Heart failure from heart muscle disease in childhood: a 5–10 year follow-up study in the UK and Ireland

Rachel E. Andrews*, Matthew J. Fenton, Troy Dominguez, and Michael Burch on behalf of the British Congenital Cardiac Association

Cardiothoracic Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

Abstract

Aims Our original study, the first national prospective study of new-onset heart failure from heart muscle disease in children, showed overall 1-year survival of 82%, and event (death or transplantation)-free survival of 66%. This study aimed to evaluate 5+ year outcomes of this important cohort.

Methods and results All centres in the UK and Ireland with 1-year event-free survivors participated (n = 14). Anonymised data based on last hospital attendance and echocardiograms were reviewed. The investigator was blinded to outcome at the time of echo review. Of sixty-nine 1-year event-free survivors, data were obtained on 64, with three lost to follow-up and two moved abroad. There were three deaths at 2.2, 3.3 and 9.0 years after presentation and one transplant, at 5.2 years. Overall/event-free survival was 77%/62% at 5 years and 73%/59% at 10 years, respectively. Overall and event-free survival conditional on 1-year survival was 94% at 5 years, and 89% at 10 years. For the 60 event-free survivors, median (range) follow-up duration was 9.04 (5.0–10.33) years for those still under review (n = 45), or time to discharge 5.25 (0.67–10.0) years (n = 15). Fifty-eight were in New York Heart Association (NYHA) Class 1, and two in Class 2. Forty-one out of sixty had normal echocardiograms at last follow-up. Predictors of better longer-term outcome were the same as for the original 1-year follow-up study, namely, younger age and higher fractional shortening measurement at presentation.

Conclusions Children who survive the first year following their first presentation with significant heart failure from heart muscle disease have a good longer-term outcome although there remains a small attrition rate.

Keywords Cardiomyopathy; Myocarditis; Morbidity; Mortality; Transplantation

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*Correspondence to: Rachel Andrews, Cardiothoracic Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, Great Ormond Street, London, UK. Tel: +0044 (0)207 4059200; Fax: 0044 (0)207 8138440. Email: rachel.andrews@gosh.nhs.uk

Introduction

Symptomatic heart failure from heart muscle disease in children is the commonest indication for heart transplant in children of all ages in the UK, and over a year of age worldwide. Although rare, it is a major cause of morbidity and mortality, and caring for this group of patients requires not only detailed knowledge of a heterogeneous group of conditions, but also significant resource allocation. However, the epidemiological data on paediatric heart failure are scarce. Two studies from the USA have used retrospective database analyses to look at heart failure-related intensive care admissions in children with cardiomyopathy and heart failure-related hospitalizations, but this latter study included children with congenital heart disease. Our original study involved prospectively collecting data on all children <16 years of age who were admitted to hospital in the UK and Ireland with a new diagnosis of heart failure from heart muscle disease through one calendar year, from January–December 2003. The impetus for this study arose from a question posed by the UK Department of Health National Speciality Commissioning Group, who commission heart transplantation and mechanical support in the National Health Service, as to the incidence of symptomatic heart failure from heart muscle disease in children. This was calculated as 0.87/100 000, with a better 1-year outcome on multivariable analysis for younger...
children and those with better systolic function at presentation. Overall, a third of children died or required transplantation within a year of presentation.

As this was the first national prospective study of paediatric heart failure from heart muscle disease, with a well defined geographical area, population and time course, we then undertook a follow-up study to determine longer-term outcomes for this important cohort of patients and to determine whether the predictors of outcome were the same as for the 1-year follow-up study. Our aim was to provide useful information for clinicians, patients and their families on the longer-term consequences of paediatric heart failure, to help guide decisions about management.

Methods

Original study cohort

As previously published, this comprised 104 children <16 years of age who required hospital admission from January–December 2003 for new-onset heart failure from heart muscle disease. The cohort included primary cardiomyopathies, those secondary to neuromuscular or metabolic disease, anthracycline toxicity and previously undiagnosed arrhythmia. The predominant phenotype was of dilated cardiomyopathy, with just one case of restrictive cardiomyopathy. No children with hypertrophic cardiomyopathy presented with symptoms of heart failure during the study enrolment period. Heart failure was diagnosed by the attending cardiology consultant on the basis of history, clinical symptoms and signs and echocardiographic evidence of heart muscle disease. Children with structural heart disease, a known history of arrhythmia, or heart failure as part of multiple-organ failure (as in septicemia, for example) were excluded.

