

Cardiomyopathy in children

Dr Heike Bruehl, MD, and Dr Colin J McMahon, MBBCh, MRCPI, FAAP, Consultant Paediatric Cardiologist, Department of Paediatric Cardiology, Our Lady's Hospital for Sick Children, Crumlin, Dublin

Introduction

Cardiomyopathy is defined as an intrinsic abnormality in systolic and/or diastolic function of the myocardium and represents a significant morbidity and mortality to both paediatric and adult populations.¹ In recent years, our understanding of the molecular and genetic mechanisms responsible for cardiomyopathy has increased exponentially. Although the disease process may appear similar in adults and children, children represent a unique population and data regarding predictors of adverse clinical outcomes in this group are lacking.

Clearer elucidation of high risk groups may have several benefits including more aggressive medical management, earlier listing for cardiac transplantation and increased understanding of the physiological stresses that impose increased morbidity and mortality on these patients.

This article aims to introduce the major forms of cardiomyopathy encountered in paediatrics and discuss current therapies and prognoses.

Classification of cardiomyopathy

There have been several frameworks provided for the classification of cardiomyopathy, with some authors advocating a molecular classification.² The Australian Cardiomyopathy study, which studied all cases between 1987 and 1996, reported an annual incidence of 1.24 per 100,000 children <10 years of age.³

The most common forms of cardiomyopathy in this cohort include dilated cardiomyopathy (DCM) (58.6%), hypertrophic cardiomyopathy (HCM) (25.5%), restrictive cardiomyopathy (RCM) (2.5%) and left ventricular non-compaction cardiomyopathy (LVNC) (9.2%). Lymphocytic myocarditis was present in 25 of 62 cases (40%) of DCM. Sudden cardiac death (SCD) occurred in 11 cases (3.5%). The North American cardiomyopathy study, which looked at Northeastern and Southern USA, found similar findings.⁴

Genetics of cardiomyopathy among children

There are characteristic racial and genetic factors which predispose patients to various forms of cardiomyopathy. For each

form of cardiomyopathy, specific mutations have been determined which are responsible for encoding proteins that compose the cytoskeletal structure. A breakdown in cytoskeletal structure consequently translates to a defective phenotype in these children.

Certain populations may have a pre-disposition to cardiomyopathy also. Arrhythmogenic right ventricular dysplasia (ARVD) has a dramatically increased prevalence among the Italian population and there have been reports of increased risk of HCM among North Americans, Western Europeans and Japanese.^{5,6}

Characterisation of cardiomyopathies

Cardiomyopathies can be classified into the following:

1. Dilated.
2. Hypertrophic.
3. Restrictive.
4. Left ventricular non-compaction.
5. Arrhythmogenic right ventricular dysplasia.
6. Others including arrhythmia-induced and anthracycline-induced.

Dilated cardiomyopathy

DCM is the most common form of cardiomyopathy and is defined as a patient having a dilated and poorly contracting left ventricle, specifically a left ventricular ejection fraction (LVEF) <40%, with left ventricular end-diastolic dimension (LVEDD) >2 Z-scores.⁷ These patients develop congestive heart failure as a consequence of impaired left ventricular (LV) +/- right ventricular (RV) systolic dysfunction.

The aetiology underlying this disease comprises multiple genetic and metabolic disorders, some of which are provided in Table 1.⁷ Differentiation from myocarditis is important as, in the latter case, there may be a significant resolution in LV contractility following a quiescence of the viral process.

Causes and prevalence of DCM

Approximately 50% of cases are idiopathic, with an overall prevalence of 36.5 per 100,000 patients (see Table 1).⁸ In

adults, the majority of cases of DCM become manifest in the fourth decade of life; however, the disease will often declare itself in childhood.

Table 1. Causes of dilated cardiomyopathy

Idiopathic
Acute and chronic myocarditis
-Viral
Enterovirus (Coxsackie A,B, echovirus, poliovirus)
Adenovirus
Cytomegalovirus
Parvovirus
Influenza
EBV
Mumps
Measles
-Non-viral
Rickettsial
Bacterial
Protozoal
Collagen vascular disease
Drugs
Endocrine
Hereditary (AD, AR, X-linked, mitochondrial)
Inborn errors metabolism
Ischaemic (Kawasaki, atheroma, ALCAPA)
Muscular dystrophies
Nutritional deficiencies (selenium, carnitine, thiamine)
Peri-partum
Structural heart disease
Toxins (lead, cobalt)

Cardiac cytoskeleton

The myocardium acts as a mechanical syncytium, coupling individual myocytes to provide a concerted myocardial contraction. Force is generated by the actin-myosin interaction and this energy is transmitted to adjacent sarcomeres at Z discs and between myocytes at the intercalated discs. There is an extensive network of proteins that links these sites. Dystrophin and actin represent two essential proteins in this process and mutations within these components often lead to defective force transmission, which is accompanied by progressive LV dilation and failure (Frank-Starling curve exceeded). The progressive dilation of the left ventricle results in increased wall stress (LaPlace's law) and increased mismatch of myocardial oxygen supply and demand.

