Ventricular Remodeling and Survival Are More Favorable for Myocarditis Than For Idiopathic Dilated Cardiomyopathy in Childhood

An Outcomes Study From the Pediatric Cardiomyopathy Registry

Susan R. Foerster, MD; Charles E. Canter, MD; Amy Cinar, PhD; Lynn A. Sleeper, ScD; Steven A. Webber, MD; Elfriede Pahl, MD; Paul F. Kantor, MD; Jorge A. Alvarez, PhD; Steven D. Colan, MD; John L. Jefferies, MD; Jacqueline M. Lamour, MD; Renee Margossian, MD; Jane E. Messere, RN; Paolo G. Rusconi, MD; Robert E. Shaddy, MD; Jeffrey A. Towbin, MD; James D. Wilkinson, MD, MPH; Steven E. Lipshultz, MD

Background—Myocarditis is a cause of a new-onset dilated cardiomyopathy phenotype in children, with small studies reporting high rates of recovery of left ventricular (LV) function.

Methods and Results—The presenting characteristics and outcomes of children with myocarditis diagnosed clinically and with biopsy confirmation (n=119) or with probable myocarditis diagnosed clinically or by biopsy alone (n=253) were compared with children with idiopathic dilated cardiomyopathy (n=1123). Characteristics at presentation were assessed as possible predictors of outcomes. The distributions of time to death, transplantation, and echocardiographic normalization in the biopsy-confirmed myocarditis and probable myocarditis groups did not differ (P=0.5), but both groups differed significantly from the idiopathic dilated cardiomyopathy group (all P≤0.003). In children with myocarditis, lower LV fractional shortening z-score at presentation predicted greater mortality (hazard ratio, 0.85; 95% confidence interval, 0.73 to 0.98; P=0.03) and greater LV posterior wall thickness predicted transplantation (hazard ratio, 1.17; 95% confidence interval, 1.02 to 1.35; P=0.03). In those with decreased LV fractional shortening at presentation, independent predictors of echocardiographic normalization were presentation with an LV end-diastolic dimension z-score >2 (hazard ratio, 0.36; 95% confidence interval, 0.22 to 0.58; P<0.001) and greater septal wall thickness (hazard ratio, 1.16; 95% confidence interval, 1.01 to 1.34; P=0.04).

Conclusions—Children with biopsy-confirmed or probable myocarditis had similar proportions of death, transplantation, and echocardiographic normalization 3 years after presentation and better outcomes than those of children with idiopathic dilated cardiomyopathy. In children with myocarditis who had impaired LV ejection at presentation, rates of echocardiographic normalization were greater in those without LV dilation and in those with greater septal wall thickness at presentation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00005391. (Circ Heart Fail. 2010;3:689-697.)

Key Words: cardiomyopathy ■ mortality ■ myocarditis ■ pediatrics ■ remodeling

Although myocarditis and idiopathic dilated cardiomyopathy (IDCM) are considered distinct diseases, myocarditis frequently presents with a phenotype of new-onset dilated cardiomyopathy.2,3 It is the next most common diagnosis associated with a new-onset dilated cardiomyopathy phenotype after IDCM in multicenter pediatric registries.4–6

A

Received August 18, 2009; accepted August 11, 2010.

From Washington University at St Louis (S.R.F., C.E.C.), Saint Louis, Mo; New England Research Institutes, Inc (A.C., L.A.S.), Watertown, Mass; the University of Pittsburgh (S.A.W.), Pittsburgh, Pa; Northwestern University (E.P.), Chicago, Ill; Hospital for Sick Children (P.F.K.), Toronto, Ontario, Canada; University of Miami (J.A.A., P.G.R., J.D.W., S.E.L.), Miami, Fla; Children’s Hospital Boston (S.D.C., R.M., J.E.M.), Boston, Mass; Baylor College of Medicine (J.L.), Houston, Tex; Albert Einstein College of Medicine (J.M.L.), New York, NY; the University of Pennsylvania (R.E.S.), Philadelphia, Pa; and the University of Cincinnati (J.A.T.), Cincinnati, Ohio.

Guest Editor for this article was Samuel S. Gidding, MD.

Correspondence to Susan R. Foerster, MD, Washington University at St Louis, 1 Children’s Place, NWT 8, St Louis, MO 63110. E-mail susanfoerster@msn.com

© 2010 American Heart Association, Inc.

