# Outcomes of Restrictive Cardiomyopathy in Childhood and the Influence of Phenotype

## A Report From the Pediatric Cardiomyopathy Registry

Steven A. Webber, MBChB; Steven E. Lipshultz, MD; Lynn A. Sleeper, ScD; Minmin Lu, MS; James D. Wilkinson, MD; Linda J. Addonizio, MD; Charles E. Canter, MD; Steven D. Colan, MD; Melanie D. Everitt, MD; John Lynn Jefferies, MD; Paul F. Kantor, MD; Jacqueline M. Lamour, MD; Renee Margossian, MD; Elfriede Pahl, MD; Paolo G. Rusconi, MD; Jeffrey A. Towbin, MD; on behalf of the Pediatric Cardiomyopathy Registry Investigators

***Background***—Restrictive cardiomyopathy (RCM) has been associated with poor prognosis in childhood. The goal of the present analysis was to use the Pediatric Cardiomyopathy Registry to analyze outcomes of childhood RCM, with a focus on the impact of phenotype comparing pure RCM with cases that have additional features of hypertrophic cardiomyopathy (HCM).

***Methods and Results***—We analyzed the Pediatric Cardiomyopathy Registry database (1990–2008; N=3375) for cases of RCM. Cases were defined as pure when RCM was the only assigned diagnosis. Additional documentation of HCM at any time was used as the criterion for RCM/HCM phenotype. RCM accounted for 4.5% of cases of cardiomyopathy. In 101 (66%), pure RCM was diagnosed; in 51 (34%), there was a mixed phenotype. Age at diagnosis was not different between groups, but 10% of the pure RCM group was diagnosed in infancy versus 24% of the RCM/HCM group. Freedom from death was comparable between groups with 1-, 2-, and 5-year survival of RCM 82%, 80%, and 68% versus RCM/HCM 77%, 74%, and 68%. Transplant-free survival was 48%, 34%, and 22% and 65%, 53%, and 43%, respectively ($P=0.011$). Independent risk factors at diagnosis for lower transplant-free survival were heart failure (hazard ratio 2.20, $P=0.005$), lower fractional shortening $z$ score (hazard ratio 1.12 per 1 SD decrease in $z$ score, $P=0.014$), and higher posterior wall thickness in the RCM/HCM group only (hazard ratio 1.32, $P<0.001$). Overall, outcomes were worse than for all other forms of cardiomyopathy.

***Conclusions***—Transplant-free survival is poor for RCM in childhood. Survival is independent of phenotype; however, the RCM/HCM phenotype has significantly better transplant-free survival.

***Clinical Trials Registration***—URL: http://www.clinicaltrials.gov. Unique Identifier: NCT00005391.

**(*Circulation*. 2012;126:1237-1244.)**

**Key Words:** hypertrophic cardiomyopathy ■ pediatrics ■ registries ■ restrictive cardiomyopathy

Restrictive cardiomyopathy (RCM) is a rare form of heart muscle disease characterized by "normal or decreased volume of both ventricles associated with biatrial enlargement, normal left ventricular wall thickness and atrioventricular valves, impaired ventricular filling with restrictive physiology, and normal (or near normal) systolic function."[1] The rarity of this condition in childhood has made it very difficult to accurately assess outcomes, and risk factors for these outcomes, as well. A number of single-center studies have suggested an extremely poor outlook for this condition in childhood, with as many as 50% dying within 2 years of diagnosis, usually of sudden death.[2–8] Limitations to these studies include collection of data over several decades, very small numbers of patients, lack of focus on the phenotypic variability that accompanies this diagnosis, and failure to identify consistent independent risk factors for adverse outcomes. Many patients with otherwise classic features of RCM have some degree of increased ventricular wall thickness, thus reflecting an overlap of phenotype with hypertrophic cardiomyopathy (HCM). Indeed, some families have been

Received March 13, 2012; accepted July 18, 2012.