With continued ventricular remodelling with ongoing heart failure, cardiac fibroblasts proliferate, mechanically stable collagen is degraded by metalloproteinases and an excess of poorly cross-linked collagen accumulates within the

interstitium.⁹ This results in increased muscle mass, ventricular dilation and wall thinning. Eventually, cardiac apoptosis occurs with non-inflammatory programmed cell death.¹⁰

Genetics of DCM

Several genetic loci have been identified as being responsible for DCM. X-linked cardiomyopathy was one of the earliest detected genetic causes of DCM, highlighting the crucial role of dystrophin in maintaining integrity of the cytoskeleton.¹¹ Other loci include 1p1-1q1, 1q32, 2q31, 3p22-p25, 9q13-q22, 10q21-23 and 15q14.¹²⁻¹⁶

Clinical features of DCM

The most common symptoms are dyspnoea, failure to thrive and orthopnoea in older children. Physical examination will reveal tachycardia, elevated jugular venous pulse (JVP), a displaced apex beat with a gallop rhythm. There may be a mitral or tricuspid valve regurgitation murmur if there is significant atrioventricular valvar dilation or elevated left ventricular end-diastolic pressure (LVEDP).

Hepatomegaly is common, although peripheral oedema is rarely seen in children compared to adults. Chest radiograph demonstrates cardiomegaly with increased pulmonary venous congestion. Echocardiography is diagnostic with a dilated left ventricle with depressed LV function.

Treatment of DCM

The mainstay of medical therapy includes diuretics, cardiac glycosides and angiotensin, converting enzyme inhibitors (afterload reduction), if tolerated. β -blockers (carvedilol, metoprolol) are increasingly used to support the failing myocardium as they reduce myocardial wall stress and myocardial oxygen consumption. Carvedilol is a particularly attractive agent as it has β -blocker, α -blocker and vasodilating actions.¹⁷

Patients in cardiogenic shock may require inotropic support. Dobutamine and milrinone (phosphodiesterase inhibitor) are the most appropriate inotropic agents.¹⁸ Adrenaline is associated with poorer outcomes in adult patients with congestive heart failure and probably results in further trauma to the cytoskeleton. Optimising pre-load and minimising afterload appear to be the optimal means of supporting the myocardium. Occasionally, patients on high inotropic support who continue to demonstrate end-organ failure require support of the myocardium using extra-corporeal membrane oxygenation (ECMO) or ventricular assist devices.

Vatta et al have provided convincing evidence that resting the myocardium results in dystrophin remodelling in patients with DCM.¹⁹ Transplantation may be the only alternative for survival, particularly in high risk groups; children with LVEDP >25mmHg, children presenting >2 years of age, decreased tissue Doppler-imaging velocities and ventricular tachyarrhythmias (VTs).²⁰⁻²⁴ The mean survival for children with DCM is 63-90% at one year to 20-80% at five years.²⁵