Circ Heart Fail is available at http://circheartfailure.ahajournals.org

DOI: 10.1161/CIRCHEARTFAILURE.109.902833
The Pediatric Cardiomyopathy Registry (PCMR) is a multi-institutional, long-term study of children with cardiomyopathy (ClinicalTrials.gov identifier NCT00005391). Although a previous PCMR analysis found children diagnosed with myocarditis to have lower risks for death and transplantation than children with IDCM, the degree of normalization of left ventricular (LV) function and size remains undetermined. The PCMR myocarditis cohort includes children with myocarditis who had endomyocardial biopsies that supported a pathological diagnosis of myocarditis and many in whom the diagnosis was made clinically with or without an associated negative endomyocardial biopsy. The objectives of the present analysis were (1) to determine the magnitude of difference in LV recovery between children with myocarditis and IDCM; (2) to determine the difference in mortality, transplantation, and echocardiographic normalization of PCMR patients with a clinical diagnosis of myocarditis confirmed by endomyocardial biopsy compared with the other children diagnosed with myocarditis; and (3) to assess the factors at presentation that may aid in predicting these outcomes. We hypothesized that myocarditis diagnosed clinically with biopsy confirmation would have better outcomes than myocarditis diagnosed without both criteria and better outcomes than those with IDCM.

Methods

The PCMR has enrolled more than 3500 infants, children, and adolescents with cardiomyopathy. Subjects were enrolled retrospectively if they were diagnosed with cardiomyopathy between 1990 and 1995 and prospectively thereafter. The PCMR has a standardized data collection protocol and manual of operations. At some institutions, local data collectors trained by the Data Coordinating Center (New England Research Institutes) and the Administrative Coordinating Center (University of Miami) collect baseline and annual data based on automated notification from the Data Coordinating Center. At other institutions, the University of Miami Data Collection Travel Team visits regularly to collect required data. Data collectors abstract clinical, echocardiographic (most recent study in the annual reporting period), and treatment data from the medical records of children until death or heart transplantation occurs. The data collection forms differed for retrospectively and prospectively enrolled patients, with limited data on family history, hospitalization, and medications for the prospective cohort. All centers obtain institutional review board approval or waiver for data transmission to the PCMR Data Coordinating Center and analyses of the data base.

Patients are eligible for PCMR enrollment if they are <18 years old and if they have 1 of the following: echocardiographic evidence of cardiomyopathy; pathological diagnosis of cardiomyopathy at autopsy or endomyocardial biopsy; or other clinical evidence of cardiomyopathy provided by the cardiologist. A dilated cardiomyopathy phenotype in the PCMR is defined as an LV fractional shortening (LVFS) <2 standard deviations (SD) for age and an LV end-diastolic dimension (LVEDD) or volume >2 SD for body surface area, evidence from autopsy or myocardial tissue analysis, or the presence of other compelling evidence from the investigator. The 14 clinical exclusion criteria include associated congenital heart disease, endocrine disorders known to cause myocardial damage, chemotherapy or pharmacological-associated cardiotoxicity, chronic arrhythmia, pulmonary parenchymal or vascular disease, or immunologic disease.

The causal diagnosis of cardiomyopathies within the PCMR is subdivided into 6 broad areas: neuromuscular disorder, when muscular dystrophy or other neuromuscular disease coexists; familial, made in the presence of specifically identified genetic cardiomyopathies, existence of cardiomyopathy in multiple family members, or on family screening; malformation syndrome, when identified congenital malformation syndromes coexist; and metabolic, when a specific disorder of metabolism or a mitochondrial disorder coexists.

A diagnosis of myocarditis is made with a presentation of new-onset cardiac symptoms and/or echocardiographic abnormalities developing after a history of recent respiratory, gastrointestinal, or other suspected viral infection. A diagnosis of “idiopathic” is made when no specific causal diagnosis is identified in the medical record.

Three groups of children were analyzed for this study. A biopsy-confirmed myocarditis (BCM) group consisted of 119 subjects who carried a causal diagnosis of myocarditis and also had endomyocardial biopsy evidence of both inflammatory infiltration and cellular necrosis, as per the Dallas criteria. The probable myocarditis (PM) group consisted of 253 subjects who were either (1) given a causal diagnosis of myocarditis but did not undergo endomyocardial biopsy or had biopsies described as “borderline” or nondiagnostic; or (2) given a causal diagnosis of IDCM but had endomyocardial biopsies demonstrating both inflammatory infiltration and myocellular necrosis (n=19), as has been done in other studies evaluating IDCM patients with endomyocardial biopsy. An IDCM group consisted of 1123 subjects who were given a causal diagnosis of IDCM and had negative biopsies, if performed. All descriptions for biopsies performed in patients in each group were reviewed by a senior investigator (C.E.C.) before any child was included in the 3 groups.

