New-Onset Heart Failure Due to Heart Muscle Disease in Childhood

A Prospective Study in the United Kingdom and Ireland

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Background—We undertook the first prospective, national, multicenter study to describe the incidence and outcome of heart muscle disease–induced heart failure in children.

Methods and Results—Data were collected on patients admitted to a hospital through 2003 with a first episode of heart failure in the absence of congenital heart disease. All 17 pediatric cardiac centers in the United Kingdom and Ireland participated. Follow-up data were obtained to a minimum of 1 year. The incidence was 0.87/100 000 population (n = 104; 53 girls; 95% confidence interval 0.71 to 1.05 per 100 000). Median age at presentation was 1 year, with 82% in New York Heart Association class III to IV. Causes of heart failure included dilated cardiomyopathy (50 idiopathic, 8 familial), probable myocarditis (23), occult arrhythmia (7), anthracycline toxicity (5), metabolic disease (4), left ventricular noncompaction (3), and other (4). Overall 1-year survival was 82%, and event (death or transplantation)-free survival was 66%. Regression analysis showed older age and reduced systolic function on admission echocardiogram increased the event risk. Only 8% of event-free survivors (n = 69) remained in New York Heart Association class III to IV, but 35 required readmission during the study period, and all but 8 remained on medication.

Conclusions—This first national prospective study of new-onset heart failure in children has shown an incidence of 0.87/100 000. Multivariable analysis of survival data indicates a better outcome for younger children and for those with better systolic function at presentation, but overall, one third of children die or require transplantation within 1 year of presentation. (Circulation. 2008;117:79-84.)

Key Words: cardiomyopathy ■ myocarditis ■ morbidity ■ mortality ■ transplantation

The impetus for the present study arose from a question from the United Kingdom Department of Health National Specialty Commissioning Group, which commissions heart transplantation and mechanical support in the National Health Service. They queried pediatric transplantation centers as to the incidence of symptomatic heart failure due to heart muscle disease in children. This problem is particularly relevant to transplantation medicine because it is the main indication for pediatric heart transplantation outside of infancy internationally and accounts for the great majority of pediatric heart transplants in the United Kingdom.1 Our aim was to prospectively record the national incidence, cause, treatment, and outcome to 1 year of children requiring hospital admission for a first presentation of heart failure due to a nonstructural cause. In the United Kingdom and Ireland, pediatric cardiologists are members of the British Congenital Cardiac Association, and the present study was approved by the council of this organization and had universal support among the centers. It was believed that the defined geography and relatively large populations provided the opportunity to answer the question outlined above. We are not aware of any other national prospective study with these entry criteria, and many single-center retrospective studies have shown conflicting outcome data.2–6 Although important epidemiological studies of incidence have been undertaken, only 1 of these, from 2 regions in the United States, was prospective, and the entry criteria included asymptomatic patients.7–10

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Methods

Study Design
The study was planned in 2002, and agreement to participate was obtained from all 17 pediatric cardiac centers in the United Kingdom.
and Ireland. Multicenter ethics committee approval was obtained before the commencement of the study, and the data were made anonymous, so that the investigators were blinded to the identity of the patients (other than those from their own unit). Data were collected prospectively through calendar year 2003 by means of a questionnaire. This questionnaire was circulated to all consultants in the United Kingdom and Ireland before the start of the study, to allow individuals to familiarize themselves with the data that were to be collected. After this, individual correspondents were identified from each unit to forward data for the study. They were asked to return a questionnaire by fax or e-mail for each eligible admission every month through 2003 and to reply even if the number of cases for their unit that month was zero. In the follow-up period, correspondents were contacted in July 2004 and January 2005 for further data, which gave a minimum of 1 year of follow-up even for those whose original presentation was at the end of 2003. Population data were obtained from the Office of National Statistics (for the United Kingdom and Northern Ireland) and from the Ireland Central Statistics Office.11,12

