Cardiology in the Young (2015), **25(Suppl. 2)**, 140–153
doi:10.1017/S1047951115000943

Original Article

Lessons learned from the Pediatric Cardiomyopathy Registry (PCMR) Study Group*

James D. Wilkinson,[1] Joslyn A. Westphal,[1] Neha Bansal,[2] Jason D. Czachor,[1] Hiedy Razoky,[1] Steven E. Lipshultz[1,3]

[1]*Department of Pediatrics, Wayne State University School of Medicine, Children's Research Center of Michigan;* [2]*Department of Pediatrics, Detroit Medical Center, Children's Hospital of Michigan, Detroit, Michigan, United States of America;* [3]*University of Miami Miller School of Medicine, Miami, Florida*

Abstract Cardiomyopathy is a rare disorder of the heart muscle, affecting 1.13 cases per 100,000 children, from birth to 18 years of age. Cardiomyopathy is the leading cause of heart transplantation in children over the age of 1. The Pediatric Cardiomyopathy Registry funded in 1994 by the National Heart, Lung, and Blood Institute was established to examine the epidemiology of the disease in children below 18 years of age. More than 3500 children across the United States and Canada have been enrolled in the Pediatric Cardiomyopathy Registry, which has followed-up these patients until death, heart transplantation, or loss to follow-up. The Pediatric Cardiomyopathy Registry has provided the most in-depth illustration of this disease regarding its aetiology, clinical course, associated risk factors, and patient outcomes. Data from the registry have helped in guiding the clinical management of cardiomyopathy in children under 18 years of age; however, questions still remain regarding the most clinically effective diagnostic and treatment approaches for these patients. Future directions of the registry include the use of next-generation whole-exome sequencing and cardiac biomarkers to identify aetiology-specific treatments and improve diagnostic strategies. This article provides a brief synopsis of the work carried out by the Pediatric Cardiomyopathy Registry since its inception, including the current knowledge on the aetiologies, outcomes, and treatments of cardiomyopathy in children.

Keywords: Cardiomyopathy; paediatrics; patient registry; heart failure; Pediatric Cardiomyopathy Registry

Received: 5 February 2015; Accepted: 1 May 2015

ALTHOUGH CARDIOMYOPATHY IS A RELATIVELY rare disease, it is the primary reason for heart transplantation in children, particularly in those older than 1 year of age.[1–4] Literature on the epidemiology of cardiomyopathy was negligible before the 1990s. Since 1994, the National Heart, Lung, and Blood Institute has funded the Pediatric Cardiomyopathy Registry Study Group, which has conducted a number of large, multi-centre observational studies of primary and idiopathic cardiomyopathies. At the time of its inception, it was primarily designed to determine the epidemiology and clinical course of cardiomyopathy in children. Since that time, the Pediatric Cardiomyopathy Registry has added studies of the aetiologies of paediatric cardiomyopathy, including gene discovery, genotype–phenotype associations, the utility of cardiac biomarkers in clinical assessment and outcome prediction, and the physical and psychosocial functional status of both affected children and their families.

Design of the Pediatric Cardiomyopathy Registry

The original Pediatric Cardiomyopathy Registry design included 98 paediatric cardiology centres in the United States and Canada, which collected clinical data regarding factors associated with the study's primary

*Presented at Johns Hopkins All Children's Heart Institute, International Pediatric Heart Failure Summit, Saint Petersburg, Florida, United States of America, 4–5 February, 2015.

Correspondence to: S. E. Lipshultz, MD, Department of Pediatrics, Wayne State University School of Medicine, 3901 Beaubien Boulevard, 1K40, Detroit, MI 48201, United States of America.Tel: +313 745 5870; Fax: +313 993 0390; E-mail: slipshultz@med.wayne.edu

outcomes: death or heart transplantation.[5] In addition, we attempted to enrol nearly 100% of cases at two Pediatric Cardiomyopathy Registry centres – Boston Children's Hospital and its New England referral centres and Texas Children's Hospital and its Central Southwest referral centres – to estimate cardiomyopathy incidence and other epidemiologic parameters.[5,6] Over the subsequent years, further Pediatric Cardiomyopathy Registry studies have focussed on 11–15 of the largest US–Canadian paediatric heart centres that could provide the largest number of eligible patients and the most complete data sets.

Since its inception, patients aged 18 years or less who were diagnosed with cardiomyopathy – via quantitative echocardiographic criteria, a pattern of cardiomyopathy matching a defined, semi-quantitative pattern; or tissue analysis – were eligible for inclusion to the Pediatric Cardiomyopathy Registry (Table 1). Each case was classified according to morphology as dilated, hypertrophic, restrictive, mixed, or other type of cardiomyopathy. Since 1994, new phenotypes of cardiomyopathy have been added to the Pediatric Cardiomyopathy Registry, such as left ventricular non-compaction. Patients with secondary causes of heart muscle disease were excluded from the study in order to focus this research on the aetiologies and outcomes of children with primary cardiomyopathies (Table 2).

Table 1. Inclusion criteria for enrolment in the Pediatric Cardiomyopathy Registry.

Echocardiographic measurements
Left ventricular fractional shortening or ejection fraction >2 SD below the normal mean for age. Fractional shortening is acceptable in patients with a normal ventricular configuration and no regional wall motion abnormalities. Echocardiographic, radionuclide or contrast angiographic, or MRI evidence of abnormal ejection fraction is also an acceptable criterion, but age-appropriate norms for each laboratory must be used
Left ventricular posterior wall thickness at end diastole >2 SD above the normal mean for body-surface area
Left ventricular posterior wall thickness at end diastole >2 SD below the normal mean for body-surface area
Left ventricular end-diastolic dimension or volume >2 SD above the normal mean for body-surface area. Dimension data are acceptable under the conditions outlined for fractional shortening above, and volume data may be derived from the imaging methods as above
Clinical patterns
Localised ventricular hypertrophy such as septal thickness >1.5 × left ventricular posterior wall thickness with at least normal left ventricular posterior wall thickness, with or without dynamic outflow obstruction
Restrictive cardiomyopathy: one or both atria enlarged relative to ventricles of normal or small size with evidence of impaired diastolic filling and in the absence of marked valvular heart disease
Contracted form of endocardial fibroelastosis, similar to restrictive cardiomyopathy plus echo-dense endocardium
Ventricular dysplasia/Uhl's anomaly: very thin right ventricle with dilated right atrium, usually better assessed by MRI than by echocardiography
Concentric hypertrophy in the absence of a haemodynamic cause: a single measurement criterion of left ventricular posterior wall thickness at end diastole >2 SD would suffice
Left ventricular myocardial non-compaction: very trabeculated spongiform left ventricle myocardium with multiple interstices

Table 2. Exclusion criteria for enrolment in the Pediatric Cardiomyopathy Registry.

Endocrine disease known to cause heart muscle disease, including infants of diabetic mothers
History of rheumatic fever
Toxic exposures known to cause heart muscle disease – for example, anthracyclines, mediastinal radiation, iron overload, or heavy metal exposure
HIV infection or born to an HIV-positive mother
Kawasaki disease
Congenital heart defects unassociated with malformation syndromes – for example, valvular heart disease or congenital coronary artery malformations
Immunological disease
Invasive cardiothoracic procedures or major surgery during the preceding month, except those specifically related to cardiomyopathy, including left ventricular assist devices, extracorporeal membrane oxygenation, and automatic implanted cardioverter defibrillator placement
Uraemia, active or chronic
Abnormal ventricular size or function that can be attributed to intense physical training or chronic anaemia
Chronic arrhythmia, unless the inclusion criteria were documented before the onset of the arrhythmia, except that a patient with chronic arrhythmia, subsequently ablated, whose cardiomyopathy persists after 2 months is not to be excluded
Malignancy
Pulmonary parenchymal or vascular disease – for example, cystic fibrosis, cor pulmonale, or pulmonary hypertension
Ischaemic coronary vascular disease
Age 18 years or older
Association with drugs known to cause hypertrophy – for example, growth hormone, corticosteroids, or cocaine

At all times, the Pediatric Cardiomyopathy Registry has utilised a highly trained outreach team that travelled to the centres to enrol new cases and extract data from medical records at regular intervals to perform standardised data collection. Data collection included demographic descriptors, quantitative echocardiographic measurements, a brief family history, transplant status, and clinical findings.

Aims of the Pediatric Cardiomyopathy Registry

Since its establishment, the aims of the Pediatric Cardiomyopathy Registry have evolved over time. The original aims were primarily epidemiological in nature and intended to describe the incidence and clinical factors at presentation of cardiomyopathy in children as well as describe the clinical outcomes – death or heart transplantation and the predictors of those outcomes. In a subsequent study, the study aims were further expanded through collaboration with the Pediatric Heart Transplant Study Group's data set to examine both pre- and post-transplant outcomes and associated risk factors.

At present, the Pediatric Cardiomyopathy Registry is the largest pediatric cardiomyopathy registry in the world containing data collected annually from 3549 children until heart transplant, death, or loss to follow-up. It provides the most comprehensive picture of this disease, and thus is the starting point for new diagnostic and treatment strategies. Analyses of the database have resulted in important findings regarding the incidence, aetiology, disease course, and estimates and determinants of mortality and transplant outcomes, with a new focus on the genetic determinants of cardiomyopathy in children.