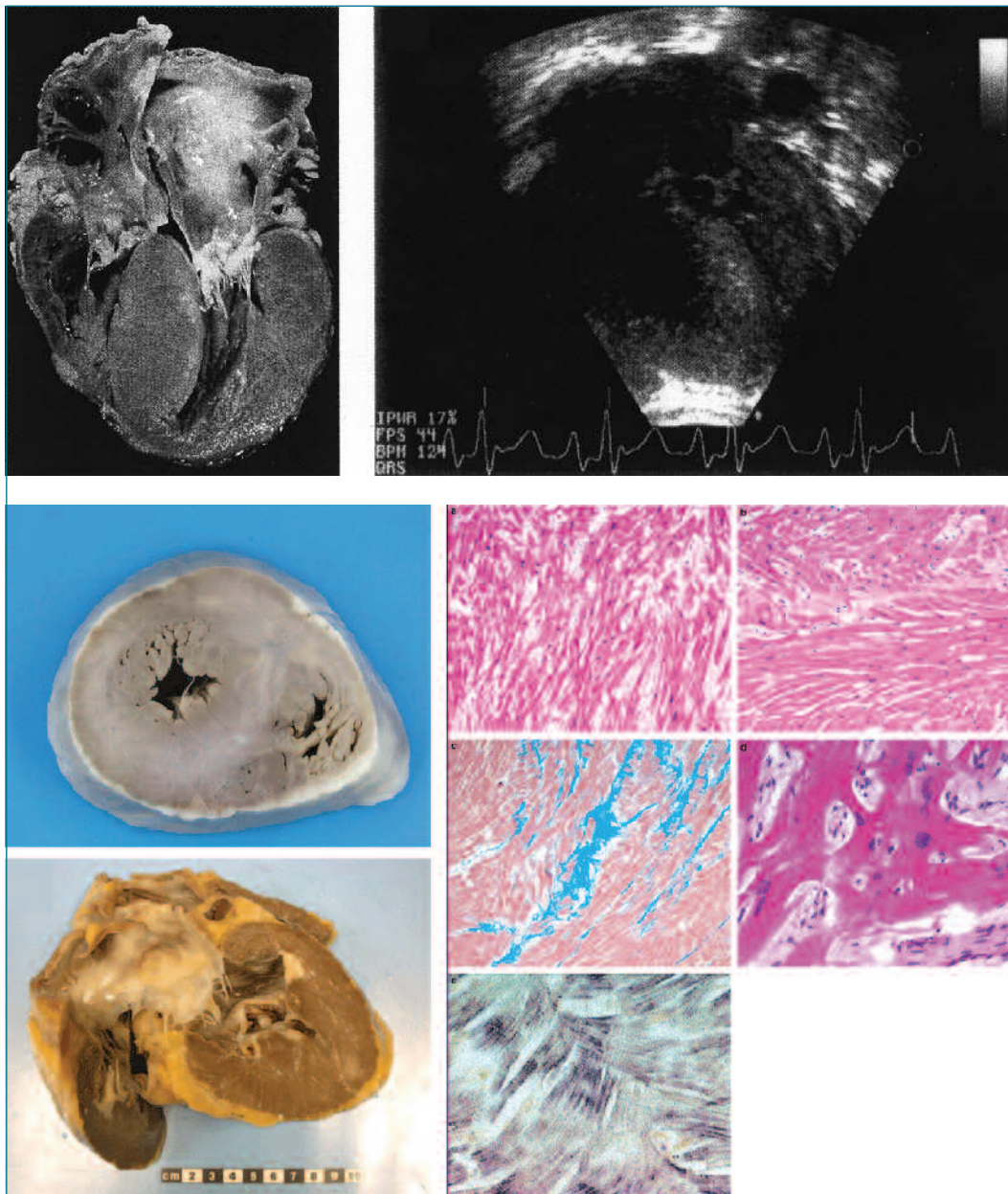


Figure 1.

Hypertrophic cardiomyopathy

HCM is a myocardial disease with a highly heterogeneous phenotype and genotype that affects both children and adult populations. Initially recognised by two French pathologists in 1867,²⁶ it fell to two British cardiologists, Brock and Teare, to first describe this disorder in the late 1950s.^{27,28} Over the last 50 years, HCM has been well defined in terms of pathology, pathophysiology, genetic aetiologies, diagnostic modalities, treatment options and clinical outcomes.

HCM can be defined as a hypertrophied but non-dilated left ventricle in the absence of another cardiac condition or systemic disease (aortic stenosis, systemic hypertension, athletic heart).²⁹ Some of the original descriptions emphasised the presence of asymmetric septal hypertrophy; however, only 25% of patients demonstrated left ventricular outflow tract

(LVOT) obstruction, hence the preferred term is 'hypertrophic cardiomyopathy', with or without obstruction.

There are several patterns of ventricular hypertrophy in HCM. These may include asymmetric septal hypertrophy, (primarily localised to the interventricular septum), concentric left ventricular hypertrophy (LVH) (see Figure 1), posterior wall hypertrophy or apical hypertrophic cardiomyopathy, localised to the apex of the ventricle.

Apical HCM was originally recognised in Japan as producing a spade-like deformity of the left ventricle on angiography with giant negative T waves on ECG.³⁰ Of note, relatives with the same underlying genetic mutation may actually manifest different patterns of hypertrophy, one of the many counter-intuitive features of this disease. Hypertrophy typically develops through life and adolescence is most typically

associated with a significant increase in wall thickness (up to 33-250%, with a mean increase of 100%) in conjunction with somatic growth.

As a consequence of asymmetric septal hypertrophy (ASH) eddy currents are generated within the LVOT, which sucks the mitral valve anterior leaflet into the LVOT, the characteristic systolic anterior motion (SAM) of the mitral valve.³¹ In severe cases, this may result in non-coaptation of the mitral valve and mitral regurgitation.

Histological changes are characteristic of HCM and include chaotic disarray in myocyte organisation.³² Even the myofibrils within the myocyte may demonstrate total disarray. There is not necessarily a relationship between the degree of myocyte disarray and the degree of hypertrophy. Eventually, patchy fibrosis develops between myocytes with an increase in intercellular collagen matrix, perimysial coils and pericellular weaves.³³ As a consequence of the muscular hypertrophy, the coronary arteries may be enveloped by muscle, with compression of the vessels during cardiac systole (myocardial bridging).³⁴ There may also be increased luminal and medial thickening of the vessels and small vessel arteriopathy may ensue.

Clinical presentation of HCM

Clinical presentation may occur in childhood including dyspnoea, angina and syncope. The occurrence of syncope with exercise or exertion always warrants a very thorough cardiac evaluation including ECG, echocardiogram and magnetic resonance imaging (MRI) where necessary. Chest pain may be a typical angina-like episode or may be atypical with a sharp or aching quality outside the substernal area. The aetiology of chest pain may be a manifestation of arteriolar abnormalities, bridging, LVOT obstruction or increased myocardial oxygen demand, given the increased muscle mass. SCD may be the first and last symptom. This is typically in association with an arrhythmic event, VT, ventricular fibrillation (VF) or torsades de pointes.