Eligibility Criteria
Children <16 years of age who presented with a first episode of heart muscle disease–induced heart failure severe enough to require hospital admission and treatment were included in the study. All children were admitted to tertiary-level pediatric cardiology centers, either directly or via district general hospitals. Children with structural heart disease, a known history of arrhythmia, or heart failure as part of multiple-organ failure (as in sepsis, for example) were excluded. Heart failure was diagnosed by the attending cardiologist consultant on the basis of history, clinical symptoms and signs, and echocardiographic evidence of heart muscle disease. The underlying cause was accepted as given. A diagnosis of myocarditis was accepted as “probable” if there was a suggestive clinical history, raised inflammatory markers (white cell count, C-reactive protein, and/or erythrocyte sedimentation rate), and troponins, and “virus confirmed” if blood polymerase chain reaction for common pathogens was positive. In the United Kingdom and Ireland, a broad consensus exists not to perform elective cardiac biopsy to distinguish between myocarditis and dilated cardiomyopathy.

Data Collection
Details requested on admission included age, weight, New York Heart Association class (with the Ross classification for infants and children), and left ventricular fractional shortening measurement on echocardiography, together with the presence or absence of intracardiac thrombus. Echocardiography reports were accepted as given, and the images were not reviewed centrally. Information on the likely cause of heart failure, family history, details of medication, need for ventilation and/or extracorporeal membrane oxygenation (ECMO), and total length of stay in the hospital was also requested. Outcome measures obtained included survival/transplantation/death, need for readmission, and medication/New York Heart Association class/left ventricular fractional shortening measurement at 1 year for survivors.

Statistical Analysis
The primary outcome measure was death or cardiac transplantation within the first year after admission for heart failure. Survival was defined either as overall survival (ie, freedom from death) or event-free survival (ie, freedom from death or transplantation). Statistical methods focused on analyzing the impact of diagnosis, age, and fractional shortening measurement in predicting death or transplantation. A Kaplan–Meier survival curve was generated with the primary outcome measure as the event occurrence, and this was used to produce 1-year survival figures. Multivariate Cox regression modeling was used to investigate the contribution of covariates to the prediction of outcome, and a hazard ratio with 95% confidence intervals (CIs) was generated for each of these factors.

### Table 1. Number of Cases and Case Frequency by Geographic Region

<table>
<thead>
<tr>
<th>Geographic Region</th>
<th>Population &lt;16 y of Age (Mid 2003)</th>
<th>No. of Cases</th>
<th>Case Frequency per 100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northern England</td>
<td>2 847 400</td>
<td>28</td>
<td>0.98</td>
</tr>
<tr>
<td>The Midlands</td>
<td>1 911 700</td>
<td>24</td>
<td>1.25</td>
</tr>
<tr>
<td>Southern England</td>
<td>5 044 400</td>
<td>36</td>
<td>0.71</td>
</tr>
<tr>
<td>Wales</td>
<td>577 300</td>
<td>1</td>
<td>0.17</td>
</tr>
<tr>
<td>Scotland</td>
<td>943 100</td>
<td>12</td>
<td>1.27</td>
</tr>
<tr>
<td>Northern Ireland</td>
<td>388 200</td>
<td>2</td>
<td>0.51</td>
</tr>
<tr>
<td>Ireland</td>
<td>895 160</td>
<td>1</td>
<td>0.11</td>
</tr>
</tbody>
</table>

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
One hundred four children (53 girls) were included in the study, representing 0.87/100 000 of the population <16 years of age (95% CI 0.71 to 1.05 per 100 000). The geographic distribution of cases and case frequency are shown in Table 1.

Median age at presentation was 1 year (range 1 day to 15.9 years), and median weight was 9.5 kg (range 1.9 to 115.0 kg). The distribution of cases by age is shown in Figure 1; the greatest number of cases occurred in infancy, with a second, smaller peak in the teenage years. No significant seasonal variation in the number of case presentations was seen.

