [32]. It is likely that many other disease-causing mutations are yet to be identified. When there is a known familial mutation, testing of relatives can rule out disease. However, in many families, no mutation is identified, or testing has not been performed. It is estimated that current screening panels for sarcomeric protein mutations reveal mutations in approximately 70% of cases. Other causes of pediatric HCM include conditions associated with left ventricular hypertrophy such as glycogen or lysosomal storage diseases, mitochondrial defects, and Noonan, LEOPARD, and Beckwith–Wiedemann syndromes.

Patients with HCM generally have thickened left ventricle walls with normal or decreased cavity size and preserved or hyperdynamic systolic function. A subgroup with pronounced restrictive physiology and atrial dilatation has been reported [33]. In some cases, there appears to be overlap of phenotype with restrictive cardiomyopathy (RCM). Cases of classical HCM and RCM have been observed in different members of the same family due to cardiac Troponin I mutations [34].

Heart failure symptoms are very rare in children and adolescents with HCM, and are most commonly a result of diastolic dysfunction. The exception is the infant with severe disease, often with biventricular hypertrophy with or without outflow obstruction. These infants commonly present with heart failure. Metabolic and genetic work-up is warranted in these cases.

Syncope and aborted sudden death may be observed in patients with HCM. The pathophysiology is often hard to define. Tachycardia and hypovolemia (e.g., due to dehydration and fever) may be poorly tolerated; impaired myocardial perfusion, severe obstruction, inappropriate peripheral vasomotor tone, and atrial and ventricular arrhythmias may all contribute to syncope and mortality in HCM.

### 44.2.3 Clinical Presentation

Patients with HCM may present in the absence of symptoms (e.g., for evaluation of a murmur) or due to a family history. Progressive activity intolerance and syncope are also common presenting complaints; however, it should be noted that in clinical practice, most children with these symptoms do not have cardiomyopathy. Affected infants may show tachypnea, hepatomegaly, and/or failure to thrive. In older children, chest pain may also be a symptom and suggests myocardial ischemia [32]. Unfortunately, it is not uncommon for sudden death (or aborted sudden death) to be the initial presentation of HCM in adolescents and young adults [35]. Undiagnosed HCM is a leading cause of sudden death in young, healthy individuals and athletes.

### 44.2.4 Management

Most children with HCM are asymptomatic and thus are not often encountered in the ICU. While progression to end-stage heart failure occurs, the diagnosis is relatively rare in children, accounting for only 2.5% of pediatric heart transplant listings in a recent analysis of over 3000 pediatric transplant candidates from a large, multicenter database [36]. With advancing symptoms of heart failure, patients may be admitted to the hospital for treatment. Although so-called burned-out HCM occurs in children in which there is progressive systolic dysfunction and left ventricular dilation, heart failure from HCM results predominantly from diastolic dysfunction. Thus, many of the therapies employed in the treatment of heart failure from DCM are not useful or are only of limited benefit.

An ideal agent for management of heart failure due to HCM would possess positive lusitropic effects, enabling relaxation of the ventricular myocardium and thus achieving improved stroke volume at lower filling pressures. Unfortunately, this agent does not yet exist and therapies directed primarily at management of diastolic ventricular

dysfunction are scant. Most common is the use of negative inotropic agents, such as non-dihydropyridine calcium channel blockers (e.g., verapamil) or beta-blockers (e.g., propranolol, atenolol). In the ICU setting, esmolol may be preferred due to its short half-life. Due to the exquisite sensitivity/dependence of the neonatal and infant heart to serum calcium levels, use of intravenous calcium channel blockers in infants less than 1 year of age is usually contraindicated. Milrinone, a phosphodiesterase III inhibitor, possesses some positive lusitropic effect [37] and thus may be of theoretical benefit in select patients with HCM and advanced heart failure symptoms in the absence of significant subaortic obstruction. As milrinone can be arrhythmogenic, careful consideration must be given to balance any potential benefits against the risks of induced tachyarrhythmias. Furthermore, vasodilatation may exacerbate any left ventricular outflow obstruction. Diuretics are often used in the outpatient setting for patients with congestive symptoms. These agents must also be used with caution in the setting of diastolic dysfunction as cardiac output and myocardial perfusion can be compromised with insufficient preload and again outflow obstruction may be increased.