Identifying children at risk of this has been the focus of much research in the last decade. The degree of outflow tract obstruction and the presence of antecedent symptoms does not predict the risk of SCD.³⁵ There are conflicting data in the adult population whether septal thickness or maximal septal thickness correlate with risk of SCD. What is more likely is the presence of certain malevolent gene mutations which predict risk of a lethal event.

Genetics of HCM

HCM typically has an autosomal-dominant mode of inheritance.³⁶ There have been multiple genes found to be responsible for mutations within the sarcomere, which results in HCM. The most common mutations include β -myosin heavy chain, cardiac troponin T, troponin I, α -tropomyosin, cardiac myosin binding protein C, essential and regulatory myosin proteins and actin.³⁷⁻³⁹ Interestingly, certain mutations are associated with malignant disease and early death such as

Arg403Gln, Arg453Cys and Arg719Trp, while Val606Met is associated with a less malignant form of disease. Mutations within cardiac troponin T are also associated with early death, despite the fact that these patients may not manifest significant ventricular hypertrophy.⁴⁰ Even though the myocyte may not hypertrophy significantly, it can be even more lethal. It is essential that siblings and children of patients who die from HCM undergo evaluation including genetic screening.

Pre-clinical diagnosis of the disease process is now essential. What is frustrating, however, is the fact that certain patients within the same family with the same mutation may manifest minimal hypertrophy compared to other family members, but have a higher risk of death. Needless to say, this results in making management exceedingly difficult.

Other important causes of HCM in children include Noonan's syndrome, Fabry's disease and several metabolic disorders including Pompe's disease (acid maltase deficiency) and glycogen storage disorders.⁴¹ Differentiation of HCM from athletic heart may prove problematic, although tissue Doppler velocities are normal in athletic heart and deconditioning the patient for several months should reveal physiologic remodelling in the athlete.⁴²

Diagnosis

Transthoracic echocardiography is the primary modality for establishing the diagnosis. In adult patients, an interventricular septal thickness of 13mm is taken as diagnostic, while in children the interventricular septal and left ventricle posterior wall measurements should be indexed to BSA or Z-scores derived for these variables. ECG may demonstrate LVH with or without T wave changes. Holter monitoring should be performed to rule out VT.

Therapies for HCM

Primarily, treatment should be medical in the majority of patients. Since the 1960s, the mainstay of therapy has been β -blocker therapy to slow heart rate, augment diastolic filling time, reduce LVOT obstruction and hence improve cardiac stroke volume also. They have the additional benefit of reducing myocardial oxygen consumption by reducing myocardial wall stress, LV contractility and heart rate.

Calcium channel blockers (verapamil) have shown in short- and long-term studies to improve symptoms and exercise capacity in adults with HCM. They are used infrequently in children and, although oral verapamil may be useful in this population, intravenous verapamil is not used because of reported cases of SCD. Diuretics should be avoided in all patients with HCM in addition to inotropic agents such as digitalis and afterload-reducing agents, which may exacerbate LVOT obstruction.

SCD rarely occurs in children less than 10 years of age and is often secondary to ventricular tachycardia/fibrillation

(VT/VF).⁴³ HCM is the most common cause of SCD in the young. This may occur after physical exercise when an increase in heart rate may result in significant haemodynamic compromise/decreased stroke volume from LVOT obstruction. Risk factors for SCD in children have been reported to include previous history of VT/VF, family history of HCM-SCD, recurrent syncope and myocardial bridging. The relationship of ventricular hypertrophy to risk of SCD remains contentious. Spirito et al reported a direct relationship between increased septal thickness and risk of SCD.⁴⁴ This relationship was not supported in a similarly designed study by Elliot et al.⁴⁵ Multiple repetitive non-sustained episodes of VT and hypotensive blood pressure response in children may not be as predictive. Tissue Doppler imaging velocities (transmitral E/Ea septal velocity ratio) have been shown to demonstrate clinical utility in predicting poor outcomes in childhood HCM.⁴⁶

An artificial implantable cardiac defibrillator (AICD) is indicated in patients with aborted cardiac arrest, VF, massive LVH/ASH with symptoms or patients with multiple risk factors.⁴⁷ Repetitive unintentional defibrillation may occasionally occur with these devices and provoke severe anxiety in patients.

Surgical intervention is occasionally required for the alleviation of severe LVOT obstruction, although this is now readily achievable in catheterisation using ethanol septal ablation.⁴⁸ This may result in complete heart block requiring a pacemaker, but tissue Doppler studies have shown significant improvements in LV diastolic relaxation following this procedure.