Statistical Methods

Patient characteristics were compared among the BCM, PM, and IDCM diagnostic groups using a Fisher exact test for categorical variables and a Kruskal-Wallis test or ANOVA for continuous variables, according to whether the distribution of the variable approximates a normal distribution. The α level was set at 0.05, and all tests were 2-sided.

Study outcomes were death, heart transplantation, and “echocardiographic normalization.” Echocardiographic normalization was defined as attaining both an age-adjusted LVFS z-score of ≥-2 or more and a body surface area–adjusted LVEDD z-score of ≥2.18 noted from the most recent echocardiogram results available in each annual reporting period of PCMR patients.

A competing-risks analysis was performed for each diagnostic group, and the cumulative incidence rates of study outcomes were calculated.20 Probability values were obtained from competing-risks Cox proportional hazards regression.21 Augmented Cox proportional hazards modeling for competing risks was used to simultaneously identify risk factors for mortality and transplantation in children with myocarditis and included tests of interaction to investigate potential differential risk factors for the BCM and PM groups. Factors with a univariate probability value <0.2 were considered in the multivariable analyses, with staged assessment of collinearities.

In the combined BCM and PM cohort, a second set of analyses focused on echocardiographic normalization was performed in children presenting with decreased LVFS (z-scores ≤-2). A primary comparison of interest was between those with and without a dilated LV (LVEDD z-scores ≥2 versus ≤2) at presentation. These subgroups were chosen on the basis of the work by Felker et al., who suggested that an echocardiographic pattern of reduced LV ejection with a lack of LV dilation at presentation was a marker for fulminant myocarditis, which has a particularly favorable outcome in children and adults with myocarditis.22,23 Cox proportional hazards modeling was used to identify predictors of echocardiographic normalization, with time to normalization censored at death or transplant. Excluded from modeling of recovery were 14 children with both normal LVFS and LVEDD z-scores at diagnosis and 4 children with normal LVFS in the presence of dilation, because of limited numbers.

The SAS statistical software package version 9.1 (SAS Institute, Cary, NC), was used for all analyses. Competing risks analyses were performed using an SAS macro provided by Tai20 and an R macro by Fine and Gray.21
Table. Demographic and Clinical Characteristics of 1495 Children With Cardiomyopathies at Diagnosis and Within 1 Month of Diagnosis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Biopsy-Confirmed Myocarditis [n]*</th>
<th>Probable Myocarditis [n]*</th>
<th>Idiopathic Dilated CM [n]*</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male, %</td>
<td>47.1</td>
<td>49.8</td>
<td>49.2</td>
<td>0.88</td>
</tr>
<tr>
<td>Median age, y (Q1, Q3)</td>
<td>1.6 (1.0, 7.4)</td>
<td>1.9 (0.6, 10.4)</td>
<td>1.2 (0.3, 9.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age &lt;1 y, %</td>
<td>25.2</td>
<td>32.2</td>
<td>46.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Retrospective cohort, %</td>
<td>58.0</td>
<td>25.3</td>
<td>24.8</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td></td>
<td></td>
<td></td>
<td>0.73</td>
</tr>
<tr>
<td>White</td>
<td>52.1</td>
<td>56.0</td>
<td>52.6</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>27.4</td>
<td>20.8</td>
<td>22.8</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>16.2</td>
<td>16.0</td>
<td>17.3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4.3</td>
<td>7.2</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure, %</td>
<td>86.4</td>
<td>77.3</td>
<td>75.0</td>
<td>0.02†</td>
</tr>
<tr>
<td>Hospitalized, %</td>
<td>96.6</td>
<td>80.0</td>
<td>75.5</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Admitted to ICU, %</td>
<td>81.7</td>
<td>52.4</td>
<td>46.1</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Characteristics within 30 d of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Listed for transplant, %</td>
<td>10.3</td>
<td>13.1</td>
<td>17.0</td>
<td>0.07</td>
</tr>
<tr>
<td>Congestive heart failure therapy, %</td>
<td>94.1</td>
<td>85.1</td>
<td>84.2</td>
<td>0.02†</td>
</tr>
<tr>
<td>ECMO, %</td>
<td>3.4</td>
<td>6.9</td>
<td>2.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Balloon pump, %</td>
<td>0.0</td>
<td>2.3</td>
<td>1.0</td>
<td>0.26</td>
</tr>
<tr>
<td>Ventricular assist device, %</td>
<td>2.3</td>
<td>2.3</td>
<td>0.8</td>
<td>0.27</td>
</tr>
<tr>
<td>IVIG therapy, %</td>
<td>23.0</td>
<td>8.6</td>
<td>3.6</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>Steroids, %</td>
<td>29.9</td>
<td>15.6</td>
<td>3.4</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>IVIG or steroids, %</td>
<td>47.1</td>
<td>24.2</td>
<td>6.6</td>
<td>&lt;0.001†</td>
</tr>
<tr>
<td>LV z-scores at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean EDD (SD)</td>
<td>3.83 (2.43)</td>
<td>3.42 (2.67)</td>
<td>4.77 (2.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EDD z-score &gt;2, %</td>
<td>75.5</td>
<td>68.4</td>
<td>86.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean ESD (SD)</td>
<td>5.58 (2.78)</td>
<td>5.24 (3.69)</td>
<td>6.54 (2.94)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(Continued)
Table. Continued