From the Children's Hospital of Pittsburgh of UPMC, Pittsburgh, PA (S.A.W.); University of Miami Miller School of Medicine, Miami, FL (S.E.L., J.D.W., P.G.R.); New England Research Institute, Watertown, MA (L.A.S., M.L.); Columbia University, New York, NY (L.J.A.); Washington University in St. Louis, St. Louis, MO (C.E.C.); Children's Hospital Boston, Boston, MA (S.D.C., R.M.); Primary Children's Medical Center, Salt Lake City, UT (M.D.E.); Cincinnati Children's Hospital Medical Center, Cincinnati, OH (J.L.J., J.A.T.); The Hospital for Sick Children, Toronto, ON, Canada (P.F.K.); The Children's Hospital at Montefiore, Bronx, NY (J.M.L.); and Children's Memorial Hospital, Chicago, IL (E.P.).

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

Correspondence to Steven A. Webber, MBChB, Division of Cardiology, Children's Hospital of Pittsburgh of UPMC, 4401 Penn Avenue, Pittsburgh, PA 15224. E-mail steve.webber@chp.edu



*Circulation* **is available at http://circ.ahajournals.org** **DOI: 10.1161/CIRCULATIONAHA.112.104638**

identified in which different members of the same family (with a common genetic mutation) have cardiomyopathy with appearances of RCM, HCM, or mixed RCM/HCM phenotype.[9] The impact of such morphological heterogeneity on outcome of RCM in childhood is unknown. Here we analyze the North American Pediatric Cardiomyopathy Registry (PCMR) database to better understand the prevalence of RCM, the phenotypic spectrum of disease, contemporary outcomes, and risk factors for adverse outcomes. Specifically, we hypothesized that the outcomes of RCM is poor in childhood, that phenotypic overlap between RCM and other forms of cardiomyopathy (especially hypertrophic) is common in children, and that morphological heterogeneity is associated with disease outcome.

Clinical Perspective on p 1244

## Methods

### Study Design and Data Collection

The PCMR study design and implementation have been described in detail elsewhere.[10] In brief, patients <18 years of age newly diagnosed with cardiomyopathy were eligible for inclusion in the Registry. The primary study cardiologist at each site determined the specific cardiomyopathy phenotype. Options included hypertrophic, dilated, restrictive, and other (such as arrhythmogenic right ventricular cardiomyopathy and left ventricular noncompaction cardiomyopathy) with the additional option of choosing mixed phenotype, specifying >1 type of cardiomyopathy (eg, RCM and HCM). Criteria for diagnosis of DCM and HCM included both morphological features and quantitative echocardiographic measures, as well, as previously described.[10] The diagnosis of RCM was based on an echocardiographic pattern with "one or both atria enlarged relative to ventricles of normal or small size with evidence of impaired diastolic filling and in the absence of significant valvar heart disease." The diagnosis of congestive heart failure was based on self-reporting by the primary treating physician without prespecified diagnostic criteria. Data were collected in 2 ways. First, 98 centers in the United States and Canada voluntarily submitted data to the PCMR. In addition, 2 geographic regions were targeted for comprehensive patient recruitment: the central Southwest (Arkansas, Oklahoma, and Texas) and New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont).[10] Data were collected either by research teams at each center or by an outreach team that regularly traveled to the participating centers, enrolling new cases and abstracting relevant data from medical records in a standardized fashion. Patients fell into 2 cohorts: The prospective cohort consisted of patients diagnosed on, or after, January 1, 1996. The retrospective cohort comprised patients with cardiomyopathy who were first diagnosed on, or after, January 1, 1990, but before 1996. The retrospective nature of enrollment in this group precluded assurance of complete capture, but the observation period is longer. This report is based on follow-up data through July 1, 2008.