Restrictive cardiomyopathy

RCM is characterised by impaired diastolic relaxation, abnormal ventricular compliance and elevated L and RV end-diastolic pressures.⁴⁹ Although these latter indices can only be quantified at cardiac catheterisation, echocardiography can demonstrate particular transmitral inflow characteristics such as an elevation in the E:A wave ratio and increased E wave deceleration time (DT).

The findings in RCM are similar to constrictive pericarditis. The ventricular volumes are decreased and, in association with impaired relaxation, progressive enlargement of both atria develops. Cardiac MRI allows assessment of the pericardial thickness.

RCM is relatively rare in children. Recent evidence has demonstrated a particularly poor prognosis once children become symptomatic and certain institutions advocate early transplantation, especially in the setting of acute abdominal or thoracic pain, which is associated with SCD.⁵⁰

Mutations within desmin and actin have been implicated in the development of RCM.⁵¹⁻⁵²

Left ventricular non-compaction cardiomyopathy

Non-compaction of the ventricular myocardium, also known as

left ventricular non-compaction (LVNC), represents an arrest in the normal process of myocardial compaction, resulting in persistence of multiple prominent ventricular trabeculations and deep intertrabecular recesses (see Figure 2).⁵³



Figure 2.

The disorder has only recently been recognised as a distinct form of cardiomyopathy. It was previously termed 'spongy myocardium', although this term has been abandoned as it underscores the hypothesis that the basic morphogenetic abnormality may be arrest of normal compaction of the loose interwoven mesh of myocardial fibres in the embryo.

To date, LVNC has been reported in excess of 100 children. It typically involves the left ventricle, although involvement of the right ventricle has been reported.⁵⁴ Clinical presentations include depressed systolic and diastolic function, systemic embolism and the development of VTs both in adult and paediatric populations.⁵⁵ Children with LVNC may manifest an undulating phenotype with initial DCM, which progresses to HCM. The medical management of LVNC depends upon the clinical phenotype. To date, a small number of patients have been identified with mutations in G4.5 (taffazin gene) and in Cypher/ZASP, but in the majority of cases there is no identified genetic locus.⁵⁶⁻⁵⁷ A small number of patients may also manifest Barth's syndrome, characterised by a dilated phenotype, neutropaenia and elevated 3,5 methylgluconic aciduria.⁵⁸

Arrhythmogenic right ventricular dysplasia (ARVD)

ARVD deserves special mention as this is a highly lethal disease and cause of SCD. There is a high prevalence of this disease in the Italian population and it is characterised by RV regional wall motion abnormalities, replacement of the right ventricular outflow tract (RVOT) by fibro-fatty infiltration and dilation of the right ventricle and atrium.⁵⁹ These findings are best delineated using cardiac MRI using fat saturation sequences (see Figure 3).⁶⁰

Familial occurrence is well recognised with an autosomal

dominant inheritance and genetic heterogeneity has been established with linkage analysis identifying four specific loci on chromosomes 14q23-q24 (ARVD 1), 1q42-q43 (ARVD 2), 14q12-q22 (ARVD 3) and 2q32.1-q32.3 (ARVD 4).⁶¹ The VT associated with this disorder has a left bundle branch block morphology, indicating its origin from the right ventricle.⁶²

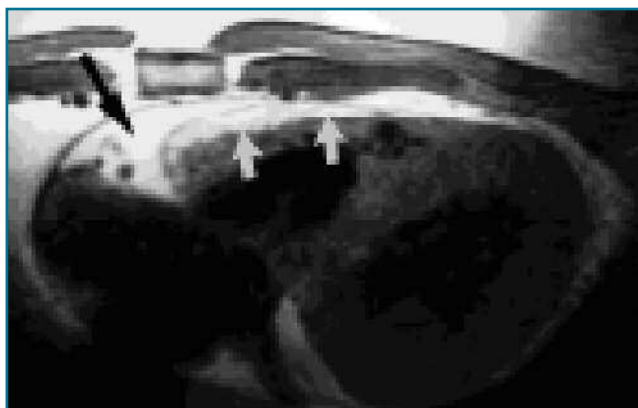


Figure 3.

Anthracycline-induced cardiomyopathy

Anthracyclines (doxorubicin and epirubicin) are well-established agents in chemotherapy that have cardiac toxicity as a side effect.⁶³ This is mediated via oxygen-free radicals. Once the cumulative dose reaches >250mg/m², there is a substantial risk of cardiac dysfunction, which may occur many years after the cessation of treatment. The administration of oxygen-free radical scavengers (dexrazoxane) may reduce the risk of cardiomyopathy and are undergoing clinical trials.⁶⁴

Arrhythmia-induced cardiomyopathy

Intractable atrial or VTs may induce L and/or RV dysfunction.⁶⁵ The most common tachycardia in this setting is atrial ectopic tachycardia. It may be difficult to prove whether the tachycardia or cardiomyopathy is the initial insult. Termination of the arrhythmia and medical therapy with β -blockage, afterload reduction and cardiac glycosides often results in normalisation of the ventricular function.