Follow-up study design

As with the original study, this follow-up study was undertaken on behalf of the British Congenital Cardiac Association. All paediatric cardiology consultants at the 17 centres in the UK and Ireland were emailed with details of the follow-up study proposal at the end of 2008. A study correspondent in each of the 14 units with 1 year event (death or transplant) was identified. Correspondents were asked to complete a questionnaire based on the most recent outpatient appointment or hospital admission, or the last visit if the patient had been discharged. They were also asked to supply anonymised echo images from that visit on disc if they were available, for central analysis.

Data collection

Details requested on the questionnaire included date of last review, weight and height, New York Heart Association class (using the Ross classification for younger children), aetiology (confirmed/suspected), status (alive/listed for transplant/dead), details of any hospital readmissions, current medications and follow-up frequency or discharge date.

As in the original study, the authors accepted diagnoses as given by the study correspondents, but where these had changed since the original study, the reason for the change was sought. Echocardiographic images requested included left ventricular dimensions and fractional shortening measurement on M-mode, and two-dimensional imaging in apical four-chamber and parasternal long axis views to show the presence or absence of intracardiac thrombus and mitral regurgitation. The echocardiograms were analysed by a single investigator who was blinded to outcome at the time of analysis. Left ventricular dimensions and fractional shortening measurements were checked and Z scores calculated using the app Cardio Z (www.ubqo.com), which is endorsed by the British Congenital Cardiac Association and widely used in the UK.

Statistical analysis

As in the original study documenting 1-year outcomes, our primary outcome measures were death, cardiac transplant or recovery during the follow-up period. Survival was defined either as overall survival, that is, freedom from death, or event-free survival, that is, freedom from death or transplant. Recovery was defined as normalization of echocardiographic findings with cessation of all cardiac medications. Statistical methods focused on analysing the impact of diagnosis, age and fractional shortening measurement at presentation on outcome. The methods used were the same as for the original study, to allow for a valid comparison of predictors of outcome. Cox regression modelling was used to generate hazard ratios with 95% confidence intervals to identify patient factors associated with event-free survival. Kaplan–Meier
survival curves were generated using death and transplant as the event occurrence, to produce 5 and 10 year overall and event-free survival figures.

**Results**

Of 104 children in the original study, there were 69 event-free survivors at 1 year after presentation. Of these, three were lost to follow-up, despite prolonged attempts to contact patients and families by local teams, and two moved abroad, leaving 64 patients on whom longer-term follow-up data were obtained. Only one of the three patients lost to follow-up had transitioned to adult cardiac services.

**Aetiology**

Since the original study, more extensive family screening revealed other affected family members in two cases, one of whom had been thought to have idiopathic dilated cardiomyopathy, and one to have had myocarditis. One further case of apparent idiopathic dilated cardiomyopathy was subsequently diagnosed with an underlying mitochondrial cytopathy, and one girl with apparently isolated left ventricular non-compaction subsequently developed a generalized myopathy and died at 9 years of age.

In addition, one child with dilated cardiomyopathy went on to develop short stature with lax joints, and one (also with dilated cardiomyopathy) to develop autism, but no underlying syndrome was identified in either case, and it may be these clinical findings are independent of each other.

**Outcome**

There were three deaths at 2.2, 3.3 and 9.0 years after presentation. The first of these was in a 2-year-old boy with dilated cardiomyopathy diagnosed at 4 months of age, the second in a 19-year-old woman diagnosed with dilated cardiomyopathy who was subsequently found to have recurrent atrial tachycardias and the third in the girl who developed an underlying generalized myopathy having been diagnosed initially with left ventricular non-compaction in the neonatal period. Only one child was transplanted more than 1 year out from presentation (in contrast to the 17 who were transplanted in their first year following diagnosis, as presented in the original study). This was carried out 5.2 years after initial presentation in a boy diagnosed with dilated cardiomyopathy at 3 months of age. No patient underwent implantation of a cardioverter defibrillator during the follow-up period.