Data were collected on standardized PCMR case report forms. Collected data included demographic characteristics and all information relevant to the cardiomyopathy, including personal medical history, family history, clinical data, laboratory data (including ECG and echocardiogram results), and outcomes. Selected variables, such as left and right atrial enlargement on echocardiogram and electrocardiographic data were collected only for retrospective cohort patients. Follow-up forms were completed on an annual basis. All participating study sites had local institutional review board approval.

### Patient Sample

Data were analyzed for all RCM subjects (N=152), and a subanalysis was performed for 2 subgroups, as well: 101 pure RCM subjects and 51 subjects with overlapping phenotype comprising RCM and HCM (mixed RCM/HCM phenotype). Cases were defined as pure when RCM was the only assigned diagnosis at all time points during follow-up. Cases were described as mixed if an additional diagnosis of HCM was given at any time. There were 4 cases classified as a mixed diagnosis of RCM with other type of cardiomyopathy (not dilated or hypertrophic). These 4 cases were excluded from further analysis.

### Statistical Methods

All data were submitted to the Data Coordinating Center at New England Research Institutes for analysis. Descriptive statistics include counts and percentages for categorical data and mean±SD for normally distributed, continuous data; the median was used for skewed data. The distributions of categorical variables in the 2 phenotypic subgroups were compared by using a Fisher exact test. Group comparisons of normal continuous variables were compared by using the Student $t$ test, and skewed data were compared by using the Wilcoxon rank-sum test. Echocardiographic $z$ scores were calculated relative to body-surface area (left ventricular [LV] end-diastolic and end-systolic dimension and LV end-diastolic posterior wall and septal thicknesses and LV mass) or relative to age (LV fractional shortening).[11] These were assessed at the diagnosis of cardiomyopathy for statistical differences from normal ($z$ score=0) by using the Student 1-sample $t$ test.

Outcomes analyzed included death (with the survival time of subjects who underwent cardiac transplantation censored at the date of transplant), transplant, and the composite end point of death or transplant. Event-free rates were calculated with the use of the Kaplan-Meier method with comparison of survival curves using the log-rank test. The Kaplan-Meier method was also used to compare event-free rates between the major types of cardiomyopathy observed within the PCMR. In addition, cumulative incidence competing risk event rates were estimated by using nonparametric competing risks methodology.[12]

Cox proportional hazards regression modeling was used to identify predictors of outcomes. The selection of predictors began with a multivariable model that contained variables significant in univariate analyses at the $\alpha=0.20$ level, and other variables judged to be of clinical importance and a set of clinically plausible interaction terms significant at $\alpha=0.05$ level, as well. Following the fit of the initial multivariable model, we used probability values from the Wald tests of the individual coefficients to identify variables that could be deleted from the model and conducted a stepwise selection to determine the final model.

All analyses were conducted using the Statistical Analysis System (SAS Institute, Inc, NC), Version 9.1 and S-Plus 6.1 (Insightful Corp).

## Results

### Patient Characteristics

One hundred fifty-two children with RCM were identified among 3375 children <18 years of age with cardiomyopathy in the PCMR (4.5%). Among the 152 patients, 101 were considered to have pure disease (3.0% of total) and 51 to have mixed RCM/HCM phenotype (1.5% of total and 34% of the RCM cases) (Table 1). The proportion of RCM diagnoses with mixed (RCM/HCM) phenotype did not change over time ($P=0.42$). The percentage of pure RCM versus RCM/HCM cases did not differ by clinical site as assessed by analysis of the 5 sites with the largest number of RCM cases (10–28 patients; $P=0.15$). The baseline characteristics of the patients are shown in Table 2. Age at diagnosis was not significantly different between the 2 groups (mean 6.2±5.0 years), but 10% of the RCM group was diagnosed in infancy versus 24% of the RCM/HCM group ($P=0.029$). Ninety-three percent of the pure group was labeled as having idiopathic disease in