Incidence of paeditric cardiomyopathy

A study by Lipshultz et al[6] estimated that the annual incidence of paediatric cardiomyopathy in the United States was 1.13 cases per 100,000 children. This estimate is comparable with reports from similar registries in other countries including Finland and Australia.[7,8] The incidence of cardiomyopathy was significantly higher in infants under 1 year of age and was also found to be higher in boys, children who were black, and children who were from the New England region of the cohort, compared with those from the Central Southwest region.[6] Dilated cardiomyopathy was the most common phenotype among children in the Pediatric Cardiomyopathy Registry, accounting for 51% of all cases. After dilated cardiomyopathy, the most common phenotypes were as follows: hypertrophic cardiomyopathy (42%), restrictive cardiomyopathy and mixed hypertrophic and restrictive cardiomyopathy (3%), and idiopathic cardiomyopathy (4%).

Aetiology and outcomes by paeditric cardiomyopathy phenotype

An analysis of 916 children enrolled in the Pediatric Cardiomyopathy Registry showed that only one-third of patients in the Pediatric Cardiomyopathy Registry had a known cause of cardiomyopathy at diagnosis.[9] Additional studies have confirmed that most cases of paediatric cardiomyopathy lack a causal diagnosis.[6,8] It is possible that this low rate of causal diagnoses may contribute to poor outcomes in children with this disease.

Aetiological results for all cardiomyopathy phenotypes

A preliminary analysis of the Pediatric Cardiomyopathy Registry examined both genetic and infectious aetiologies of the dilated, hypertrophic, restrictive, and mixed functional cardiomyopathy phenotypes in 160 children. This targeted genetic analysis found that the prevalence of variants of the G4.5 mutation of the taffazin gene was similar in both boys and girls (25 versus 22%, respectively; Table 3).[10]

Table 3. G4.5 gene variants found in 37 of 160 children enrolled in the Pediatric Cardiomyopathy Registry.*

Sex	n/N (%)	Hemizygous SNP (n/N (%))	Intronic substitution, SNP (n/N (%))	Missense substitution, unclassified (n/N (%))	Hemizygous mutation* (n/N (%))
Boys	27/110 (25)**	22/27 (81)	24/27 (89)	3/27 (11)	2/27 (7)
Girls	10/48 (22)**	3/10 (30)	10/10 (100)	0/10 (0)	0/10 (0)

DCM = dilated cardiomyopathy; HCM = hypertrophic cardiomyopathy; SNP = single nucleotide polymorphism
Source: Towbin et al.[10]
*The number of children with G4.5 gene variants as a proportion of all children with the same diagnosis was nine of 45 (20%) children with hypertrophic cardiomyopathy; 19 of 79 (24%) with dilated cardiomyopathy; three of 10 (30%) with restrictive cardiomyopathy; four of 22 (18%) with other or mixed forms of cardiomyopathy; and two of two with unknown forms
**Causes of cardiomyopathy in boys included two with Barth syndrome, two with probable myocarditis, one with Cori disease, one with Noonan syndrome, one with familial DCM, and six with idiopathic disease; causes in girls included two with familial HCM, two with confirmed myocarditis, and six with idiopathic disease. Children with Barth syndrome each had two variants, denoted here as hemizygous mutations, hemizygous SNPs were not counted

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

Table 4. Prevalence of congestive heart failure and median fractional shortening z-scores for 1426 children with dilated cardiomyopathy at the time of diagnosis.

Cause of DCM	Heart failure at diagnosis (%)	Fractional shortening z-score (IQR)
Idiopathic (n = 941)	74	−9.62 (−11.42 to −7.16)
Myocarditis (n = 222)	84	−9.11 (−11.05 to −6.67)
Neuromuscular disorders (n = 125)	35	−5.88 (−8.02 to −3.32)
Familial (n = 66)	53	−7.07 (−9.63 to −3.68)
Inborn errors of metabolism (n = 54)	60	−8.94 (−10.30 to −5.33)
Malformation syndromes (n = 15)	67	−5.95 (−9.49 to −5.10)

DCM = dilated cardiomyopathy; IQR = interquartile range
Data are from the Pediatric Cardiomyopathy Registry

G4.5 variants were found in 30% of children with restrictive cardiomyopathy, 24% with dilated cardiomyopathy, 20% with hypertrophic cardiomyopathy, and 18% with a mixed type of cardiomyopathy.

In addition to examining the variants of the G4.5 mutation, the same study also analysed possible viral aetiologies using myocardial tissue samples from 44 children.[10] Viral genome analysis of the tissues was positive for Epstein–Barr virus (4.5%) and for parvovirus B19 (13.6%). Tests for cytomegalovirus, adenovirus, and enterovirus were negative, which may indicate that these viruses are rarely seen in viral myocarditis.

Dilated cardiomyopathy

Outcomes for children with dilated cardiomyopathy depend on an aggregate of disease aetiology, age at diagnosis, echocardiographic parameters, and heart failure at presentation. A particular study of the Pediatric Cardiomyopathy Registry showed that children with dilated cardiomyopathy had a 31% death or transplant rate at 1 year, increasing to 46% at 5 years of age;[3] however, these rates showed wide variation based on the aetiology of the disease (Fig 1). Only 34% of children with dilated cardiomyopathy had a known aetiology: 16% myocarditis, 9% neuromuscular disorders, 5% familial, 4% inborn errors of metabolism, and 1% malformation syndromes. A separate analysis of the Pediatric Cardiomyopathy Registry found that a family history, older age at diagnosis, smaller left ventricular end-diastolic and end-systolic dimensions, higher left ventricular shortening fraction, viral serologic testing, and endomyocardial or skeletal biopsy were associated with the establishment of a causal diagnosis for children with dilated cardiomyopathy.[9]

Overall, 71% of children with dilated cardiomyopathy presented with congestive heart failure at diagnosis, although the percentage of those with congestive heart failure varied by aetiology (Table 4).[3] In addition,

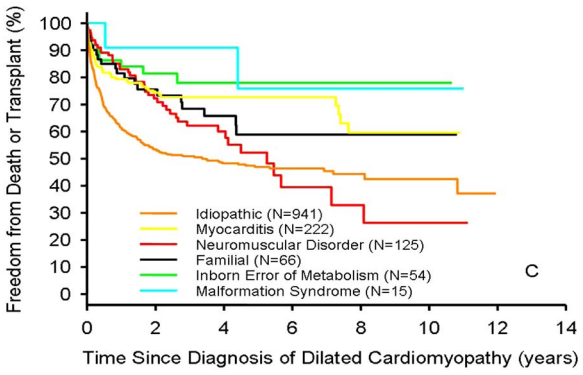

Figure 1.
Freedom from death or transplantation for 1423 children with dilated cardiomyopathy, by cause. Data are from the Pediatric Cardiomyopathy Registry collected between 1990 and 2002 (reproduced with permission from Towbin et al[3]).

children with dilated cardiomyopathy who were under the age of 6 had better survival rates than older children ($p < 0.001$). We found that congestive heart failure at the time of diagnosis and lower left ventricular fractional shortening z-scores were predictors of worse outcomes in patients with idiopathic dilated cardiomyopathy.[11]

Although children with dilated cardiomyopathy often have poor outcomes, normalisation of systolic function and ventricular size was demonstrated in 22% of children with dilated cardiomyopathy within 2 years of diagnosis in the Pediatric Cardiomyopathy Registry.[12] Predictors of normalisation of ventricular function included younger age and lower left ventricular dilation at diagnosis; however, a small percentage of children who experienced recovery later died or were transplanted, which may indicate the need for close follow-up of these patients.

Analysis of the Pediatric Cardiomyopathy Registry data at the time of diagnosis and up to 12 months later showed that children with dilated cardiomyopathy who survived at least for 1 year had a significant decrease in left ventricular end-diastolic dimension and

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

an increase in left ventricular thickness-to-dimension ratio, consistent with favourable left ventricular re-modelling.[13] In addition, children with dilated cardiomyopathy who survived at least for 1 year had a significant improvement in left ventricular function compared with those who died or received a heart transplant during the 12 months after diagnosis.

Before the Pediatric Cardiomyopathy Registry, little was known regarding risk factors for sudden cardiac death in children with dilated cardiomyopathy. We found that the 5-year cumulative incidence of sudden cardiac death in children with dilated cardiomyopathy in the Pediatric Cardiomyopathy Registry was only 2.4%.[14] Factors that increased this risk included presence of congestive heart failure and anti-arrhythmic medications. The same study helped develop a model to aid clinicians in identifying children who may be at high risk for sudden cardiac death (sensitivity 86%, specificity 57%). Based on this model, children with dilated cardiomyopathy who have a left ventricular end-systolic dimension z-score greater than 2.6, an age at diagnosis <14.3 years, and a left ventricular posterior wall thickness-to-dimension ratio <0.14 are considered to be at high risk for sudden cardiac death.

A competing risks model, stratified by aetiology, was used to identify differential predictors of death or transplantation in children with dilated cardiomyopathy.[15] For children with neuromuscular disorders and dilated cardiomyopathy, decreased left ventricular fractional shortening was associated with both death and heart transplantation. In addition, higher left ventricular end-diastolic dimension predicted transplantation in the same group. In children with myocarditis and dilated cardiomyopathy, an increased risk of death or transplantation was associated with an older age at diagnosis, the presence of congestive heart failure, and an increased left ventricular end-diastolic dimension. When comparing children with familial dilated cardiomyopathy, the risk of death or transplantation was increased in those who had congestive heart failure at diagnosis and lower left ventricular fractional shortening z-scores.