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Biopsy-Confirmed Myocarditis [n]</th>
<th>Probable Myocarditis [n]</th>
<th>Idiopathic Dilated CM [n]</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median FS (Q1, Q3)</td>
<td>$-9.10 (-11.0, -6.7)$ [103]</td>
<td>$-8.56 (-11.01, 5.46)$ [202]</td>
<td>$-9.68 (-11.47, -9.40)$ [903]</td>
<td>0.001</td>
</tr>
<tr>
<td>FS z-score &lt;−2, %</td>
<td>92.2</td>
<td>93.1</td>
<td>96.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Median PWT (Q1, Q3)</td>
<td>$0.16 (-1.47, 1.84)$ [87]</td>
<td>$-0.34 (-1.65, 1.01)$ [141]</td>
<td>$-0.64 (-1.82, 0.87)$ [684]</td>
<td>0.005</td>
</tr>
<tr>
<td>Median SWT (Q1, Q3)</td>
<td>$0.02 (-1.31, 0.91)$ [75]</td>
<td>$-0.39 (-1.35, 0.39)$ [128]</td>
<td>$-0.87 (-1.96, 0.14)$ [623]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median mass (Q1, Q3)</td>
<td>$3.08 (1.07, 4.16)$ [86]</td>
<td>$1.92 (0.55, 3.61)$ [136]</td>
<td>$2.56 (0.86, 4.24)$ [671]</td>
<td>0.03‡</td>
</tr>
<tr>
<td>Median PWT:EDD ratio (Q1, Q3)</td>
<td>$0.14 (0.11, 0.17)$ [89]</td>
<td>$0.14 (0.11, 0.18)$ [150]</td>
<td>0.12</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

CM indicates cardiomyopathy; EDD, end-diastolic dimension; ESD, end-systolic dimension; FS, fractional shortening; ICU, intensive care unit; PWT, posterior wall thickness; SWT, septal wall thickness; Q1, Q3, interquartile range, defined as the 25th to 75th percentiles.

* n refers to the total available sample size for the variable specified.
† Pairwise comparison between biopsy-confirmed and probable myocarditis groups significant at α = 0.05.
‡ P value is from analysis of variance where means are presented and Kruskal-Wallis test where medians are presented.

Results

Clinical Profiles at Presentation

The median follow-up time for survivors not undergoing heart transplantation was 3.1 years ([Q1, Q3], 0.9 to 6.2 years) in the BCM group and 2.7 years ([Q1, Q3], 1.0 to 6.0 years) in the PM group. Median follow-up time for survivors with IDCM not undergoing heart transplantation was 1.9 years ([Q1, Q3], 0.4 to 4.3 years). Complete data for some variables were not available for all children, especially with regard to hospitalization and specific therapies because of differing data collection for the prospective and retrospective cohorts (Table). Although all groups were similar with regard to sex and race/ethnicity, the children with IDCM tended to be diagnosed at a younger age than the myocarditis groups: The percentage of children presenting before 1 year of age was 47% in the IDCM group and 33% and 25% in the PM and BCM groups, respectively (P<0.001). The age distributions of the BCM and PM groups were not significantly different.