Our original study reported overall 1-year survival of 82%, and event (death or transplant)-free survival of 66%. Data from this study showed the overall survival at 5 years to be 77%, and event-free survival 62%. At 10 years, these figures were 73% and 59%, respectively. Kaplan–Meier curves for overall and event-free survival are shown in Figures 1 and 2, respectively. For both curves, survival conditional on 1-year survival was 94% at 5 years, and 89% at 10 years.

For the 60 longer-term event-free survivors, the median (range) follow-up duration was 9.04 (5.0–10.33) years for the 45 patients still under review, and for the 15 patients who had been discharged, their median (range) time to discharge was 5.25 (0.67–10.0) years. Follow-up frequency varied from monthly to 5 yearly. Fifty-eight patients were in NYHA Class 1, and two in Class 2. Twenty-seven patients (45%) required one or more readmissions to hospital. The most frequent cardiac indication for readmission was to commence carvedilol therapy (n = 9). Other cardiac indications included further episodes of heart failure, medical or catheter treatment of arrhythmias and one child with dilated cardiomyopathy developed endocarditis on the mitral valve, which eventually required surgery. Non-cardiac indications included respiratory infections, diarrhoea and vomiting, ear, nose and throat procedures and admissions for management of other pre-existing conditions such as juvenile chronic arthritis and liver disease.

On echocardiogram, 41/60 patients had normal studies at last follow-up, defined as left ventricular dimensions and wall thicknesses within the normal range for weight and height (Z scores −2 to +2), a fractional shortening measurement > = 30%, and no evidence of mitral regurgitation or intracardiac thrombus. This group included all 15 patients who were discharged from cardiac follow-up. Fourteen cases had mild functional impairment, defined as a fractional shortening measurement of 20–29%, and one had moderate impairment with a fractional shortening measurement of 18%. Mitral regurgitation was mild in 8 and
Figure 2 Kaplan–Meier curve to show event-free survival from original presentation to 5 and 10 years.

Figure 3 Flow diagram to show outcomes for entire study cohort, from original presentation in 2003. FU, follow-up; Tx, transplant; EFS, event-free survivors; D/C, discharged; meds, medications.

Of the 45 patients under continuing follow-up, 23 remained on medication, all of whom were on afterload reduction either in the form of an Angiotensin Converting Enzyme inhibitor \((n = 22);\) lisinopril 12, enalapril 4, captopril 3 and ramipril 3), or losartan \((n = 1).\) Thirteen patients were additionally on \(\beta\)-blockers (carvedilol nine, propranolol, bisoprolol, atenolol and metoprolol one each), two on diuretics, three on digoxin, three on aspirin and one on flecainide. No patients moderate in 1. No intracardiac thrombi were seen, and there were no further reports of thrombotic events.

Outcomes for the entire study cohort, through from their original presentation in 2003, are shown in the flow diagram in Figure 3.

Treatment

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Treatment
Factors predicting outcome

Variables analysed included age, diagnosis and fractional shortening measurement on echocardiogram, all from the time of presentation in 2003. The same methodology was used as in the original study, to ensure a valid comparison. As in the original study, when all diagnostic groups were included in the multivariable model, only older age at presentation predicted death or transplantation significantly. However, when patients with a diagnosis of restrictive cardiomyopathy-induced or arrhythmia-induced heart failure were removed from the analysis (because of their tendency to have relatively preserved fractional shortening at presentation), fractional shortening also contributed significantly to the model. The hazard ratios and 95% confidence intervals are shown in Table 1. The hazard ratio for fractional shortening implies a 9% reduction in hazard for each point increase in fractional shortening measurement.

Therefore the predictors of outcome are the same as for the original study; with younger age and better fractional shortening measurement at presentation predictive of improved outcome both at 1 year and over the longer term.

Discussion

Unique features of this study

This study has shown for the first time that children who survive an initial hospitalization with heart failure from heart muscle disease have a good medium-term survival (82% overall 1-year survival but 77% at 5 years and 73% at 10 years, with survival conditional on 1-year survival 94% & 89% at 5 and 10 years respectively). There is a good functional outcome for survivors with 97% in New York Heart Association class I and 3% in class II.

Few studies are published on heart failure in children, and comparison between them is difficult because of variation in inclusion criteria, especially due to the inclusion of children with congenital heart disease. In developing countries, anaemia and infection also contribute to differences in incidence. Little is known about the longer-term outcomes in survivors of new-onset heart failure. Our study was initiated by Public Health Commissioners and focussed on children with heart muscle disease as they are the population most likely to need transplantation and mechanical support. Their good longer-term outcome is encouraging.