Future directions

Transcatheter delivery of stem cells may enable regeneration of myocytes and resolution of interstitial fibrosis in patients with dilated and hypertrophic cardiomyopathy.⁶⁶ The utility of ventricular assist devices needs to be further evaluated and the role of portable devices, which children can go home with while awaiting transplantation, needs further advocacy and development.⁶⁷

Gene therapy will undoubtedly have a major role to play in restoring normal function to the misdirected myocyte once effective vectors have been developed and gene transfer can be achieved.

References

1. Towbin JA. Paediatric myocardial disease. *Pediatr Clin North Am* 1999; 46: 289-312.
2. Thiene G, Corrado D, Basso C. Cardiomyopathies: is it time for a molecular classification? *Eur Heart J* 2004; 25: 1772-5.
3. Nugent AW, Daubeney PE, Chondros P et al. National Australian Childhood Cardiomyopathy Study. *New Engl J Med* 2003; 348: 1639-46.
4. Lipschultz SE, Sleeper LA, Towbin JA et al. The incidence of paediatric cardiomyopathy in two regions of the United States. *New Engl J Med* 2003; 348: 1647-55.
5. Fontaine G, Fontaliran F, Frank R. Arrhythmogenic right ventricular cardiomyopathies. Clinical forms and main differential diagnoses. *Circulation* 1998; 97: 1532-5.
6. Maron BJ. Hypertrophic cardiomyopathy. *Moss and Adams' Heart Disease in Infants, Children and Adolescents*. Lippincott, Williams and Wilkins, Baltimore. Chapter 56: 1167-87.
7. Schwartz ML, Cox GF, Lin AE et al. Clinical approach to genetic cardiomyopathy in children. *Circulation* 1996; 94: 2021-38.
8. Manolio TA, Baughman KL, Rodeheffer R et al. Prevalence and aetiology of idiopathic dilated cardiomyopathy (summary of a National Heart, Lung and Blood Institute workshop). *Am J Cardiol* 1992; 69: 1458-66.
9. Gunja-Smith Z, Morales AR, Romanelli R et al. Remodelling of human myocardial collagen in idiopathic dilated cardiomyopathy. Role of metalloproteinases and pyridinoline cross-links. *Am J Pathol* 1996; 148: 1639-48.
10. Narula J, Haider N, Virmani R et al. Apoptosis in myocytes in end-stage heart failure. *New Engl J Med* 1996; 335: 1182-9.
11. Towbin JA, Hejtmancik JF, Brink P et al. X-linked dilated cardiomyopathy: molecular genetic evidence of linkage to the Duchenne muscular dystrophy (dystrophin) gene at the Xp21 locus. *Circulation* 1993; 87: 1854-65.
12. Durand J-B, Bachinski LL, Bieling LC et al. Localisation of a gene responsible for familial dilated cardiomyopathy to chromosome 1q32. *Circulation* 1995; 92: 3387-9.
13. Siu BL, Nimura H, Osborne JA et al. Familial dilated cardiomyopathy locus maps to chromosome 2q31. *Circulation* 1999; 99: 1022-6.
14. Bowles KR, Gajarski R, Porter R et al. Gene mapping of familial autosomal dominant dilated cardiomyopathy to chromosome 10q21-23. *J Clin Invest* 1996; 98: 1355-60.
15. Kass S, MacRae AC, Graber HL et al. A gene defect that causes conduction system disease and dilated cardiomyopathy maps to chromosome 1p1-1q1. *Nat Genet* 1994; 7: 546-51.
16. Muntoni F, Cau M, Ganau A et al. Brief report: deletion of the dystrophin muscle-promoter region associated with x-linked dilated cardiomyopathy. *New Engl J Med* 1993; 329: 921-5.
17. Azeka E, Ramires JA, Ebaid M, Bocchi E. Clinical outcome