Although at least three fourths of the children in each group were hospitalized, had congestive heart failure, and were treated with congestive heart failure therapy within 30 days of presentation, a significantly greater proportion of the BCM group had these characteristics than did either of the other groups. Among children with hospitalization data, 82% of the BCM group was admitted to an intensive care unit, compared with 70% to 50% of the PM or IDCM groups (P<0.001).

None of the patients were recorded to have been diagnosed with giant cell or eosinophilic myocarditis. Data on viral serological testing and the presence of virus in the myocardium by polymerase chain reaction techniques were very limited in the database. It was documented that viral serology or polymerase chain reaction was performed in 94 patients. Of these, 31 (33%) had a positive finding, which included 10 cytomegalovirus, 6 Coxsackie virus, 5 enterovirus, 3 adenovirus, 2 Epstein-Barr virus, 2 herpes simplex virus, and 1 each of hepatitis B virus, respiratory syncytial virus, and parvovirus.

More than two thirds of each group demonstrated LV dilation (LVEDD z-score >2), and >90% had evidence of decreased LV systolic function (LVFS z-score <−2) at presentation (Table). However, the IDCM group had a higher mean (±standard deviation) LVEDD z-score (4.8±2.6) than that of the BCM (3.8±2.4) and PM (3.4±2.7) groups (P<0.001) and a lower median LVFS z-score (median, −9.7) than that of the 2 myocarditis groups (−9.1 and −8.6), respectively (P=0.001). In addition, the myocarditis groups had significantly higher LV posterior and septal wall thickness z-scores than did the IDCM group, but all group medians were within 1 SD of normal (z-score=−1 to +1).

Outcomes

The analyzed outcomes of echocardiographic normalization, heart transplantation, or death occurred in >70% of children in each group within 3 years of presentation, with the remainder having persistent echocardiographic abnormalities in LV size or systolic function (Figure 1A through 1C). All groups continued to have events, primarily echocardiographic normalization, >3 years after presentation. Both the BCM and the PM group had 4 subjects die >3 months after presentation. All of these late deaths were attributed to heart failure and persistent LV dysfunction except for 1 patient who died from a respiratory syncytial virus infection superimposed on chronic heart failure. No patient died after echocardiographic normalization. The 1 patient (in the BCM group) reported to have transplantation after echocardiographic normalization was noted to have “global LV dysfunction” on the echocardiogram report, suggesting an error in the specific LVFS and LVEDD measurements on that study.

In the BCM, PM, and IDCM groups, there were 10, 17, and 168 deaths, respectively. In the BCM, PM, and IDCM groups,
there were 21, 38, and 323 transplants, respectively. The distributions of time to death, transplantation, and echocardiographic normalization in the BCM and PM groups did not differ by group \((P > 0.5)\), but both groups differed significantly from the IDCM group \((P < 0.003)\) (Figure 1). For example, at 3 years after presentation, 6% and 7% of the BCM and PM groups, respectively, had died without heart transplantation; 19% and 17% had received heart transplantation; and 54% and 52% had achieved echocardiographic normalization. In the IDCM group, 17% died without transplantation, 33% had undergone heart transplantation, and only 21% had achieved echocardiographic normalization at 3 years.

Characteristics at Presentation Associated With Death, Transplantation, or Echocardiographic Normalization

Because outcomes did not differ between the BCM and PM groups, they were combined in competing risk factor analyses for death and transplantation. Tests of interaction found no evidence that risk factors differed between BCM and PM children. The following factors at presentation had probability values \(P > 0.2\) in univariate Cox proportional hazards models for death (controlling for myocarditis group) and were assessed in multivariable modeling: congestive heart failure \((HR, 2.56; 95\% \text{ CI}, 0.76 \text{ to } 8.61; P = 0.13)\) and LVFS \(z\)-score \((HR, 0.85; 95\% \text{ CI}, 0.73 \text{ to } 0.98; P = 0.03)\). The multivariable model indicated that only LVFS \(z\)-score at presentation was independently a significant risk factor for death \((n = 305)\).