Overall, 26% of children with dilated cardiomyopathy in the Pediatric Cardiomyopathy Registry with a known cause of cardiomyopathy had an underlying neuromuscular disorder.[3] The primary neuromuscular disorders observed in the cohort were Duchenne muscular dystrophy and Becker muscular dystrophy. In comparing survival rates for children with each type of muscular dystrophy, we found that children with Becker muscular dystrophy had better survival rates at 5 years than those with Duchenne muscular dystrophy (57 versus 100%, respectively). On the other hand, patients with Becker-type muscular dystrophy had a higher transplantation rate than patients with Duchenne muscular dystrophy (25 versus 0%, respectively).[16] The same analysis also compared patients with a neuromuscular disorder – either Duchenne- or Becker-type muscular dystrophy – and patients with non-neuromuscular disease-related dilated cardiomyopathies to examine differences in outcomes. Survival did not differ significantly between children with a neuromuscular disorder and children with other non-neuromuscular dilated cardiomyopathies (59 versus 71% at 5 years, respectively).

Myocarditis accounts for almost 50% of cases of dilated cardiomyopathy with a known cause of disease in the Pediatric Cardiomyopathy Registry.[9] An analysis of the Pediatric Cardiomyopathy Registry showed no differences in the outcomes for children with probable myocarditis and biopsy-confirmed cases of myocarditis (Fig 2).[17] In children with myocarditis and dilated cardiomyopathy, normalisation of echocardiographic findings occurred in nearly half the patients, and the mortality and transplant rates were much lower, when compared with idiopathic dilated cardiomyopathy. Lower left ventricular fractional shortening at presentation predicted mortality, whereas a higher left ventricular posterior wall thickness predicted transplantation in this group.

Overall, 14% of children with a known cause of dilated cardiomyopathy were found to have familial isolated cardiomyopathy, defined as having two or more family members with a history of cardiomyopathy.[3] The Pediatric Cardiomyopathy Registry found that 1-year survival was significantly better in patients with familial dilated cardiomyopathy (87%) compared with idiopathic dilated cardiomyopathy (60%).[18] In addition, patients with familial isolated cardiomyopathy had higher left ventricular ejection fractions, lower end-diastolic and end-systolic dimensions, and lower left ventricular mass than those with idiopathic dilated cardiomyopathy. Left ventricular end-diastolic dimension z-scores predicted an increased risk of death or transplantation in children with familial isolated cardiomyopathy.

Hypertrophic cardiomyopathy

Outcomes for children with hypertrophic cardiomyopathy varied widely with age and cause of diagnosis (Figs 3 and 4).[19] In one study of the Pediatric Cardiomyopathy Registry, only 26% of children with hypertrophic cardiomyopathy had a known aetiology.[19] For the 26% of patients with a known aetiology, causes of diagnosis included malformation syndromes (9%), inborn errors of metabolism (9%), and neuromuscular disorders (8%). Decreased height and weight for age, sex (female), and higher posterior wall thickness were associated with establishing a causal diagnosis.[9] Left ventricular fractional shortening and

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

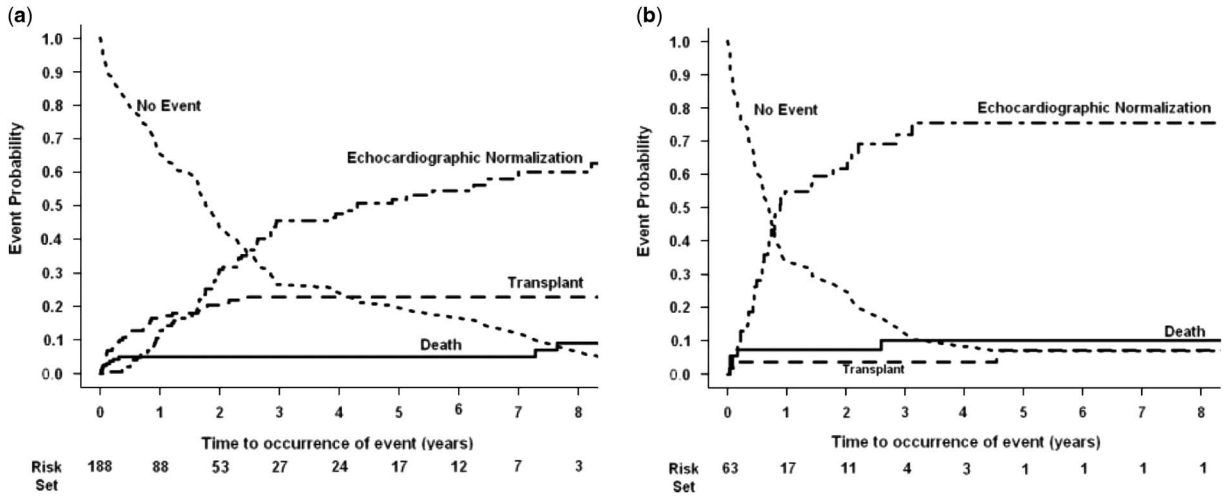

Figure 2.
*Crude cumulative incidences of echocardiographic normalisation, cardiac transplantation, and death among children with myocarditis – combined biopsy-confirmed myocarditis and probable myocarditis groups – and abnormal function at presentation with left ventricular end-diastolic dilation at diagnosis (**a**) or no left ventricular end-diastolic dilation at diagnosis (**b**). The two groups differed in the incidence of cardiac transplant ($p = 0.02$) and echocardiographic normalisation rates ($p < 0.001$) but not mortality ($p = 0.45$). Curves are truncated at 8 years (reprinted with permission from Foerster et al[17]).*

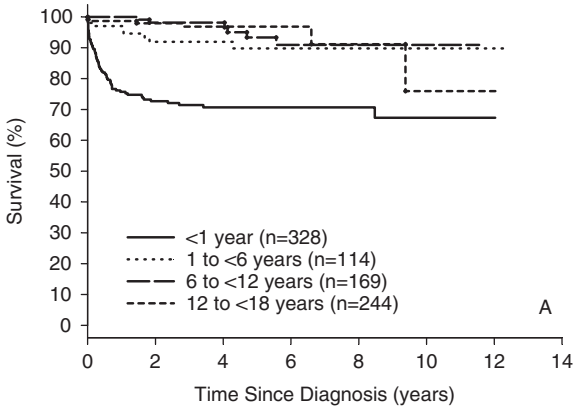

Figure 3.
Freedom from death or transplantation for 855 children with idiopathic hypertrophic cardiomyopathy, by age at diagnosis. Data are from the Pediatric Cardiomyopathy Registry collected between 1990 and 2002 (reproduced with permission from Colan et al[19]).

prevalence of congestive heart failure varied greatly by the aetiological group (Table 5).[19]

The poorest outcomes for children with hypertrophic cardiomyopathy were seen in those with a concurrent diagnosis of hypertrophic cardiomyopathy and inborn errors of metabolism (2-year rate of death or transplantation, 57%).[20] Children with mixed hypertrophic and dilated cardiomyopathy or mixed hypertrophic and restrictive cardiomyopathy also had high rates of death or transplantation at 2 years (45 and 38%, respectively). Although risk factors for death or transplantation differed by the aetiology of hypertrophic cardiomyopathy, in general, these included younger age, lower weight, presence of congestive heart failure, increased left ventricular posterior wall thickness, decreased left ventricular fractional shortening, increased left ventricular septal thickness, or the presence of any two or more of these risk factors (Fig 5). The risk of death or transplantation increased significantly as the number of risk factors increased.

Results from the Pediatric Cardiomyopathy Registry showed that children with Noonan syndrome and hypertrophic cardiomyopathy were more likely to present in the first 6 months of life, were three times more likely to present with heart failure, and had a significantly higher mortality in the 1st year of life compared with other children with hypertrophic cardiomyopathy.[21] This increased mortality rate was at least partially attributable to the younger age and increased prevalence of congestive heart failure in the children with Noonan syndrome compared with other children with hypertrophic cardiomyopathy. Children with Noonan syndrome and hypertrophic cardiomyopathy who presented with congestive heart failure in the first 6 months of life were at the highest risk for mortality. Children with Noonan syndrome and hypertrophic cardiomyopathy in the Pediatric Cardiomyopathy Registry were rarely listed and none of them received a heart transplant. This group should be considered for listing for heart transplantation at the time of diagnosis in the absence of contraindications for listing.