- after starting carvedilol in infants and children with severe dilated cardiomyopathy candidates for heart transplantation. *J Heart Lung Transplant* 2001; 20 (2): 222.
18. Brecker SJ, Xiao HB, Mbaissouroum M, Gibson DG. Effects of intravenous milrinone on left ventricular function in ischaemic and idiopathic dilated cardiomyopathy. *Am J Cardiol* 1993; 71 (2): 203-9.
 19. Vatta M, Stetson SJ, Perez-Verdia A et al. Molecular remodelling of dystrophin in patients with end-stage cardiomyopathies and reversal in patients on assistance-device therapy. *Lancet* 2002; 359: 936-41.
 20. McMahon CJ, Nagueh SF, Eapen RS et al. Echocardiographic predictors of adverse clinical events in children with dilated cardiomyopathy: a prospective clinical study. *Heart* 2004; 90: 908-15.
 21. Nugent AW, Davis AM, Kleinert S et al. Clinical, electrocardiographic, and histological correlations in children with dilated cardiomyopathy. *J Heart Lung Transplant* 2001; 20: 1152-7.
 22. Lewis AB. Late recovery of ventricular function in children with idiopathic dilated cardiomyopathy. *Am Heart J* 1999; 138: 334-8.
 23. Arola A, Tuominen J, Ruuskanen O, Jokinen E. Idiopathic dilated cardiomyopathy in children: prognostic indicators and outcome. *Pediatrics* 1998; 101: 369-76.
 24. Burch M, Siddiqi SA, Celermajer DS et al. Dilated cardiomyopathy in children: determinants of outcome. *Br Heart J* 1994; 72: 246-50.
 25. Akagi T, Benson LN, Lightfoot NE et al. Natural history of dilated cardiomyopathy. *Am Heart J* 1991; 121: 1502-6.
 26. Wigle ED, Rakowski H, Kimball BP et al. Hypertrophic cardiomyopathy. Clinical spectrum and treatment. *Circulation* 1995; 92: 1680-92.
 27. Brock RC. Functional obstruction of the left ventricle. *Guys Hosp Rep* 1957; 106: 221-38.
 28. Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J* 1958; 20: 1-8.
 29. Roberts R, Sigwart U. Current concepts of the pathogenesis and treatment of hypertrophic cardiomyopathy. *Circulation* 2005; 112: 293-6.
 30. Alfonso F, Nihoyannopoulos P, Stewart J et al. Clinical significance of giant negative T waves in hypertrophic cardiomyopathy. *J Am Coll Cardiol* 1990; 15: 965-71.
 31. Pollick C, Rakowski H, Wigle ED. Muscular subaortic stenosis: the quantitative relationship between systolic anterior motion and pressure gradient. *Circulation* 1984; 69: 43-9.
 32. Maron BJ, Anan TJ, Roberts WC. Relation between extent of cardiac muscle cell disorganisation and left ventricular wall thickness in hypertrophic cardiomyopathy. *Am J Cardiol* 1992; 70: 785-90.
 33. Shirani J, Pick R, Roberts RWC, Maron BJ. Morphology and significance of the collagen network in the ventricular septum of young patients with hypertrophic cardiomyopathy and sudden cardiac death. *J Am Coll Cardiol* 2000; 35: 36-44.
 34. Yetman AT, McCrindle BW, MacDonald LC et al. Myocardial bridging in children with hypertrophic cardiomyopathy – a risk factor for sudden death. *New Engl J Med* 1998; 339:1201-9.
 35. Romeo F, Pelliccia F, Cristofani R, et al. Hypertrophic cardiomyopathy: is a left ventricular outflow tract gradient a major prognostic determinant? *Eur Heart J* 1990; 11: 233-40.
 36. Thierfelder L, Watkins H, MacRae C et al. Alpha-tropomyosin and cardiac troponin T mutations cause familial hypertrophic cardiomyopathy: a disease of the sarcomere. *Cell* 1994; 77: 701-2.
 37. Niimura H, Bachinski LL, Sangwatanaroj S et al. Mutations in the gene for human cardiac myosin-binding protein C and late onset familial hypertrophic cardiomyopathy. *New Engl J Med* 1998; 338: 1248-57.
 38. Watkins H, McKenna WJ, Thierfelder L et al. Mutations in the genes for cardiac troponin T and alpha-tropomyosin in hypertrophic cardiomyopathy. *New Engl J Med* 1995; 332: 1058-64.
 39. Morgensen J, Klausen IBC, Pedersen AK et al. Alpha-cardiac actin is a novel disease gene in familial hypertrophic cardiomyopathy. *J Clin Invest* 1999; 103: R39-43.
 40. Moolman JC, Corfield VA, Posen B et al. Sudden death due to cardiac troponin T mutations. *J Am Coll Cardiol* 1997; 29: 549-55.
 41. Burch M, Sharland M, Shinebourne E et al. Cardiologic abnormalities in Noonan syndrome: phenotypic diagnosis and echocardiographic assessment of 118 patients. *J Am Coll Cardiol* 1993; 22: 1189-92.
 42. Maron BJ, Pelliccia A, Spataro A et al. Reduction in left ventricular wall thickness after deconditioning in highly trained Olympic athletes. *Br Heart J* 1993; 69: 125-8.
 43. Cannan CR, Reeder GS, Bailey KR et al. Natural history of hypertrophic cardiomyopathy: a population-based study, 1976 through 1990. *Circulation* 1995; 92: 2488-95.
 44. Spirito P, Bellone P, Harris KM, et al. Magnitude of left ventricular hypertrophy and risk of sudden cardiac death in hypertrophic cardiomyopathy. *New Engl J Med* 2000; 342: 1778-85.
 45. Elliot PM, Gimeno Blanes JR, Mahon NG et al. Relation between severity of left-ventricular hypertrophy and prognosis in patients with hypertrophic cardiomyopathy. *Lancet* 2001; 357: 420-4.
 46. McMahon CJ, Nagueh SF, Pignatelli RH, et al. Characterisation of left ventricular diastolic function using tissue Doppler imaging and clinical status in children with hypertrophic cardiomyopathy. *Circulation* 2004; 109: 1756-62.