Length of stay in the hospital for the original admission varied from 1 to 246 days (median 15 days), and 82% of cases were in New York Heart Association class III to IV. The left ventricular fractional shortening measurement on initial echocardiogram varied from <5% to 25% (median 11%). Nine children had intracardiac thrombus, all of whom had very reduced fractional shortening measurements. All of these were given anticoagulant therapy, and only 1 embolization was documented, to the left middle cerebral artery in a 19-month-old girl who subsequently made a good recovery both from her dilated cardiomyopathy and from her stroke.

Cause of Heart Failure
The cause of heart failure was reported as idiopathic dilated cardiomyopathy in 50 cases, with a further 8 cases of familial dilated cardiomyopathy in which at least 1 first- or second-degree relative was affected. Twenty-three cases of probable myocarditis were reported, of which 8 were virus-confirmed with positive polymerase chain reaction results (5 parvovirus and 3 enterovirus). Four children presented with heart failure as a result of metabolic disease, of whom 2 had mitochondrial cytopathies, 1 had long-chain 3-hydroxy acyl-coenzyme A dehydrogenase deficiency, and 1 had Barth syndrome. Seven cases with occult arrhythmia were included in the study; these were children who were originally thought to have either dilated cardiomyopathy or myocarditis but who were subsequently found to have an underlying arrhythmia either later in the course of their original admission or on a subsequent admission. This was due to atrial tachycardia in 4, atrioven-
tricular reentry tachycardia in 2, and His bundle tachycardia in 1. Other reported causes included 5 cases of anthracycline toxicity, 3 of isolated left ventricular noncompaction, 2 of Duchenne muscular dystrophy, and 1 each of rickets and restrictive cardiomyopathy.

**Treatment**

All children received drug therapy, which consisted of diuretics in all but 4 and angiotensin-converting enzyme inhibitors in all but 7. Eighty children were given anticoagulant therapy, 40 were treated with digoxin, and 38 were given carvedilol. Forty-three required mechanical ventilation, including ECMO in 13, and 56 required intravenous inotropic support. Twenty-nine children had sustained arrhythmias that required therapy (including the 7 for whom arrhythmia was found to be the underlying cause).

**Outcome**

Seventeen children underwent cardiac transplantation; 11 of these transplantations were performed as emergency procedures when the patient was already hospitalized with severe heart failure. One posttransplantation death occurred. In addition, 3 children died while on the transplant waiting list. Overall, 19 deaths occurred, which yielded a 1-year overall survival rate of 82% (Figure 2). Of 8 ECMO survivors, 5 received transplants (after 5 to 22 days on ECMO), and 3 were bridged to recovery. When transplantation or death was taken as an adverse event, the 1-year event-free survival rate was 66% (Figure 3). The deaths were spread across all ages and etiologies of heart failure, except for the occult arrhythmia group, all of whom survived.

Seven of the 23 children thought to have myocarditis died, of whom 3 were blood polymerase chain reaction–positive, virus-confirmed cases. Consent for postmortem examination was obtained in 5 children and showed lymphocytic myocarditis in each case. One transplantation was performed for a case of probable myocarditis after 7 days of mechanical support, and the diagnosis was confirmed on histological examination of the explanted heart. (Similarly, histological examination of the explanted hearts from patients with dilated cardiomyopathy confirmed the diagnosis in each case.)

Just 4 deaths occurred out of hospital: 2 in teenagers with Duchenne muscular dystrophy, who opted for terminal care at home, and 2 sudden deaths secondary to presumed arrhythmias. The first of these was a 23-month–old girl who was recovering after probable myocarditis (which was confirmed at postmortem examination), and the second was a 5-month–old boy with dilated cardiomyopathy who was referred for transplant assessment but had been too well to have his name

![Figure 1. Number of cases by age group.](image1)

![Figure 2. Kaplan–Meier curve showing overall survival with a minimum of 1 year of follow-up.](image2)

![Figure 3. Kaplan–Meier curve showing event-free survival with a minimum of 1 year of follow-up.](image3)
placed on the transplant list. Three deaths were primarily attributable to noncardiac causes: 1 to a relapse of acute myeloid leukemia, 1 to klebsiella meningitis, and 1 to pneumonia.