The following univariate risk factors at presentation had probability values \(P < 0.2\) in Cox proportional hazards models for transplantation (again controlling for myocarditis group) and were assessed in multivariable modeling: congestive heart failure \((HR, 2.02; 95\% \text{ CI}, 0.85 \text{ to } 4.82; P = 0.12)\), older age at diagnosis of cardiomyopathy \((HR, 1.03 \text{ per year}; 95\% \text{ CI}, 1.00 \text{ to } 1.06; P = 0.10)\), higher end-diastolic posterior wall thickness \(z\)-score \((HR, 1.17; 95\% \text{ CI}, 1.02 \text{ to } 1.35; P = 0.025)\), and lower end-diastolic posterior wall-to-septal thickness ratio \((HR, 0.91 \text{ per } 0.1 \text{ U decrease}; 95\% \text{ CI}, 0.84 \text{ to } 0.98; P = 0.018)\). The multivariable model indicated that only posterior wall thickness \(z\)-score at presentation independently predicted transplantation \((n = 228)\).

In children with myocarditis presenting with reduced systolic function, Cox modeling for echocardiographic normalization found an LVEDD \(z\)-score \(>2\) at presentation highly predictive for lower rates of normalization \((HR, 0.39; 95\% \text{ CI}, 0.27 \text{ to } 0.59; P < 0.001)\). Controlling for this factor, other risk factors in bivariable models were age category at diagnosis \((HR, 2.01 \text{ for } 1 \text{ to } <6 \text{ years versus } <1 \text{ year}; 95\% \text{ CI}, 1.25 \text{ to } 3.23; P = 0.03)\); a family history of sudden death \((HR, 10.73; 95\% \text{ CI}, 1.97 \text{ to } 58.39; P = 0.006)\); increasing LV septal wall thickness \((HR, 1.16; 95\% \text{ CI}, 1.01 \text{ to } 1.34; P = 0.04)\); and use of intravenous gamma-globulin \((IVIG)\) \((HR, 2.99; 95\% \text{ CI}, 1.69 \text{ to } 5.29; P < 0.001)\).

Multivariable analysis resulted in a 2-variable model in those presenting with decreased systolic function \((n = 170)\): LVEDD \(z\)-score \(>2\) at presentation was associated with a lower chance for echocardiographic normalization \((HR, 0.36; 95\% \text{ CI}, 0.22 \text{ to } 0.58; P < 0.001)\), whereas a greater septal wall thickness at presentation was associated with an increased likelihood of echocardiographic normalization \((HR, 1.16; 95\% \text{ CI}, 1.01 \text{ to } 1.34; P = 0.04)\). The use of IVIG was not an independent predictor of echocardiographic normalization because of its association with LVEDD \(z\)-score at
by guest on June 20, 2017 http://circheartfailure.ahajournals.org/Downloaded from

myopathy Study4,5 have established that children with a new-onset dilated cardiomyopathy phenotype have a better prognosis if they are diagnosed with myocarditis than with IDCM. However, these studies did not evaluate differences in the resolution of echocardiographic abnormalities between subgroups. Recent single-center case series of pediatric myocarditis diagnosed histopathologically by the Dallas criteria and treated with IVIG, steroids, and/or other immunosuppressants have reported a majority of children with myocarditis will demonstrate resolution of their dilated cardiomyopathy phenotype within a few months after presentation.9–12 Furthermore, Gagliardi et al found biopsy-dependent differences in response to therapy. In their study, LV function normalized in 77% of patients with biopsies showing “active” myocarditis by the Dallas criteria when treated with prednisone and cyclosporine compared with only 46% of patients diagnosed with “borderline” myocarditis who received the same treatment.

We also found that the dilated cardiomyopathy phenotype resolved in the majority of children with myocarditis within the PCMR; in addition, we noted that histopathologic findings using the Dallas criteria were not related to outcomes. We observed that the dilated cardiomyopathy phenotype can resolve years after its initial presentation, even in patients with IDCM.

A marked disparity in outcomes exists in children with a new-onset dilated cardiomyopathy phenotype associated with myocarditis compared with those with idiopathic cardiomyopathy, which means that differentiating these diseases is an important part of the initial diagnostic and treatment plan. Clinical differentiation on the basis of a preceding viral prodrome as is used in adults26,27 may be more difficult in children, given their increased frequency of viral infections or viral syndromes in general.6 In the Arola28 study of idiopathic pediatric dilated cardiomyopathy in Finland, 47% of the patients reported a recent respiratory or gastrointestinal illness. This experience would make histopathologic analysis of endomyocardial biopsies an attractive option for diagnosing pediatric myocarditis.