The role of ICDs in the management of children with HCM is unclear. Data from a multicenter registry of pediatric and congenital heart disease patients showed HCM was the second most common diagnosis for which subjects received an ICD [38]. In patients with HCM who experience syncope or aborted sudden death, implantation of an ICD is likely indicated. Use of ICDs for primary prevention in patients with HCM is not established.

### 44.2.5 Long-Term Outlook

Although the natural history of HCM in adults is quite variable [32], survival tends to be worse the younger a patient presents. In particular, infants who present with heart failure have a poor prognosis. Patients who present older than 1 year of age are unlikely to die of progressive heart failure from HCM, but may succumb to sudden death [39]. Sudden death predominates in adolescents and young adults with HCM and is thought to be more likely in those with a family history of sudden death or personal history of recurrent syncope, ventricular tachycardia, or massive left ventricular hypertrophy [35].

Hypertrophy often progresses (or may first become apparent) during periods of rapid growth (i.e., puberty), and thus, patients with HCM should be monitored closely during adolescence. In a small percentage of patients, there may be a regression of hypertrophy, with ultimate development of left ventricular dilation and poor systolic function. This so-called end-stage or "burned-out" HCM typically requires treatment for systolic heart failure much like DCM and may necessitate transplantation [40]. It is rare in childhood.

Our knowledge of outcome in pediatric HCM has recently been greatly advanced through analyses from the two large multicenter registries. In the National Australian Childhood Cardiomyopathy Study [27, 41], less than 10% presented with heart failure, most presenting with a murmur for family screening. A third were syndromic (mostly Noonan syndrome). Freedom from death or transplant was 83% at 5 years and 76% at 10 years. Presentation by 1 year of age was an important predictor of mortality. Annual mortality for patients presenting beyond this age was only 1.5%. In the Pediatric Cardiomyopathy Registry [29, 42], survival for idiopathic HCM ($n$ = 634) was 82% at 5 and 10 years for infantile presentation and 94% and 86% at the same time intervals for presentation beyond infancy.

## 44.3 Restrictive Cardiomyopathy

### 44.3.1 Anatomy

Restrictive cardiomyopathy (RCM) is a rare form of cardiomyopathy characterized by normal or decreased volume of both ventricles associated with atrial enlargement (often massive) and with normal LV wall thickness (Figs. 44.1c and 44.2c). As mentioned earlier, there is some phenotypic overlap seen with HCM, and mild left ventricular hypertrophy is sometimes observed. Systolic function is generally normal [1].

### 44.3.2 Etiology and Pathophysiology

Overall, RCM is a rare diagnosis, accounting for approximately 5% of pediatric cardiomyopathies [5, 6]. The underlying cause(s) are generally unknown [43–45]. This is in contrast to adult patients with RCM, in whom infiltrative diseases such as amyloidosis and sarcoidosis are sometimes identified. While some children may present with familial forms, most cases are sporadic. Cardiac troponin I mutations have been reported as a cause of restrictive (and hypertrophic) cardiomyopathy [34]. The severe restrictive physiology leads to decreased cardiac output, elevated filling pressures, and atrial stretch that may lead to arrhythmias. Some patients demonstrate presumptive evidence of ischemia based on ST segment depression, especially during tachycardia. Elevation of pulmonary vascular resistance is frequently seen (even at presentation) and may contribute to right heart failure. Loss of systolic function is rare, although it is occasionally seen in advanced disease.

### 44.3.3 Clinical Presentation

Exercise intolerance, exertional angina, syncope, tachyarrhythmias, or sudden death may all occur. Atrial tachycardias are not uncommon and likely result from severe atrial dilation due to poor ventricular compliance. These are poorly tolerated in the setting of diastolic compromise.

Much like those with HCM, children and adolescents with RCM often present incidentally for evaluation of a murmur or for follow-up of an atypical cardiac silhouette on chest radiography obtained for unrelated reasons. Patients may also present with symptoms of heart failure, angina, palpitations, or syncope. Syncope may be precipitated by atrial or ventricular tachycardia, both of which are poorly tolerated in the setting of limited ventricular compliance. Similar to HCM, sudden death is also not an uncommon presentation of RCM [44].