Cox regression analysis was used to generate hazard ratios for factors related to event-free survival. Variables included age at presentation and fractional shortening on echocardiography. When all diagnostic groups were included in the model, only older age at presentation predicted death or transplantation significantly. The hazard ratios per year and 95% CIs are shown in Table 2. When patients with a diagnosis of restrictive cardiomyopathy or arrhythmia-induced heart failure were excluded from the analysis (because of their tendency to have relatively preserved fractional shortening at presentation), fractional shortening contributed significantly to the hazard model. The hazard ratio (95% CI) for fractional shortening was 0.88 (0.80 to 0.96). This ratio implies a 12% reduction in hazard for each point increase in fractional shortening measurement. For event-free survivors (n=69), median left ventricular fractional shortening measurement at 1-year follow-up was 25%, and only 8% of children remained in New York Heart Association class III to IV. However, 35 of these children required at least 1 readmission to hospital, and 61 continued to require medication, which left only 8 children completely well without any further treatment.

Discussion

Pediatric heart failure due to heart muscle disease remains the leading cause of cardiac transplantation in children >1 year of age.1 The present study is the first national prospective study of this problem and is the largest annual cohort ever reported. Comparison between studies is complicated by a number of factors, including differing age ranges, diagnostic entry criteria, and diagnostic classifications of study populations. An earlier crude estimate of the incidence of idiopathic dilated cardiomyopathy in adult and pediatric patients, based on a random selection of hospitals in Japan, was 3.58/100 000.13 More complete population studies have been undertaken in children, of which 2 were retrospective and 1, from 2 regions of the United States, was prospective.8–10 In these reports, the incidence of dilated cardiomyopathy per 100 000 population varied, being 0.34 in Finland, 0.73 in Australia, and 0.58 in the United States. (The American data varied in the 2 geographic regions, being 0.74 in New England and 0.50 in the Central Southwest.) The variation in figures can be explained to some extent by differences in entry criteria. Whereas the Finnish study reported idiopathic dilated cardiomyopathy only, the Australian study additionally included familial cases, metabolic disease, and myocarditis, and the American study included all of these causes together with neuromuscular diseases. In the present study population, the incidence of dilated cardiomyopathy (used in its broadest sense to include familial cases, myocarditis, and metabolic and neuromuscular disease) was 0.76/100 000.

All of the patients in the present study were in symptomatic heart failure and required hospitalization and treatment, whereas the other 3 studies included asymptomatic patients and/or those not requiring treatment. The inclusion of asymptomatic patients also contributes to variations in incidence by changing proportions of certain groups; for example, in the American study, 12.5% of cases were associated with skeletal myopathy, whereas only 2.2% of cases in the present study were, which explains the higher incidence in boys in the American study.

Despite differences in the age range of study populations, infants were numerous in all studies, although the proportion they represented varied according to the upper age limit of the study population. A further problem with comparison of studies relates to the diagnosis of myocarditis. This can be a difficult diagnosis to make, and the limitations of the Dallas criteria have been highlighted recently.14,15 In the United Kingdom and Ireland, it is widely believed that the risks of anesthesia and cardiac biopsy outweigh the benefits of histological confirmation of the diagnosis. Although a possibility exists that individual cases of myocarditis or dilated cardiomyopathy in the present study may have been misclassified, it is reassuring that such tissue diagnoses as were available confirmed the clinical diagnosis in each case; in addition, the present study was not designed to assess outcomes of pediatric myocarditis. Comparison between epidemiological studies is probably more accurate when myocarditis and dilated cardiomyopathy are combined in a broad group.