Since our original study, follow-up of patient cohorts from the Australian Childhood Cardiomyopathy Study and the American Pediatric Cardiomyopathy Registry have now provided valuable data about longer-term outcomes for specific diagnostic groups. This UK and Ireland National cohort differs in that it was selected to look at outcomes of symptomatic new-onset heart failure in children, rather than cardiomyopathy per se. The original entry criteria stipulated that whatever the underlying cause of the heart muscle disease, the symptoms of heart failure at presentation had to be severe enough to warrant hospital admission. These criteria were designed to detect children with the highest risk of morbidity and mortality, with the initial aim of helping with service provision and resource allocation within the National Health Service. The study is also unique as all the data for both the original and follow-up studies were acquired prospectively, and being a national study has provided a clearly defined geographical area and study population. Therefore, despite the relatively small numerical size of this study cohort compared with cardiomyopathy registry series, the findings are an important addition to the current literature and will hopefully help guide clinicians and families in making decisions about treatment options at each stage of the patient journey.

Myocarditis

In the original paper, myocarditis was diagnosed on clinical grounds, together with raised inflammatory markers and positive viral serology. Myocardial biopsy was not undertaken routinely in these cases due to the risks associated with the procedure, and because the disease is often patchy, such that there is a significant possibility that an affected area of myocardium may be missed. While this may lead to an underestimate of myocarditis, encouragingly suspected/probable myocarditis has a similar outcome to biopsy proven myocarditis. However, myocarditis may also be overdiagnosed, as it may be difficult to distinguish from an intercurrent infection unmasking an underlying case of dilated cardiomyopathy. Indeed, one case of suspected myocarditis from our original
series was subsequently found to have a familial dilated cardiomyopathy. Fortunately, recovery of function is also seen in children with dilated cardiomyopathy. 9

Familial dilated cardiomyopathy

The proportion of dilated cardiomyopathy cases which are familial varies in the published literature, with some series reporting a frequency up to 40%. 10 This figure may rise further as new mutations are identified. As only two additional cases of this longer-term follow-up cohort were found to have familial disease, this is probably an underestimate of the true total. This may be partly due to the disease not yet having manifested in other family members, but also the possibility that screening of first degree relatives, though usually recommended, may not always be completed. Although the genetic basis for the majority of cases of dilated cardiomyopathy is poorly understood at present, there is increasing awareness amongst the paediatric cardiac community of the need for screening for familial disease, and an increasing willingness amongst primary care physicians in the UK and Ireland to make the necessary referrals, so hopefully the situation will improve in the coming years. At the time of enrolment of the original study cohort in 2003, genetic testing for childhood cardiomyopathy was not routinely undertaken in the UK and Ireland, but this is now carried out in selected cases in the majority of centres.

Results from the Australian Cardiomyopathy in Childhood Study showed that outcome for familial cases of dilated cardiomyopathy was worse than non-familial cases, but other studies have shown no difference between these two groups. 5,11

Risk of sudden cardiac death

There were no cases of sudden cardiac death in dilated cardiomyopathy patients in this cohort. Pahl et al. calculated a 5-year incidence rate of 3% of sudden cardiac death in a cohort of 1803 children with an underlying diagnosis of dilated cardiomyopathy. Risk factors included age at diagnosis younger than 14 years, worse left ventricular dilatation, and left ventricular posterior wall thinning. 12 Data on 289 patients from the National Australian Cardiomyopathy Study have shown a cumulative incidence of sudden cardiac death at 15 years of 5% in dilated cardiomyopathy, 12% in restrictive cardiomyopathy and 23% in left ventricular non-compaction, indicating that type of cardiomyopathy is an important predictor of risk. 13 Although one of the three deaths in this study was sudden, this was in a patient who had initially presented with heart failure, which was subsequently found to be associated with a chronic atrial tachyarrhythmia. The other two deaths occurred in hospital following multiple admissions for worsening heart failure. The fact that one of these two was associated with neuromuscular disease, as were two of the early deaths in the original study, reinforces the positive longer-term outcome for children who do not have systemic progressive disease.