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

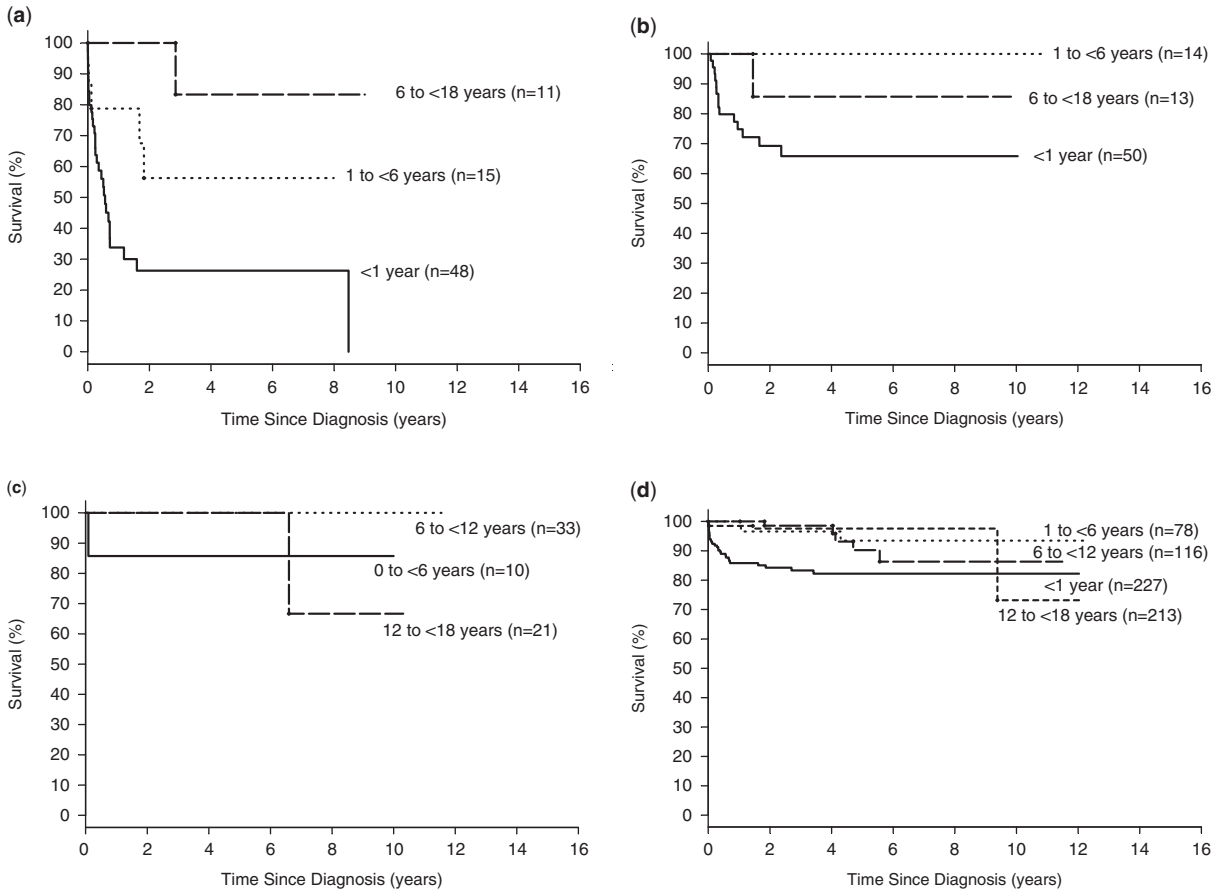

Figure 4.
*Survival rates from the date of diagnosis of cardiomyopathy in children with (**a**) inborn errors of metabolism ($n = 74$, logrank $p < 0.001$); (**b**) malformation syndromes ($n = 77$, logrank $p = 0.07$); (**c**) neuromuscular disease ($n = 64$, logrank $p = 0.22$); and (**d**) idiopathic hypertrophic cardiomyopathy ($n = 634$, logrank $p < 0.001$), by age at diagnosis (reproduced with permission from Colan et al[19])*

Table 5. Prevalence of congestive heart failure and mean fractional shortening z-scores for 849 children with hypertrophic cardiomyopathy at the time of diagnosis.

Cause of HCM	Heart failure at diagnosis (%)	Fractional shortening z-score (SD)
Inborn errors of metabolism (n = 74)	40.3	−1.11 (5.65)
Malformation syndromes (n = 77)	23.4	5.42 (4.31)
Neuromuscular disorders (n = 64)	6.4	3.01 (3.40)
Infantile (n = 634)	9.9	3.62 (5.15)

HCM = hypertrophic cardiomyopathy; IQR = interquartile range
Data are from the Pediatric Cardiomyopathy Registry

Inborn errors of metabolism accounted for 27% of the cases of hypertrophic cardiomyopathy with a known cause of disease in the Pediatric Cardiomyopathy Registry.[9] Almost 50% of children with cardiomyopathy caused by inborn errors of metabolism had an unspecified disorder. Across all cardiomyopathy phenotypes, the most common mitochondrial disorder was Barth syndrome (27%). Poor survival rates were observed in children with hypertrophic cardiomyopathy caused by a metabolic gene deficiency, with a 2-year survival rate of only 51%. In addition, a diagnosis of cardiomyopathy before 1 year of age was associated with an increased risk of death in patients with inborn errors of metabolism who present with hypertrophic cardiomyopathy.

Restrictive cardiomyopathy

Restrictive cardiomyopathy is the least common form of all phenotypes, accounting for only 4.5% of all

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

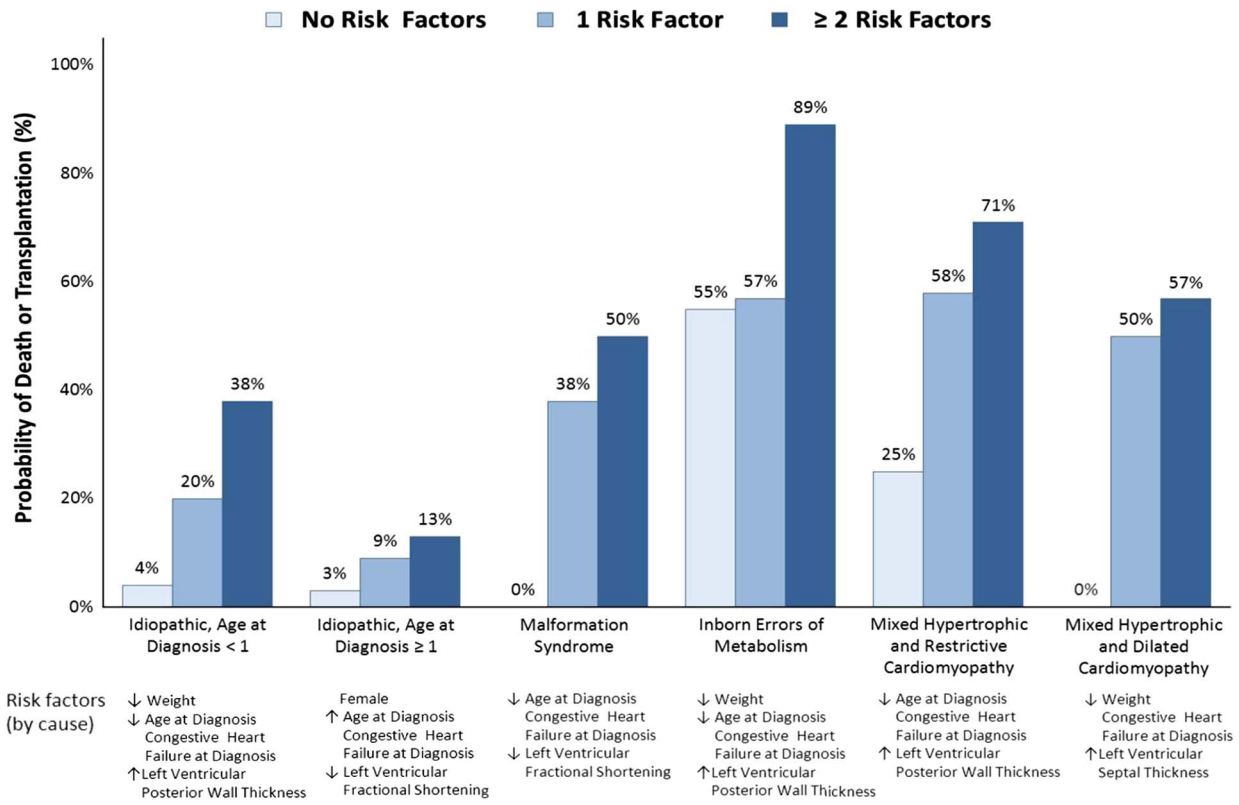

Figure 5.
Risk of death or transplantation in 882 children with hypertrophic cardiomyopathy, by number of cause-specific risk factors. Data are from the Pediatric Cardiomyopathy Registry collected between 1990 and 2002 (from Lipshultz et al[20]).

cardiomyopathies, and can occur as an isolated phenotype or as a mixed phenotype with hypertrophic cardiomyopathy.[22] The mixed restrictive and hypertrophic cardiomyopathy phenotype comprised 33% of all restrictive cardiomyopathies in the Pediatric Cardiomyopathy Registry. Children with restrictive cardiomyopathy were found to have the poorest outcomes compared with other phenotypes of cardiomyopathy (Fig 6). The 5-year survival was 68% for children with both the mixed restrictive and hypertrophic cardiomyopathy and pure restrictive cardiomyopathy phenotypes. In addition, transplant-free survival was only 28% for pure restrictive cardiomyopathy vsersus 43% for the mixed phenotype. Risk factors for poor survival included the presence of congestive heart failure at diagnosis, a decreased left ventricular fractional shortening z-score for both phenotypic groups, as well as an increased left ventricular posterior wall thickness z-score for children with the mixed phenotype.

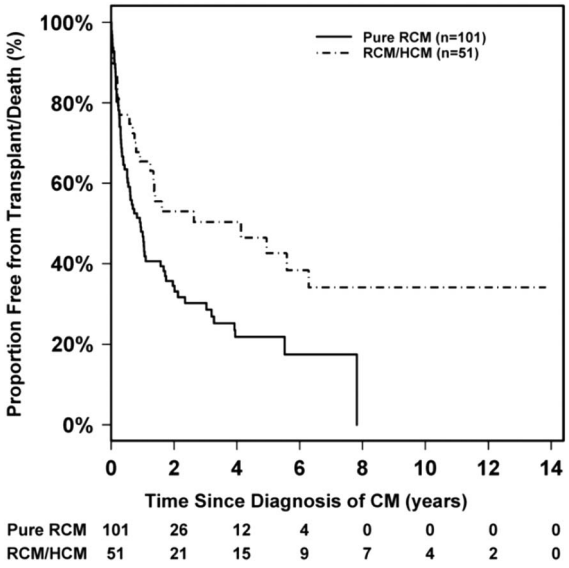

Figure 6.
Probability of freedom from death, censored at transplantation, among 152 children with RCM stratified by phenotype, pure RCM versus mixed/overlapping phenotype RCM/HCM. CM = cardiomyopathy; HCM = hypertrophic cardiomyopathy; and RCM = restrictive cardiomyopathy (reprinted with permission from Webber et al[22]).