### 44.3.4 Management

Therapeutic options for pediatric RCM are very limited. Many of the same physiologic considerations (and thus limitations in management) discussed for patients with HCM are also pertinent for those with RCM. Gentle diuresis is indicated if there is pulmonary venous congestion or pulmonary edema, but excessive diuresis may lead to reduction in cardiac output. Vasodilators may lead to hypotension, since augmented cardiac output may not occur when stroke volume is fixed. The role of beta-blockers is unclear. Slowing of the heart rate will prolong diastolic filling time, but since stroke volume is relatively fixed, increasing heart rate may be an important mechanism for augmenting cardiac output.

As short-term survival is poor after a diagnosis of RCM, many centers recommend early evaluation for cardiac transplantation. Cardiac catheterization should be performed during the evaluation process because of the high likelihood of increased pulmonary vascular resistance. Hemodynamic assessment may also help with the distinction from constrictive pericarditis. Computed tomography is indicated if pericardial disease is suspected. Although secondary causes of RCM, such as amyloidosis and sarcoidosis, are exceedingly rare in children, biopsy should be considered in older children presenting with RCM to assess for these systemic diseases.

For patients managed out of hospital, implantation of an ICD in combination with antiarrhythmic agents may be considered, especially if prior near-syncope, syncope, or tachyarrhythmia has occurred.

### 44.3.5 Long-Term Outlook

Children with RCM have very poor prognosis in the absence of heart transplantation. Survival at 5 and 10 years after diagnosis was 39% and 20%, respectively, at our center [43], and others have reported similar outcomes [46]. A minority of patients has been reported to survive upward of 8–12 years [45, 47–49]; however, strong, independent predictors of prolonged survival remain to be identified. The presence of symptoms at diagnosis did not correlate with survival in our cohort. Since excessive elevation in pulmonary vascular resistance may necessitate heart–lung transplantation, progressive elevation in pulmonary resistance should also lead to consideration of early transplantation.

## 44.4 Noncompaction Cardiomyopathy

### 44.4.1 Anatomy

In left ventricular noncompaction (LVNC) cardiomyopathy, the left ventricle shows prominent trabeculations and deep intertrabecular recesses (Fig. 44.4a, b). These findings are most commonly observed at the apex of the left ventricle but can be seen in an isolated fashion along the lateral wall. There is often dilation of the left ventricle with associated depressed systolic function. There may also be coincident ventricular hypertrophy, or at least lack of expected ventricular wall thinning for the degree of chamber dilation. Noncompaction can also occur in the setting of congenital heart disease, particularly hypoplastic left heart syndrome, ventricular septal defects, and pulmonary stenosis [50].

### 44.4.2 Etiology and Pathophysiology

LVNC has been increasingly diagnosed over the last 10 years. Previously, cases of LVNC may have been classified as HCM or DCM in part because of a lack of awareness of the diagnosis, limited resolution of earlier generations of echocardiography machines, and lack of standardized diagnostic criteria. LVNC may account for up to 9% of pediatric cardiomyopathies [6]. It can occur in isolation or with other congenital cardiac disease, and both sporadic and familial forms have been described [51]. When LVNC is inherited, X-linked inheritance appears to be most common, but autosomal-dominant, autosomal-recessive, and mitochon-