Predictors of outcome

The predictors of outcome identified in this study cohort were the same as for our original 1-year follow-up study. They are also consistent with and enhance the data from cardiomyopathy series, despite the fact that this patient cohort was selected on the basis of clinically significant heart failure, rather than a diagnosis of cardiomyopathy per se. There is a broad and expanding consensus that there is a better outcome with younger age at presentation, excepting those under 4 weeks of age, who were identified as a separate group with a worse outcome in the Australian dilated cardiomyopathy study. 6,9,14,15 A variety of echocardiographic parameters have been used in different studies as predictors of recovery, including left ventricular end diastolic dimensions, left ventricular fractional shortening or ejection fraction measurements and septal peak systolic tissue Doppler velocities. Fractional shortening measurement was chosen in this study as it is the functional measurement most widely used by paediatric cardiologists in the UK and Ireland, and it is quick to perform, which is important given that children may not be cooperative for echocardiography. The limitation of this form of functional assessment is that it is load dependent, but despite this, the findings of multiple studies are consistent in that, whichever echocardiographic parameter is used, worse measurements on presentation equate with a worse outcome.

Serial serum N-terminal prohormone brain natriuretic peptide levels have also been used as a predictor of outcome in children with dilated cardiomyopathy 16,17 with falling levels both an early and an accurate predictor of recovery. However, in the UK at the present time, these levels are not routinely measured in paediatric heart failure patients in all centres, and therefore, it was not possible to collate data about peptide levels for this study. Hopefully, with increasing awareness of the usefulness of this marker, its use will become more widespread.

Drug treatments for heart failure

This study was not designed to assess the impact of drug therapy. The good longer-term outcomes may be interrelated with the therapies used, but this cannot be determined from this study.

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Have paediatric heart failure outcomes improved?

There is an ongoing debate about the extent to which outcomes of heart failure from heart muscle disease in children have improved over the years. Differences of opinion arise partly because of varying lengths of historical perspective, and partly because of the criteria used to judge improvement. An entire generation of paediatric cardiologists in the UK and internationally was taught the maxim that in children with myocardial disease, a third die, a third develop chronic impairment, and a third get better. This originated from Greenwood’s 1976 study of 161 children with a mean age of 3.7 years, whose heart failure symptoms were treated with a combination of diuretics, digoxin and steroids. The data from this heart failure cohort and published cardiomyopathy series would suggest that a third of patients do either die or require a transplant within the first year of life, but that thereafter the majority get better with medical management and the passage of time, albeit with a small attrition rate.

Conclusions

While our original study showed that early morbidity and mortality in new-onset heart failure from heart muscle disease in children were significant, this follow-up study shows that children who survive the first year have a good longer-term outcome with survival conditional to 1 year of 94% at 5 years and 89% at 10 years, even though all of this unique cohort were hospitalized due to their heart failure at presentation.

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Conflicts of interest

The authors declare that they have no competing interests.