47. Begley DA, Mohiddin SA, Tripodi D et al. Efficacy of implantable cardioverter defibrillator therapy for primary and secondary prevention of sudden cardiac death in hypertrophic cardiomyopathy. *Pacing Clin Electrophysiol* 2003; 326: 1887-96.
48. Chang SM, Lakkis NM, Franklin J et al. Predictors of outcome after alcohol septal ablation therapy in patients with hypertrophic cardiomyopathy. *Circulation* 2004; 109: 824-7.
49. Russo LM, Webber SA. Idiopathic restrictive cardiomyopathy in children. *Heart* 2005; 91: 1199-202.
50. Rivenes SM, Kearney DL, Smith EO, Towbin JA, Denfield SW. Sudden death and cardiovascular collapse in children with restrictive cardiomyopathy. *Circulation* 2000; 102: 876-82.
51. Weller RJ, Weintraub R, Addonizio LJ, Chrisant MR, Gersony WM, Hsu DT. Outcome of idiopathic restrictive cardiomyopathy. *Am J Cardiol* 2002; 90: 501-6.
52. Kimberling MT, Balzer DT, Hirsch R, Mendeloff E, Huddleston CB, Canter CE. Cardiac transplantation for paediatric restrictive cardiomyopathy: presentation, evaluation, and short-term outcome. *J Heart Lung Transplant* 2002; 21: 455-9.
53. Chin TK, Perloff JK, Williams RG et al. Isolated non-compaction of the left ventricular myocardium. A study of eight cases. *Circulation* 1990; 82: 507-13.
54. Oechslin EN, Attenhofer JCH, Rojas JR et al. Long-term follow-up of 34 adults with isolated left ventricular non-compaction: a distinct cardiomyopathy with poor prognosis. *J Am Coll Cardiol* 2000; 36: 493-500.
55. Pignatelli RH, McMahon CJ, Dreyer WJ et al. Clinical characterisation of left ventricular non-compaction in children: a relatively common form of cardiomyopathy. *Circulation* 2003; 108: 2672-8.
56. Kenton AB, Sanchez X, Coveler KJ et al. Isolated left ventricular non-compaction is rarely caused by mutations in G4.5, alpha-dystrobrevin and FK Binding Protein-12. *Mol Genet Metab* 2004; 82: 162-6.
57. Vatta M, Mohapatra B, Jimenez S et al. Mutations in Cypher/ZASP in patients with dilated cardiomyopathy and left ventricular non-compaction. *J Am Coll Cardiol* 2003; 42: 2014-27.
58. Ichida F, Tsubata S, Bowles KR et al. Novel gene mutations in patients with left ventricular non-compaction or Barth syndrome. *Circulation* 2001; 103: 1256-63.
59. Naccarella F, Naccarelli G, Fattori R et al. Arrhythmogenic right ventricular dysplasia cardiomyopathy: current opinions on diagnostic and therapeutic aspects. *Curr Opin Cardiol* 2001; 16: 8-16.
60. Abbara S, Migrino RQ, Sosnovik DE et al. Value of fat suppression in the MRI evaluation of suspected arrhythmogenic right ventricular dysplasia. *AJR Am J Roentgenol* 2004; 182: 587-91.
61. Towbin JA, Vatta M, Li H. Genetics of Brugada, long QT, and arrhythmogenic right ventricular dysplasia. *J Electrocardiol* 2000; 33: 11-22.
62. Marcus FI, Fontaine G. Arrhythmogenic right ventricular dysplasia/cardiomyopathy: a review. *Pacing Clin Electrophysiol* 1995; 18: 1298-314.
63. Hale JP, Lewis JJ. Anthracyclines: cardiotoxicity and its prevention. *Arch Dis Child* 1994; 71: 457-62.
64. Hellmann K. Preventing the cardiotoxicity of anthracyclines by dexrazoxane. *Br Med J* 1999; 319: 1085-6.
65. Anselme F, Boyle N, Josephson M. Incessant fascicular tachycardia: a cause of arrhythmia induced cardiomyopathy. *Pacing Clin Electrophysiol* 1998; 21: 760-3.
66. Nagaya N, Kangawa K, Itoh T et al. Transplantation of mesenchymal cells improves cardiac function in a rat model of dilated cardiomyopathy. *Circulation* 2005; 112: 1332-8.
67. Van Doorn C, Karimova A, Burch M, Goldman A. Sequential use of extra-corporeal membrane oxygenation and the Berlin Heart Left Ventricular Assist Device for 106-day bridge to transplant in a two-year-old child. *ASAIO J* 2005; 51: 668-9.

Correspondence to: Dr Colin J McMahon, MB, BCh, MRCPI, Consultant Paediatric Cardiologist, Department of Paediatric Cardiology, Our Lady's Hospital for Sick Children, Crumlin, Dublin 12. Tel: (01) 409 6153; email: colin.mcmahon@olhsc.ie