Left ventricular non-compaction

Left ventricular non-compaction is one of the rarest phenotypes of cardiomyopathy in children with an incidence of only 4.9%, according to an analysis of

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

the Pediatric Cardiomyopathy Registry.[23] Left ventricular non-compaction in children can present in isolation or with other cardiomyopathy phenotypes. Diagnosis of this phenotype is often made on the basis of echocardiographic findings, although at present there is no clear consensus on diagnostic criteria. A decreased left ventricular fractional shortening z-score was a strong predictor of death or transplantation in children with left ventricular non-compaction; however, when the left ventricular systolic function was preserved, children with left ventricular non-compaction had better outcomes than children with dilated or restrictive cardiomyopathy.

Treatment of cardiomyopathies in children

Medical management

Pharmacological treatment patterns were compared between Pediatric Cardiomyopathy Registry patients diagnosed with idiopathic dilated cardiomyopathy between 1990 and1995 and those diagnosed between 2000 and 2006.[24] We found that the use of heart failure medications, including digoxin, a diuretic, or both (84% of children diagnosed between 1990 and 1995 and 87% of children diagnosed between 2000 and 2006), as well as angiotensin-converting enzyme inhibitors (66 and 70%, respectively) did not change significantly between the two time periods; however, β-blocker usage increased from 4 to 18%. Anti-heart-failure therapy remains the most common treatment, and was reported in 84% of all children with idiopathic dilated cardiomyopathy. Anti-heart-failure medications were reported in 60% of children with asymptomatic heart failure and in 93% of children with an NYHA class greater than II. Angiotensin-converting enzyme inhibitors were reported in 74% of children; however, in contrast to anti-heart-failure therapies, angiotensin-converting enzyme inhibitor therapy was often not initiated in children with asymptomatic left ventricular dysfunction in the absence of echocardiographic evidence of more advanced disease.

Surgical management

For many children with severe or end-stage cardiomyopathy, heart transplantation remains one of the only long-term surgical solutions.[25] The Pediatric Heart Transplant Study Group collects morbidity and mortality data on children under 18 years of age beginning at the date of listing for heart transplantation.[26] As the Pediatric Cardiomyopathy Registry does not collect data on patients after transplantation, collaboration with the Pediatric Heart Transplant Study Group gave the Pediatric Cardiomyopathy Registry Study Group the ability to examine patient outcomes before and after transplantation.

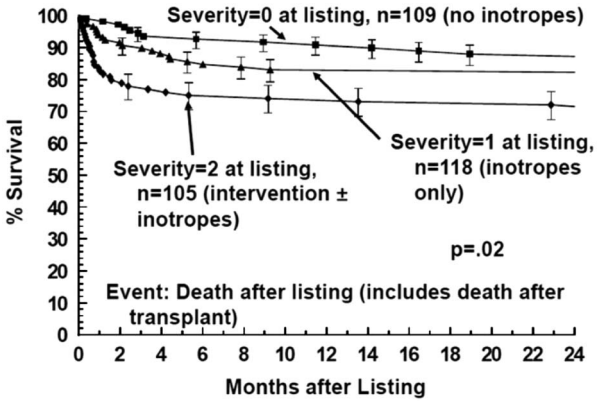

Figure 7.
Survival after listing for heart transplantation among children with cardiomyopathy by heart failure severity score. Severity score 2 = children on mechanical ventilatory or circulatory support; 1 = children on intravenous inotropic support without mechanical support; 0 = children on neither intravenous inotropic nor mechanical support (reprinted with permission from Larsen et al[27]).

An analysis of the combined Pediatric Heart Transplant Study and Pediatric Cardiomyopathy Registry data sets examined mortality in children with varying levels of support before transplantation (Fig 7).[27] For children with no pre-transplant circulatory or mechanical support, mortality primarily occurred after transplantation. Although we observed no difference in pre- and post-transplant mortality rates in children who received only inotropic support, for children requiring both circulatory and mechanical support, mortality occurred most frequently while on the waiting list for heart transplantation. This suggests that patients with cardiomyopathy requiring higher degree of support at listing might have a survival benefit with transplantation compared with children who require no support or only inotropic support before transplantation.

Heart transplantation was found to be most common among children with dilated cardiomyopathy in the combined Pediatric Cardiomyopathy Registry and Pediatric Heart Transplant Study data set.[28] For patients with dilated cardiomyopathy who were listed for transplant, the median age was 3.4 years at diagnosis and 4.4 years at transplantation; 30% of these patients were ventilator-dependent at the time of listing, and pre-transplant mortality was 11%.[29] Mechanical ventilation and older age at diagnosis – without mechanical ventilation – were predictors of mortality while waiting for a heart transplant. Post-transplant outcomes were worse for children with myocarditis, which suggests that infectious or immune mechanisms affected patient mortality.

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

A separate analysis of the combined Pediatric Cardiomyopathy Registry and Pediatric Heart Transplant Study data set examined the association between measures of left ventricular dilation or function and the risk of death in children with dilated cardiomyopathy after listing for transplantation or within 6 months of transplantation. Increased left ventricular end-diastolic dimension close to the time of listing was independently associated with an increased risk of death after listing or up to 6 months after transplant for children with dilated cardiomyopathy who were under 5 years of age at diagnosis.[30] This association was not observed in children who were older than age 5 at diagnosis; however, the association was strongest for those diagnosed before 6 months of age. Left ventricular function and mass were not associated with an increased risk of death after listing or within 6 months of transplantation.

Functional status of children with cardiomyopathy

Few studies have systematically studied the functional status in children with cardiomyopathy and their corresponding quality of life in comparison with healthy children. We collected parent-reported functional status of children with cardiomyopathy above 5 years of age using two validated surveys: the Child Health Questionnaire and the Functional Status II(R) Reports Instrument. On average, children with cardiomyopathy had impaired physical and psychosocial functioning compared with healthy children (Figs 8 and 9).[31] Several socioe-conomic variables were associated with impaired functional status – for example, lower total household income, lower parental education level, etc. Predictors of poorer physical function specifically included increased left ventricular size and higher left ventricular thickness-to-dimension ratio; however, improved functional status was directly associated with time since diagnosis, suggesting that functional status in children with cardiomyopathy may improve with time.

The Pediatric Cardiomyopathy Registry in the present era

At present, the Pediatric Cardiomyopathy Registry is funded by the National Heart, Lung, and Blood Institute with supplemental funding from the Children's Cardiomyopathy Foundation to conduct two new studies. The first study, PCM Genes – Genotype–Phenotype Associations in Pediatric Cardiomyopathy – has at present enrolled more than 400 children with dilated cardiomyopathy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, or left ventricular non-compaction, with an enrolment goal of 600, who will receive next-generation whole-exome sequencing for both gene discovery as well as genotype–phenotype associations. The phenotypes of interest include cardiomyopathy functional type, age at onset, as well as 2-year echocardiographic outcomes. The PCM Genes study is also enrolling parents and affected relatives of the probands to better understand inheritance patterns and moderator gene influences.

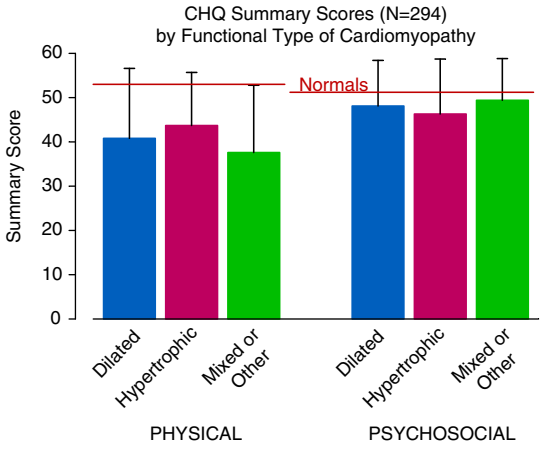

Figure 8.
Physical and psychosocial function of 294 children with cardiomyopathy, by functional type, compared with scores for healthy children. Data are from the Child Health Questionnaire administered by the Pediatric Cardiomyopathy Registry between 1990 and 2002 (from Sleeper et al[31]).

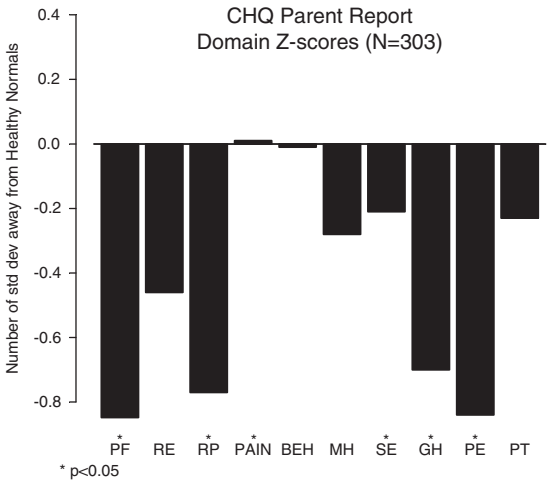

Figure 9.
Mean Child Health Questionnaire (CHQ) z-scores for 303 children with cardiomyopathy, by domain. Data are from the Pediatric Cardiomyopathy Registry and were collected between 1990 and 2002. PF = physical functioning; RE = role/social limits-emotional; RP = role/social limits-physical; PAIN = bodily pain; BEH = behaviour; MH = mental health; SE = self-esteem; GH = general health perception; PE = parental impact-emotional; PT = parental impact-time (from Sleeper et al[31]).

https://doi.org/10.1017/S1047951115000943 Published online by Cambridge University Press

The second study named PCM Biomarkers – Cardiac Biomarkers in Pediatric Cardiomyopathy – which is at present enrolling up to 400 children with dilated cardiomyopathy or hypertrophic cardiomyopathy has the following three aims: to determine the association of specific cardiac biomarkers and echocardiographic parameters in accurately assessing newly diagnosed dilated cardiomyopathy patients' clinical status; to determine the association of biomarkers of cardiac fibrosis with fibrosis as measured on cMRI in children with hypertrophic cardiomyopathy; and to determine which cardiac biomarkers are associated in children with either dilated cardiomyopathy or hypertrophic cardiomyopathy who continue to be clinically stable up to 2 years after diagnosis to better inform transplantation listing decisions.