References

1. Dipchand AI, Kirk R, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dobbels F, Lund LH, Rahmel AO, Yusen RD, Stehlik J. The Registry of the International Society for Heart and Lung Transplantation: sixteenth official pediatric heart transplantation report—2013; focus theme: age. J Heart Lung Transplant 2013; 32: 979–98.
2. Shamszad P, Hall M, Rossano JW, Denfield SW, Knudson JD, Penny DJ, Towbin JA, Cabrera AG. Characteristics and outcomes of heart failure-related intensive care unit admissions in children with cardiomyopathy. J Card Fail 2013; 19: 672–7.
3. Rossano JW, Kim JJ, Decker JA, Proce JF, Zafar F, Graves DE, Morales DL, Heinle JS, Bozkurt B, Towbin JA, Denfield SW, Dreyer WJ, Jefferies JL. Prevalence, morbidity, and mortality of heart failure-related hospitalizations in the United States: a population-based study. J Card Fail 2012; 18: 459–70.
4. Andrews RE, Fenton MJ, Ridout DA, Burch M. New onset heart failure from heart muscle disease in childhood: a prospective study in the United Kingdom and Ireland. Circulation 2008; 117: 79–84.
5. Massin MM, Astadicko I, Deasy H. Epidemiology of heart failure in a tertiary pediatric center. Clin Cardiol 2008; 31: 388–391.
6. Alexander PM, Daubeney PE, Nugent AW, Lee KJ, Turner C, Colan SD, Rosenberg T, Davis AM, Ramsay J, Justo R, Sholler GF, King I, Weintraub RG. Long-term outcomes of dilated cardiomyopathy diagnosed during childhood: results from a national population-based study of childhood cardiomyopathy. Circulation 2013; 128: 2039–46.
7. Wilkinson D, Landy DC, Colan SD, Towbin JA, Sleeper LA, Orav EJ, Cox GF, Canter CE, Hsu DT, Webber SA, Lipshultz SE. The pediatric cardiomyopathy registry and heart failure: key results from the first 15 years. Heart Fail Clin 2010; 6: 401–13.
8. Foerster SR, Canter CE, Cinar A, Sleeper LA, Webber SA, Pahl E, Kantor PF, Alvarajez CA, Colan SD, Jefferies JL, Lamour JM, Margossian R, Rusconi PG, Shaddy RE, Towbin JA, Wilkinson JD, Lipshultz SE. Ventricular remodeling and survival are more favorable for myocarditis than for dilated cardiomyopathy in childhood: an outcomes study from the Pediatric Cardiomyopathy Registry. Circ Heart Fail 2010; 3: 689–97.
9. Everitt MD, Sleeper LA, Lu M, Canter CE, Pahl E, Wilkinson JD, Addonizio LJ, Towbin JA, Rossano J, Singh RK, Lamour J, Webber SA, Colan SD, Margossian R, Kantor PF, Jefferies JL, Lipshultz SE. Recovery of echocardiographic function in children with idiopathic dilated cardiomyopathy: results from the pediatric cardiomyopathy registry. J Am Coll Cardiol 2014; 63: 1405–13.
10. Towbin JA, Lowe AM, Colan SD, Sleeper LA, Orav EJ, Clunie S, Messere J, Cox GF, Lurie PR, Hsu D, Canter C, Wilkinson JD, Lipshultz SE. Incidence, causes and outcomes of dilated cardiomyopathy in children. JAMA 2006; 296: 1867–1876.
11. Michels VV, Driscoll DJ, Miller FA, Olson TM, Atkinson EJ, Olszewd CL, Schaid DJ. Progression of familial and non-familial dilated cardiomyopathy: long-term follow up. Heart 2003; 89: 757–61.
12. Pahl E, Sleeper LA, Canter CE, Hsu DT, Lu M, Webber SA, Colan SD, Kantor PF, Everitt MD, Towbin JA, Jefferies JL, Kaufman BD, Wilkinson JD, Lipshultz SE.
SE. Incidence of and risk factors for sudden cardiac death in children with dilated cardiomyopathy: a report for the Pediatric Cardiomyopathy Registry. J Am Coll Cardiol 2012; 59: 607–15.

13. Barucha T, Lee KJ, Daubeney PE, Nugent AW, Turner C, Sholler GF, Robertson T, Justo R, Ramsey J, Cardlin JB, Colan SD, King I, Weintraub RG, Davis AM. Sudden death in childhood cardiomyopathy: results from a long-term national population-based study. J Am Coll Cardiol 2015; 65: 2302–10.

14. Molina KM, Shrader P, Colan SD, Mital S, Margossian R, Sleeper LA, Shirali G, Barker P, Canter CE, Altmann K, Radojewski E, Tierney ES, Rychik J, Tani LY. Predictors of disease progression in pediatric dilated cardiomyopathy. Circ Heart Fail 2013; 6: 1214–22.

15. Alvarez JA, Wilkinson JD, Lipshultz SE. Outcome predictors for pediatric dilated cardiomyopathy: a systematic review. Prog Pediatr Cardiol 2007; 23: 25–32.

16. Mangat J, Carter C, Riley G, Foo Y, Burch M. The clinical utility of brain natriuretic peptide in paediatric left ventricular failure. Eur J Heart Fail 2009; 11: 48–52.

17. Kim G, Lee OJ, Kang IS, Song J, Huh J. Clinical implications of serial serum N-terminal prohormone brain natriuretic peptide levels in the prediction of outcome in children with dilated cardiomyopathy. Am J Cardiol 2013; 112: 1455–60.

18. Greenwood RD, Nadas AS, Fyler DC. The clinical course of primary myocardial disease in infants and children. Am Heart J 1976; 92: 549–560.