Multicenter, prospective survival data for pediatric heart failure due to heart muscle disease have not been reported previously. The present data show one third of children die or undergo transplantation within 1 year of presentation. It could be argued that the high incidence of transplantation after ECMO with duration of support between 5 and 22 days did not allow an adequate time for recovery. However, the improvement in survival with pediatric heart failure does appear to be related to an earlier and more aggressive recourse to transplantation both in the United Kingdom and Ireland, as well as in the United States, which would appear to justify this approach.16–18 The rate of sudden death in the present series was 1.9%, which, although lower than that reported in adult series, is consistent with pediatric series.7,19,20

Whether infants and younger children have a better outcome than older children with heart failure is contentious, and several earlier reports have differing conclusions.2–7 The present data showed an improved survival in younger children after multivariable analysis. It is unclear why this was the case. It is attractive to speculate that the more active marrow of younger children has a greater propensity to generate circulating stem cells, which could aid myocardial recovery, but no proof of this has appeared as yet.21 Systolic function at the time of presentation was also predictive of

Table 2. Cox Regression Analysis to Determine Factors Related to Event-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>Significance</th>
<th>Hazard Ratio</th>
<th>95% CI Lower</th>
<th>95% CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at presentation</td>
<td>0.002</td>
<td>1.095</td>
<td>1.034</td>
<td>1.159</td>
</tr>
<tr>
<td>Fractional shortening</td>
<td>0.171</td>
<td>0.950</td>
<td>0.882</td>
<td>1.022</td>
</tr>
</tbody>
</table>
outcome in children with diagnoses other than restrictive cardiomyopathy or primary arrhythmias, and although this may not seem surprising, it is interesting that it has not always been found to be the case.2

The present study was not designed to assess the effects of drugs such as angiotensin-converting enzyme inhibitors and carvedilol in the pediatric heart failure population, and although we have data on the usage of these drugs, it would be wrong to overinterpret this information. Others have reported improved cardiac function and symptomatology with these drugs in children but have stopped short of demonstrating an impact on survival.22–24 In the present study, only those well enough to be treated with β-blockers and angiotensin-converting enzyme inhibitors received them, and without randomization, the equivalence of the treated and untreated groups cannot be ensured. Further studies are needed to clarify which therapies or combinations of therapies may be beneficial in the longer term in this group of patients. Other limitations of the study are that it was not designed to examine long-term outcomes, given the relatively short follow-up period, and both diagnosis and echocardiographic findings were accepted as given rather than being reviewed centrally. The wide differences in regional incidence shown in Table 1 may most likely be attributed to the relatively small numbers in each geographic area, but a theoretical risk of ascertainment bias exists; however, the study was designed to try to minimize this.

Summary
This first national prospective study of new-onset heart failure due to nonstructural causes requiring hospitalization in children has shown an overall incidence of 0.87/100 000 and an incidence of dilated cardiomyopathy (due to all causes, including myocarditis) of 0.76/100 000. This result appears remarkably similar to data from Australia and the United States. The present multivariable analysis of the survival data is at variance with some earlier work and indicates a better outcome for younger children and for those with better systolic function at presentation. Overall, one third of children died or required transplantation within 1 year of presentation.

Acknowledgments
The authors thank the British Congenital Cardiac Association and UK Department of Health National Specialty Commissioning Group for support of this idea. The authors also wish to extend their thanks to the following contributors: Aaron Bell, Katie Butler, Janet Burns, Giovanna Ciotti, David Crossland, Piers Daubeney, Joe De Giovanni, Jaspal Dun, Robert Johnson, Subramanian Jothimurugan, Sujeev Mathur, Colin McMahon, Shubha Narayanaswami, Liam O’Connell, Philip Roberts, Tony Salmon, Andrew Sands, Anna Seale, Roy Sievers, Graham Stuart, Eapen Thomas, Robert Tulloh, Joseph Vettukattil, Pauline Whitmore, Dirk Wilson, and Christopher Wren.

Sources of Funding
The authors wish to thank the British Congenital Cardiac Association for funding travel expenses incurred during the study.

Disclosures
None.

References
CLINICAL PERSPECTIVE

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Circulation. 2008;117:79-84; originally published online December 17, 2007; doi: 10.1161/CIRCULATIONAHA.106.671735
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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