Both of these studies in progress will end enrolment by 2016, and their results will be disseminated for the next generation of paediatric cardiomyopathy research proposals, which will focus on early diagnosis and disease screening, targeted treatment interventions via randomised clinical trials, and improved patient and family support interventions. We are also proud that during its more than two decades of study, the Pediatric Cardiomyopathy Registry has also helped train the next generation of paediatric cardiomyopathy and heart failure investigators who will carry on this important research.

In addition, the Pediatric Cardiomyopathy Registry Study Group is at present conducting ancillary analyses of the Pediatric Cardiomyopathy Registry database to determine the importance of renal function, growth and body composition, electrophysiological parameters, and pharmacological interventions as determinants of clinical outcomes in this population.

Pediatric Cardiomyopathy Study Group-sponsored international conferences on paediatric cardiomyopathy

The first International Workshop on Idiopathic and Primary Pediatric Cardiomyopathies was organised by the Pediatric Cardiomyopathy Registry investigators in 2007. More than 30 participants attended the conference, which was co-sponsored by the Children's Cardiomyopathy Foundation and the National Heart, Lung, and Blood Institute. The results of the conference were published in three issues of the journal Progress in Pediatric Cardiology.[15,28,32–63] The Second International Conference on Cardiomyopathy in Children was held in May, 2010, with more than 50 participants in attendance. The Children's Cardiomyopathy Foundation and the National Heart, Lung, and Blood Institute were also the principle co-sponsors for this conference. Similar to the 2007 conference, the results from the second conference were published in three issues of Progress in Pediatric Cardiology.[25,64–98] The Third International Conference on Cardiomyopathy in Children was held in May, 2014 and was attended by more than 60 world experts. Again, the principle co-sponsors for this conference were the Children's Cardiomyopathy Foundation and the National Heart, Lung, and Blood Institute. The third conference added new themes focussed on paediatric heart failure, the next generation of left ventricular support devices, novel cardiac imaging, and personalised medicine for children with cardiomyopathy and heart failure. The main outcome of this third conference was to propose a "future research agenda" in paediatric cardiomyopathy and heart failure to be presented to the National Heart, Lung, and Blood Institute and patterned on the recently published results from a National Heart, Lung, and Blood Institute Working Group on paediatric heart failure.[99] The results of the third conference will be published in the current and future issues of Progress in Pediatric Cardiology in 2014 and 2015, including the proposed future research agenda for paediatric cardiomyopathy and heart failure.[100–111]

Future directions of the Pediatric Cardiomyopathy Registry

With the continual collection of prospective follow-up data from enrolled Pediatric Cardiomyopathy Registry patients, Pediatric Cardiomyopathy Registry Study Group researchers will be able to provide a more complete description of the clinical course of paediatric cardiomyopathy and the associated risk factors. This will also allow for a more thorough examination of previously identified risk factors and a better understanding of their long-term utility in the diagnosis, prognosis, and care of these children. This type of registry data and their usefulness in guiding clinical decision-making is continuing to gain appreciation from research methodologists and is becoming increasingly useful as advances in analytical and statistical theory are made.[112] Pediatric Cardiomyopathy Registry investigators are at present working to proposing to leverage the Pediatric Cardiomyopathy Registry infrastructure to identify the genetic aetiologies of paediatric cardiomyopathy and the usefulness of cardiac biomarkers in the evaluation of these patients. The ultimate goal of the Pediatric Cardiomyopathy Registry is to identify robust diagnostic strategies, aetiology-specific treatments informed by genotyping, and the most clinically effective evidence-based approaches for these children. An associated goal is to recruit and develop the next generation of paediatric cardiomyopathy and heart failure researchers and clinicians.

Acknowledgements

The work of the Pediatric Cardiomyopathy Registry would not have been possible without the collaboration of many physicians and other healthcare professionals, scientists, and research staff from the United States and Canada. Special acknowledgement should be given to the Pediatric Cardiomyopathy Registry investigators: Steven D. Colan, MD; Gerald Cox MD, PhD; Jane Messere, RN; Lynn Sleeper, ScD; Jeffrey A. Towbin, MD; Stephanie Ware, MD, PhD; John Lynn Jefferies, MD, MPH; E. John Orav, PhD; Daphne Hsu, MD; Steven Webber, MBChB; Charles Canter, MD; Linda Addonizio, MD; Beth Kaufman, MD; Melanie Everitt, MD; Elfriede Pahl, MD; Paul Kantor, MBBCh; Paolo Rusconi, MD; Robert E. Shaddy, MD; Paul R. Lurie, MD; David Connuck, MD; April Lowe, MS; Bonnie Salbert, DO; Tajinder Singh, MD, MSc; Jorge Alvarez, AB; Biagio Pietra, MD; Ranae Larsen, MD; Jacqueline Lamour, MD; Renee Margossian, MD; Beth Kaufman, MD; Susan Foerster, MD; Wendy Chung, MD; Rakesh Singh, MD, MS; and Juanita Hunter, MD. The authors acknowledge Mrs Lisa Yue and the Children's Cardiomyopathy Foundation for their continuing support of the Pediatric Cardiomyopathy Registry. They also acknowledge the Parker Foundation for their support of the Registry. In addition, the authors acknowledge the Myocarditis Foundation, GeneDx, and the Department of Pediatrics of the Miller School of Medicine at the University of Miami for their support of the Second International Conference on Cardiomyopathy in Children, as well as the Macquarie Group Foundation, Global Productivity Solutions, MyoKardia, Berlin Heart, and the Children's Hospital of Pittsburgh of the University of Pittsburgh Medical Center for their support of the Third International Conference on Cardiomyopathy in Children. Finally, the authors express their most sincere gratitude to the children with cardiomyopathy and their families whose participation has made the Pediatric Cardiomyopathy Registry possible.

Financial Support

This work was principally supported by the National Heart, Lung, and Blood Institute (S.E.L., grant numbers R01HL53392, R13HL087708, and R13HL123256) and the Children's Cardiomyopathy Foundation. Additional support of this work is included in the acknowledgements section.

Conflicts of Interest

None.

Ethical Standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation The U.S. Department of Health and Human Services Title 45, Part 46 Protection of Human Subjects, 'The Common Rule' and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees.

References

1. Andrews RE, Fenton MJ, Ridout DA, Burch M. New-onset heart failure due to heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. Circulation 2008; 117: 79–84.
2. Massin MM, Astadicko I, Dessy H. Epidemiology of heart failure in a tertiary pediatric center. Clin Cardiol 2008; 31: 388–391.
3. Towbin JA, Lowe AM, Colan SD, et al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA 2006; 296: 1867–1876.
4. Webber SA. New-onset heart failure in children in the absence of structural congenital heart disease. Circulation 2008; 117: 11–12.
5. Grenier MA, Osganian SK, Cox GF, et al. Design and implementation of the North American Pediatric Cardiomyopathy Registry. Am Heart J 2000; 139: S86–S95.
6. Lipshultz SE, Sleeper LA, Towbin JA, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med 2003; 348: 1647–1655.
7. Arola A, Jokinen E, Ruuskanen O, et al. Epidemiology of idiopathic cardiomyopathies in children and adolescents. A nationwide study in Finland. Am J Epidemiol 1997; 146: 385–393.
8. Nugent AW, Daubeney PE, Chondros P, et al. The epidemiology of childhood cardiomyopathy in Australia. N Engl J Med 2003; 348: 1639–1646.
9. Cox GF, Sleeper LA, Lowe AM, et al. Factors associated with establishing a causal diagnosis for children with cardiomyopathy. Pediatrics 2006; 118: 1519–1531.
10. Towbin JA, Sleeper L, Jefferies JL, et al. Genetic and viral genome analysis of childhood cardiomyopathy: the PCMR/PCSR experience (abstract). J Am Coll Cardiol 2010; 55: E409.
11. Alvarez JA, Orav EJ, Wilkinson JD, et al. Competing risks for death and cardiac transplantation in children with dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. Circulation 2011; 124: 814–823.
12. Everitt MD, Sleeper LA, Lu M, et al. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. J Am Coll Cardiol 2014; 63: 1405–1413.
13. Kantor PF, Orav EJ, Wilkinson J, et al. Progressive left ventricular changes predict the likelihood of survival in pediatric dilated cardiomyopathy: findings from the Pediatric Cardiomyopathy Registry (abstract). J Am Coll Cardiol 2012; 59: E740.
14. Pahl E, Sleeper LA, Canter CE, et al. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report from the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol 2012; 59: 607–615.
15. Alvarez JA, Wilkinson JD, Lipshultz SE. Outcome predictors for pediatric dilated cardiomyopathy: a systematic review. Prog Pediatr Cardiol 2007; 23: 25–32.
16. Connuck DM, Sleeper LA, Colan SD, et al. Characteristics and outcomes of cardiomyopathy in children with Duchenne or Becker muscular dystrophy: a comparative study from the Pediatric Cardiomyopathy Registry. Am Heart J 2008; 155: 998–1005.
17 Foerster SR, Canter CE, Cinar A. Ventricular remodeling and survival are more favorable for myocarditis than for idiopathic dilated cardiomyopathy in childhood: an outcomes study from the Pediatric Cardiomyopathy Registry. Circ Heart Fail 2010; 3: 689–697.
18. Rusconi P, Wilkinson JD, Sleeper LA, et al. Outcomes in children with familial dilated cardiomyopathy compared to children with idiopathic dilated cardiomyopathy (abstract). Circulation 2010; 122: A16092.