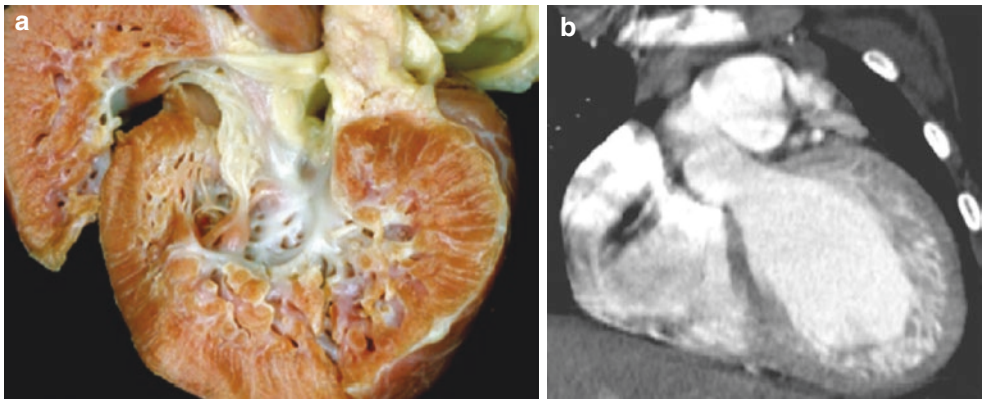


**Fig. 44.4** Left ventricular noncompaction (LVNC) cardiomyopathy. (**a**) Pathologic specimen showing typical "spongiform" myocardium of left ventricle. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh). (**b**) Intertrabecular recesses and dilation of the left ventricle in a teenager with noncompaction cardiomyopathy as shown by computed tomography. (Courtesy of William Devine, Department of Pathology, Children's Hospital of Pittsburgh)

drial inheritance may also occur. Mutations in the G4.5 gene at Xq28 (that encodes tafazzin) are responsible for X-linked LVNC [52] and also some other infantile DCMs, including Barth syndrome, which is characterized by cardiomyopathy (often with LVNC), intermittent neutropenia, peripheral myopathy, and growth delay [53, 54]. LVNC has been postulated to result from an arrest in early embryonic endomyocardial morphogenesis, resulting in a spongy meshwork of fibers and myocardial sinusoids [55]. Patients often have features most consistent with DCM, including symptomatic heart failure and arrhythmias, although some are found to have only asymptomatic LV dysfunction. Waxing and waning of ventricular function has also been described. Some series also report relative high prevalence of ventricular thrombosis and/or systemic embolic events, particularly in adults [56–58].

### 44.4.3 Clinical Presentation

Approximately half of children with LVNC who present for evaluation have signs and symptoms of heart failure. Others may come to evaluation incidentally for cardiomegaly on chest X-ray, abnormal ECG findings, or for assessment of a murmur. Patients may also present with arrhythmias. Most series show a tendency to progression in heart failure symptoms over time [58, 59], although a waxing and waning course is not rare. Presentation in infancy with heart failure due to severe systolic ventricular dysfunction is not unusual, and some of these cases show marked improvement over time, though this may be transient.

### 44.4.4 Management

Discerning LVNC from the broader category of DCM can require a high index of suspicion. Echocardiographic diagnostic criteria have been described [60] and recently called into question [61]. Adjunctive imaging modalities such as CT or MRI may provide better diagnostic information [62] but are less readily accessible and may be impractical during the initial diagnostic evaluation of a critically ill child with heart failure. Genetic testing for mutations in the G4.5 gene may help lead to a specific diagnosis, especially when the family history suggests X-linked inheritance.

Patients who manifest primarily with heart failure due to depressed systolic ventricular function are treated in a fashion similar to those with DCM. Therapy with diuretics and ACE inhibitors, with or without beta-blockers, is often employed during long-term follow-up. Although systemic embolism and arrhythmias (atrial fibrillation and ventricular tachycardia) are relatively common in the adult LVNC population, these are relatively rare in pediatric series. Ventricular ectopy may also be observed. Systemic anticoagulation is indicated when there is severe systolic ventricular dysfunction.

### 44.4.5 Long-Term Outlook

The relative infrequency of LVNC does not allow for proper characterization of the clinical course of children with this diagnosis, as in patients with DCM. Ichida and colleagues [59] report the longest follow-up in their series

of patients with childhood LVNC (median 6 years, range 0–17 years) and described the development of ventricular dysfunction or death in 75% of those followed for ≥10 years. In another series, transplant-free survival in infants with LVNC and no congenital heart defect was 52% at 3 years [50]. This was almost identical to transplant-free survival of 53% among 29 subjects with LVNC in the National Australian Cardiomyopathy Study [27]. Although these studies of LVNC in childhood report median ages at presentation of between 3 months and 7 years [50, 58, 59], there are various reports in adults that describe initial diagnosis as late as 70–75 years [56, 57] with absence of depressed cardiac function in some cases. This suggests that LVNC may be more common than has been observed, with some having only the morphologic findings (deep trabeculations) without overt ventricular dysfunction until much later in life.

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