However, numerous recent reviews of adult myocarditis2,3,14 have concluded that the diagnosis of myocarditis should not be based on histological findings alone because of the lack of association of biopsy findings in large cohorts of patients with suspected myocarditis, inconsistencies with clinical and histological features of myocarditis, and the inherent insensitivity of histological diagnosis, including with use of the Dallas criteria. Thus, although our study is limited by the lack of a central laboratory to evaluate endomyocardial biopsies and echocardiographic findings and a common and specific prospective, noninvasive evaluative protocol for the clinical diagnosis of myocarditis, our results indicate that children listed in the PCMR who were suspected of having myocarditis clinically, with or without biopsy confirmation, had substantially better outcomes than did children with a diagnosis of IDCM.

Although outcomes were poorer in the IDCM group, a substantial proportion of these children (21%) exhibited LV echocardiographic normalization by 3 years after diagnosis. Recovery of LV function in pediatric IDCM has been observed in single-center reviews in proportions similar to what we observed.29–31 Some of these patients may truly have had myocarditis; in our own cohort, a few children given a causal diagnosis of IDCM had biopsies diagnostic of myocarditis.

Many cases of IDCM are hypothesized to evolve from an initial viral infection of the heart,32 and multiple studies have
identified viral genomes within the myocardium of IDCM patients. One study found a correlation with disappearance of myocardial viral genomes and LV recovery in adults with IDCM. “Recovery” may also reflect the effects of pharmacotherapy. A recent study in children with IDCM who recovered LV function demonstrated recurrence of LV dysfunction when drug therapy was withdrawn.

**Limitations of the Study**

Since the inception of data collection within the PCMR in the early 1990s, the clinical entity of “fulminant myocarditis” has been identified and found to be associated with high rates of resolution of abnormalities in LV size and function. The timing of this discovery precluded incorporation of the diagnostic criteria for fulminant myocarditis in the analysis of outcomes for myocarditis in subjects in the PCMR. However, our findings confirm that the echocardiographic phenotype of fulminant myocarditis observed in adults (reduced LV function with normal LV chamber size) was also associated with a very high (nearly 80%) rate of echocardiographic normalization in PCMR subjects with myocarditis.

We have estimated the time to echocardiographic normalization based on data from the most recent echocardiogram in each annual reporting period. For many patients, surveillance is indeed composed of only an annual examination. Therefore, the estimated times to normalization presented here are an upper limit, because normalization may have occurred at some time before the time of the echocardiogram.

Information about specific viral etiologies for myocarditis is limited in the PCMR data base. The technologies for detecting viral genomes in the myocardium largely evolved after the inception of the PCMR. Viruses such as adenovirus, parvovirus B19, and human herpes virus 6 were not considered common viral agents for pediatric myocarditis. Although there is some evidence that certain viruses may be associated with poorer outcomes than others, the presence of viral genome (or histopathologic findings as in the Dallas criteria) was not associated with outcome in a recent study of adult myocarditis.

The Australian registry has identified failure to increase LVFS at follow-up as a risk factor for death or heart transplantation in children with a new-onset dilated cardiomyopathy phenotype. In that study, echocardiographic data are recorded, if available, quarterly in the first year after presentation, compared with annually in the PCMR. Because a large number of outcome events occurred within the first year of presentation in this study, the availability of only annual echocardiographic data in the PCMR precludes assessment of changes in LVFS as an outcomes marker in this study.

Multivariable analyses in our study found no association of IVIG or corticosteroids with survival or LV normalization. These findings are similar those of the Children’s Hospital of Pittsburgh, previous adult and pediatric systematic reviews, and randomized trials in adults. Recent pediatric studies using various regimens of IVIG and immunosuppression have reported somewhat higher rates of LV recovery than we did. The power of our assessment of the effects of IVIG and steroids on outcome is limited by capture of therapeutic information in only a subset of patients and may be biased by the lack of random assignment to these treatments. Thus, our findings do not necessarily mean that IVIG and steroids do not have a role in the treatment of myocarditis in children.

The PCMR data base did not collect information on patient status at the time of listing or performance of heart transplantation. However, many PCMR centers also participate in the Pediatric Heart Transplant Study (PHTS), in which this information is collected and in which myocarditis and IDCM are specifically identified subgroups for patients listed with a dilated cardiomyopathy phenotype. A recent PHTS study found 77% of patients with such a phenotype were listed while on inotropic, mechanical ventilatory, and/or mechanical circulatory support, and 85% of such patients were transplanted while on such support. These findings suggest that children listed for transplantation with a dilated cardiomyopathy phenotype, including those with myocarditis, are severely ill and few have been transplanted who do not require high levels of support.