19. Colan SD, Lipshultz SE, Lowe AM, et al. Epidemiology and cause-specific outcome of hypertrophic cardiomyopathy in children: findings from the Pediatric Cardiomyopathy Registry. Circulation 2007; 115: 773–781.
20. Lipshultz SE, Orav EJ, Wilkinson JD, et al. Risk stratification at diagnosis for children with hypertrophic cardiomyopathy: an analysis of data from the Pediatric Cardiomyopathy Registry. Lancet 2013; 382: 1889–1897.
21. Wilkinson JD, Lowe AM, Salbert BA, et al. Outcomes in children with Noonan syndrome and hypertrophic cardiomyopathy: a study from the Pediatric Cardiomyopathy Registry. Am Heart J 2012; 164: 442–448.
22. Webber SA, Lipshultz SE, Sleeper LA, et al. Outcomes of restrictive cardiomyopathy in childhood and the influence of phenotype: a report from the Pediatric Cardiomyopathy Registry. Circulation 2012; 126: 1237–1244.
23. Jefferies JL, Colan SD, Sleeper LA, et al. Outcomes and risk stratification for children with left ventricular noncompaction: findings from the pediatric cardiomyopathy registry (abstract). Circulation 2009: 120.
24. Harmon WG, Sleeper LA, Cuniberti L, et al. Treating children with idiopathic dilated cardiomyopathy (from the Pediatric Cardiomyopathy Registry). Am J Cardiol 2009; 104: 281–286.
25. Kirklin JK PF, McGiffin DC, Dabal R. Surgical therapies for advanced heart failure in pediatric patients with cardiomyopathy. Prog Pediatr Cardiol 2011; 31: 3–6.
26. Hsu DT, Naftel DC, Webber SA, et al. Lessons learned from the pediatric heart transplant study. Congenit Heart Dis 2006; 1: 54–62.
27. Larsen RL, Canter CE, Naftel DC, et al. The impact of heart failure severity at time of listing for cardiac transplantation on survival in pediatric cardiomyopathy. J Heart Lung Transplant 2011; 30: 755–760.
28. Canter CE, Kantor PF. Heart transplant for pediatric cardiomyopathy. Prog Pediatr Cardiol 2007; 23: 67–72.
29. Pietra BA, Kantor PF, Bartlett HL, et al. Early predictors of survival to and after heart transplantation in children with dilated cardiomyopathy. Circulation 2012; 126: 1079–1086.
30. Singh TP, Sleeper LA, Lipshultz S, et al. Association of left ventricular dilation at listing for heart transplant with postlisting and early posttransplant mortality in children with dilated cardiomyopathy. Circ Heart Fail 2009; 2: 591–598.
31. Sleeper LA, Colan SD, Towbin JA, et al. Functional status is impaired and correlated with clinical status in pediatric cardiomoypathy (abstract). Proceedings of the 5th World Congress on Pediatric Cardiology and Cardiac Surgery 2009; 5: 134.
32. Alcalai R, Arad M, Depreux F, et al. Hypertrophy, electrical abnormalities, autophagic vacuoles accumulation and cardiac fibrosis in LAMP2 cardiomyopathy mouse model. Prog Pediatr Cardiol 2007; 24: 73–74.
33. Chung WK. Predictive genetic testing for cardiomyopathies. Prog Pediatr Cardiol 2007; 23: 33–38.
34. Colan SD. Classification of the cardiomyopathies. Prog Pediatr Cardiol 2007; 23: 5–15.
35. Cooper LT Jr. Giant cell myocarditis in children. Prog Pediatr Cardiol 2007; 24: 47–49.
36. Cox GF. Diagnostic approaches to pediatric cardiomyopathy of metabolic genetic etiologies and their relation to therapy. Prog Pediatr Cardiol 2007; 24: 15–25.
37. Dellefave LM, McNally EM. Cardiomyopathy in neuromuscular disorders. Prog Pediatr Cardiol 2007; 24: 35–46.
38. Hsu DT. Age-related factors in child heart transplants. Prog Pediatr Cardiol 2007; 23: 73–79.
39. Jefferies JL. Novel medical therapies for pediatric heart failure. Prog Pediatr Cardiol 2007; 23: 61–66.
40. Joshi VA, Roberts AE, Kucherlapati RS. Noonan syndrome associated congenital hypertrophic cardiomyopathy and the role of sarcomere gene mutations. Prog Pediatr Cardiol 2007; 24: 75–76.
41. Kaufman BD, Shaddy RE. Beta-adrenergic receptor blockade and pediatric dilated cardiomyopathy. Prog Pediatr Cardiol 2007; 24: 51–57.
42. Kishnani PS, BurnsWechsler S, Li JS. Enzyme-deficiency metabolic cardiomyopathies and the role of enzyme replacement therapy. Prog Pediatr Cardiol 2007; 23: 39–48.
43. Mestroni L, Miyamoto SD, Taylor MRG. Genetics of dilated cardiomyopathy conduction disease. Prog Pediatr Cardiol 2007; 24: 3–13.
44. Miller TL, Neri D, Extein J, Somarriba G, Strickman-Stein N. Nutrition in pediatric cardiomyopathy. Prog Pediatr Cardiol 2007; 24: 59–71.
45. Ratnasamy C, Kinnamon DD, Lipshultz SE, Rusconi PG. Associations between neurohormonal and inflammatory activation and heart failure in children. Prog Pediatr Cardiol 2007; 24: 81–82.
46. Rodrigues CO, Shehadeh LA, Webster KA, Bishopric NH. Myocyte deficiency as a target in the treatment of cardiomyopathy. Prog Pediatr Cardiol 2007; 23: 49–59.
47. Rossano JW, Dreyer WJ, Kim JJ, et al. Pre-transplant serum creatinine predicts long-term outcome in pediatric heart transplant patients. Prog Pediatr Cardiol 2007; 24: 77–78.
48. Sheikh F, Chen J. Mouse models for cardiomyopathy research. Prog Pediatr Cardiol 2007; 24: 27–34.
49. Sokol KC, Armstrong FD, Rosenkranz ER, et al. Ethical issues in children with cardiomyopathy: making sense of ethical challenges in the clinical setting. Prog Pediatr Cardiol 2007; 23: 81–87.
50. Taylor MRG. When echocardiogram screening "is not enough". Prog Pediatr Cardiol 2007; 24: 79–80.
51. Weintraub RG, Nugent AW, Daubeney PEF. Pediatric cardiomyopathy: the Australian experience. Prog Pediatr Cardiol 2007; 23: 17–24.
52. Bublik N, Alvarez JA, Lipshultz SE. Pediatric cardiomyopathy as a chronic disease: a perspective on comprehensive care programs. Prog Pediatr Cardiol 2008; 25: 103–111.
53. Colan SD. Clinical issues in the pediatric hypertrophic cardiomyopathies. Prog Pediatr Cardiol 2008; 25: 27–29.
54. Fisher SD, Etherington A, Schwartz DB, Pearson GD. Peripartum cardiomyopathy: an update. Prog Pediatr Cardiol 2008; 25: 79–84.
55. Hill KD, Hamid R, Exil VJ. Pediatric cardiomyopathies related to fatty acid metabolism. Prog Pediatr Cardiol 2008; 25: 69–78.
56. Menon SC, Olson TM, Michels VV. Genetics of familial dilated cardiomyopathy. Prog Pediatr Cardiol 2008; 25: 57–67.
57. Negro A, Dodge-Kafka K, Kapiloff MS. Signalosomes as therapeutic targets. Prog Pediatr Cardiol 2008; 25: 51–56.
58. Somarriba G, Extein J, Miller TL. Exercise rehabilitation in pediatric cardiomyopathy. Prog Pediatr Cardiol 2008; 25: 91–102.
59. Towbin JA. Molecular mechanisms of pediatric cardiomyopathies and new targeted therapies. Prog Pediatr Cardiol 2008; 25: 3–21.
60. Webber SA. Primary restrictive cardiomyopathy in childhood. Prog Pediatr Cardiol 2008; 25: 85–90.
61. Wilkinson JD, Lipshultz SE. Epidemiological and outcomes research in children with pediatric cardiomyopathy: discussions from the international workshop on primary and idiopathic cardiomyopathies in children. Prog Pediatr Cardiol 2008; 25: 23–25.
62. Wilkinson JD, Sleeper LA, Alvarez JA, Bublik N, Lipshultz SE. The Pediatric Cardiomyopathy Registry: 1995–2007. Prog Pediatr Cardiol 2008; 25: 31–36.
63. Young K, Hare JM. Stem cells in cardiopulmonary development: implications for novel approaches to therapy for pediatric cardiopulmonary disease. Prog Pediatr Cardiol 2008; 25: 37–49.
64. Bernstein D, Fajardo G, Zhao M. The role of β-adrenergic receptors in heart failure: differential regulation of cardiotoxicity and cardioprotection. Prog Pediatr Cardiol 2011; 31: 35–38.
65. Chung WK. Novel gene discovery in pediatric cardiomyopathy. Prog Pediatr Cardiol 2011; 31: 89–91.
66. Colan SD. Treatment of hypertrophic cardiomyopathy in childhood. Prog Pediatr Cardiol 2011; 31: 13–19.

67. Dadlani GH, Harmon WG, Perez-Colon E, et al. Diagnosis and screening of hypertrophic cardiomyopathy in children. Prog Pediatr Cardiol 2011; 31: 21–27.
68. Daly KP, Colan SD, Blume ED, et al. Echocardiographic measures of systolic and diastolic function worsen in children 1 year after Hematopoietic Stem Cell Transplantation. Prog Pediatr Cardiol 2011; 31: 135.
69. Foerster SR, Canter CE. Contemporary etiology, outcomes, and therapy in pediatric myocarditis. Prog Pediatr Cardiol 2011; 31: 123–128.
70. Frazier AH, Ramirez-Correa GA, Murphy AM. Molecular mechanisms of sarcomere dysfunction in dilated and hypertrophic cardiomyopathy. Prog Pediatr Cardiol 2011; 31: 29–33.
71. Gambetta K, Tambur A, Kaushal S, Backer C, Pahl E. The impact of serial donor specific antibody testing in pediatric heart transplant recipients – an early experience. Prog Pediatr Cardiol 2011; 31: 137–138.
72. Hlaing WM, Messiah SE, Lipshultz SE, Ludwig DA. Obesity and length of hospital stay in children: a retrospective review of Florida Agency for Health Care Administration data. Prog Pediatr Cardiol 2011; 31: 67–72.
73. Ho CY. New paradigms in hypertrophic cardiomyopathy: insights from genetics. Prog Pediatr Cardiol 2011; 31: 93–98.
74. Hollander SA, Rosenthal DN. Cardiac resynchronization therapy in pediatric heart failure. Prog Pediatr Cardiol 2011; 31: 111–117.
75. Kantor PF, Rusconi P. Biomarkers in pediatric heart failure: their role in diagnosis and evaluating disease progression. Prog Pediatr Cardiol 2011; 31: 53–57.
76. Landy DC, Miller TL, Mitnik GL, et al. LV structure, LV function, and serum NT-proBNP in childhood cancer survivors without anthracycline or cardiac radiation exposures. Prog Pediatr Cardiol 2011; 31: 141–142.
77. Messiah SE, Miller TL, Lipshultz SE, Bandstra ES. Potential latent effects of prenatal cocaine exposure on growth and the risk of cardiovascular and metabolic disease in childhood. Prog Pediatr Cardiol 2011; 31: 59–65.
78. Payne RM. The heart in Friedreich's ataxia: basic findings and clinical implications. Prog Pediatr Cardiol 2011; 31: 103–109.
79. Peter AK, Cheng H, Ross RS, Knowlton KU, Chen J. The costamere bridges sarcomeres to the sarcolemma in striated muscle. Prog Pediatr Cardiol 2011; 31: 83–88.
80. Pincott ES, Burch M. New biomarkers in heart failure. Prog Pediatr Cardiol 2011; 31: 49–52.
81. Porter GA Jr, Hom JR, Hoffman DL, et al. Bioenergetics, mitochondria, and cardiac myocyte differentiation. Prog Pediatr Cardiol 2011; 31: 75–81.
82. Purevjav E, Arimura T, Augustin S, et al. Cardiomyopathies due to mutations in the myopalladin gene: genotype–phenotype correlation. Prog Pediatr Cardiol 2011; 31: 139–140.
83. Rampersaud E, Siegfried JD, Norton N, et al. Rare variant mutations identified in pediatric patients with dilated cardiomyopathy. Prog Pediatr Cardiol 2011; 31: 39–47.
84. Shaddy RE. Randomized clinical trials and the treatment of pediatric cardiomyopathy. Prog Pediatr Cardiol 2011; 31: 7–11.
85. Wang H, Xin B. Hypertrophic cardiomyopathy in the Amish community – what we may learn from it. Prog Pediatr Cardiol 2011; 31: 129–134.
86. Ware SM. Genetic diagnosis in pediatric cardiomyopathy: clinical application and research perspectives. Prog Pediatr Cardiol 2011; 31: 99–102.
87. Weintraub RG, Nugent AW, Davis A, et al. Presentation, echocardiographic findings and long-term outcomes in children with familial dilated cardiomyopathy. Prog Pediatr Cardiol 2011; 31: 119–122.
88. Bernstein D, Webber S. New directions in basic research in hypertrophy and heart failure: relevance for pediatric cardiology. Prog Pediatr Cardiol 2011; 32: 5–9.
89. Canter CE, Cunningham MW, Cooper LT. Recent clinical and translational research on pediatric myocarditis. Prog Pediatr Cardiol 2011; 32: 15–18.
90. Chung W, Towbin J. Genetic issues in pediatric cardiomyopathy: future research directions. Prog Pediatr Cardiol 2011; 32: 3–4.
91. Conway J, Dipchand AI. Transplantation and pediatric cardiomyopathies: indications for listing and risk factors for death while waiting. Prog Pediatr Cardiol 2011; 32: 51–54.
92. Gambetta K, Tambur A, Pahl E. Immune monitoring of pediatric heart transplant recipients through serial donor specific antibody testing – an initial experience and review of the literature. Prog Pediatr Cardiol 2011; 32: 43–49.
93. Kantor PF, Rusconi P, Lipshultz S, et al. Current applications and future needs for biomarkers in pediatric cardiomyopathy and heart failure: summary from the Second International Conference on Pediatric Cardiomyopathy. Prog Pediatr Cardiol 2011; 32: 11–14.
94. Kindel SJ, Pahl E. Cardiac allograft vasculopathy in children – treatment challenges. Prog Pediatr Cardiol 2011; 32: 37–42.
95. Mital S. Biomarkers of cardiac fibrosis: new insights. Prog Pediatr Cardiol 2011; 32: 35–36.
96. Ricci M, Lincoln J. Molecular markers of cardiomyopathy in cyanotic pediatric heart disease. Prog Pediatr Cardiol 2011; 32: 19–23.
97. Wilkinson JD, Diamond M, Miller TL. The promise of cardiovascular biomarkers in assessing children with cardiac disease and in predicting cardiovascular events in adults. Prog Pediatr Cardiol 2011; 32: 25–34.
98. Wilkinson JD, Zebrowski JP, Hunter JA, et al. Assessing the global and regional impact of primary cardiomyopathies: the Global Burden Of Diseases, Injuries And Risk Factors (GBD 2010) Study. Prog Pediatr Cardiol 2011; 32: 55–63.
99. Burns KM, Byrne BJ, Gelb BD, et al. New mechanistic and therapeutic targets for pediatric heart failure: report from a National Heart, Lung, and Blood Institute working group. Circulation 2014; 130: 79–86.
100. Asimaki A, Kleber AG, MacRae CA, Saffitz JE. Arrhythmogenic cardiomyopathy – new insights into disease mechanisms and drug discovery. Prog Pediatr Cardiol 2014; 37: 3–7.
101. Bernstein D, Burridge P. Patient-specific pluripotent stem cells in doxorubicin cardiotoxicity: a new window into personalized medicine. Prog Pediatr Cardiol 2014; 37: 23–27.
102. Dedieu N, Hussain T, Burch M. Imaging for coronary allograft vasculopathy in children and adolescents. Prog Pediatr Cardiol 2014; 37: 29–35.
103. Mann DL. The evolution of modern theory and therapy for heart failure. Prog Pediatr Cardiol 2014; 37: 9–12.
104. Mason SE, Lipshultz SE, Kaushal S, Fisher S. The implication of coronary artery malformations and congenital heart disease on cardiomyopathy. Prog Pediatr Cardiol 2014; 37: 19–22.
105. Mestroni L, Brun F, Spezzacatene A, Sinagra G, Taylor MRG. Genetic causes of dilated cardiomyopathy. Prog Pediatr Cardiol 2014; 37: 13–18.
106. Parent JJ. Fibrillin-1 gene mutations in left ventricular noncompaction cardiomyopathy. Prog Pediatr Cardiol 2014; 37: 41.
107. Schuetze KB, McKinsey TA. Suppression of pathological cardiac fibrosis by histone deacetylase inhibitors. Prog Pediatr Cardiol 2014; 37: 37.
108. Simpson KE, Cunningham MW, Lee CK, et al. Children with myocarditis and new onset dilated cardiomyopathy have evidence of autoimmunity and viremia at presentation. Prog Pediatr Cardiol 2014; 37: 39–40.
109. VanderPluym CJ. Mechanical circulatory support strategies for myocardial recovery. Prog Pediatr Cardiol 2014; 37: 45.
110. Weintraub RG, Everitt MD, Alexander PMA, Wilkinson JD, Lipshultz SE. Do selection criteria for children with dilated cardiomyopathy enrolled in national registries explain differences in outcomes? Prog Pediatr Cardiol 2014; 37: 47–48.
111. Wittlieb-Weber CA, Lin KY, Zaoutis TE, et al. Pediatric versus adult cardiomyopathy and heart failure related hospitalizations: a value-based analysis. Prog Pediatr Cardiol 2014; 37: 43.
112. Dreyer NA, Garner S. Registries for robust evidence. JAMA 2009; 302: 790–791.