**Conclusions**

Although our findings must be considered in the context of coming from a retrospective registry with incomplete data capture, they support the concept that children having a dilated cardiomyopathy phenotype who are diagnosed with myocarditis have better outcomes than those in whom no cause can be found, regardless of endomyocardial biopsy findings. Endomyocardial biopsy may still be helpful to determine etiology in an otherwise undiagnosed dilated cardiomyopathy phenotype in a child or to exclude rare conditions in children, such as giant cell or hypersensitivity myocarditis, as suggested in recently developed guidelines. Any biopsy findings must be interpreted in the context of the entire clinical picture. Other diagnostic modalities such as cardiac MRI may further refine the noninvasive diagnosis of myocarditis, but their efficacy remains to be defined in children.

The fact that we found no differences in outcomes in patients treated with IVIG or corticosteroids does not mean that these drugs have no benefit, especially in patients showing evidence of autoimmunity. However, the generally high rate of LV normalization observed in our patients suggests that randomized studies with very large patient sample sizes would be necessary to answer this question definitively. The good chance for echocardiographic normalization in pediatric myocarditis argues against heart transplantation for children who do not require high levels of cardiac support, as continued echocardiographic normalization can occur even after 3 years.

When to abandon high levels of support for cardiac replacement therapy is not clear-cut, but our findings suggest that this decision might be deferred for a longer period in those patients who present with a normal chamber size than in those who present with LV dilation. As they become increasingly available, ventricular assist devices, such as the Berlin Heart for infants and children, may possibly be used as a bridge to recovery, as well as a bridge to heart transplantation, in children with myocarditis.
Sources of Funding
This study was supported by National Heart, Lung, and Blood Institute grant R01HL53392, Children’s Cardiomyopathy Foundation.

Disclosures
Dr Lipshultz has several active grants from the National Institutes of Health (> $10,000) and Health Resources and Services Administration (> $10,000) related to research on cardiomyopathies.

References
CLINICAL PERSPECTIVE

A child presenting with a newly diagnosed dilated cardiomyopathy phenotype often has myocarditis that may spontaneously resolve, lead to a chronic dilated cardiomyopathy, or lead to death or heart transplantation. We sought to determine the frequency of these divergent outcomes in children diagnosed with myocarditis and to define characteristics at presentation that might be predictive of ultimate outcome using the Pediatric Cardiomyopathy Registry data base (PCMR). The analysis resulted in several important findings: (1) We noted that most patients diagnosed with myocarditis have normalization of their ventricular size and systolic function over time, often within several months. Normalization is especially likely to occur when patients with diminished systolic function present with a normal left ventricular diastolic diameter or with a greater left ventricular posterior wall thickness. (2) Children who have poorer systolic function at presentation are more likely to die, when assessed by multivariable analysis. About one fourth of patients diagnosed with myocarditis died or were transplanted by 3 years from presentation. (3) There were no significant differences in outcomes in myocarditis patients with and without biopsy confirmation of active myocarditis, using the Dallas criteria. In fact, these 2 groups of patients were remarkably similar to one another in terms of demographics, initial echocardiographic findings, and outcomes. However, these patients had markedly better outcomes than PCMR patients diagnosed with idiopathic dilated cardiomyopathy.
Ventricular Remodeling and Survival Are More Favorable for Myocarditis Than for Idiopathic Dilated Cardiomyopathy in Childhood: An Outcomes Study From the Pediatric Cardiomyopathy Registry

Susan R. Foerster, Charles E. Canter, Amy Cinar, Lynn A. Sleeper, Steven A. Webber, Elfriede Pahl, Paul F. Kantor, Jorge A. Alvarez, Steven D. Colan, John L. Jefferies, Jacqueline M. Lamour, Renee Margossian, Jane E. Messere, Paolo G. Rusconi, Robert E. Shaddy, Jeffrey A. Towbin, James D. Wilkinson and Steven E. Lipshultz

_Circ Heart Fail._ 2010;3:689-697; originally published online September 10, 2010; doi: 10.1161/CIRCHEARTFAILURE.109.902833

_Circulation: Heart Failure_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/3/6/689

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation: Heart Failure_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation: Heart Failure_ is online at:
http://circheartfailure.ahajournals.org//subscriptions/