**Table 1. Types of Cardiomyopathy Observed in the Pediatric Cardiomyopathy Registry Patients Diagnosed 1990–2008**

| Type | n | % All Cases |
|---|---|---|
| RCM | 152 | 4.5 |
| Pure RCM | 101 | 3.0 |
| RCM/HCM | 51 | 1.5 |
| Pure HCM | 745 | 22.1 |
| Pure DCM | 1776 | 52.6 |
| Other | 702 | 20.8 |
| Total | 3375 | 100 |

DCM indicates dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; and RCM, restrictive cardiomyopathy.

comparison with 77% of the mixed group ($P=0.008$). Inborn errors of metabolism (diagnosed in 6 cases;10% versus 1%) and familial history of cardiomyopathy (42% versus 14%) were more common in the mixed group in comparison with the group with pure RCM. Among those with familial cardiomyopathy, 16 had documentation of familial RCM. No patient was diagnosed with cardiomyopathy secondary to generalized neuromuscular disorder. Peripheral muscle biopsy was performed in only 4 cases of 57 where biopsy information was queried; these 4 cases had no specific diagnostic findings. Genotyping analysis for known mutations of cardiac genes was not available for patients with RCM.

Echocardiographic characteristics of the 2 groups, expressed as $z$ scores relative to healthy children, demonstrated primarily greater end-diastolic interventricular and LV posterior wall thicknesses and greater LV mass in the group with mixed phenotype (Table 2). Mean LV end-diastolic dimension $z$ score approximated zero and 88% had LV end-diastolic dimension $z$ score of $<2$. Thus, any degree of LV dilatation was rare.

## Survival and Transplant-Free Survival

A total of 29 patients died without transplantation. Median time to death for these patients from the time of diagnosis was 0.3 months (range, 4 days–4.1 months). The probability of freedom from death (censored at transplant), heart transplantation, and the composite end point of death or transplantation for all patients with RCM in comparison with patients with pure (ie, only specified diagnosis) dilated cardiomyopathy (DCM; N=1776) and pure HCM (N=745) in the PCMR are shown in Figure 1A through 1C. It can be seen that time to event for all 3 end points is shorter for PCMR patients with RCM in comparison with those with DCM or HCM. Probabilities of freedom from death at 1, 2, and 5 years after diagnosis of cardiomyopathy in the PCMR were as follows: all RCM 81%, 79%, and 71%; pure DCM 88%, 85%, and 78%; and pure HCM 94%, 93%, and 90%.

Figure 2 shows the probability of freedom from death (censored at transplant), heart transplantation, and the composite end point of death or transplantation for all patients with pure RCM (N=101) in comparison with those with mixed RCM/HCM phenotype (N=51). In this analysis, it can be seen that survival did not differ between the 2 subgroups (1-, 2-, and 5-year survival of pure RCM 82%, 80%, and 68% versus RCM/HCM 77%, 74%, and 68%; $P=0.67$), but that transplant-free survival was lower in the pure RCM group (1-, 2-, and 5-year transplant-free survival 48%, 34%, and 22%) in comparison with the RCM/HCM group (1-, 2-, and 5-year transplant-free survival of 65%, 53%, and 43%; $P=0.01$). This difference was due to reduced freedom from transplantation in patients with pure RCM in comparison with the mixed RCM/HCM phenotype (1-, 2-, and 5-year freedom from transplantation 58%, 43%, and 32% versus 85%, 72%, and 62%, respectively; hazard ratio for transplant, 2.7, $P<0.001$). There was a total of 67 transplantations. The median (interquartile range) time to listing among those

**Table 2. Selected Baseline Characteristics of Patients With Restrictive Cardiomyopathy**

| Variable | RCM (n=152) | Pure RCM (n=101) | RCM/HCM (n=51) | *P* |
|---|---|---|---|---|
| Age at diagnosis, y | 6.2±5.0 | 6.1±4.9 | 6.3±5.3 | 0.784 |
| Age <1 y at diagnosis, % | 15 | 10 | 24 | 0.029 |
| Male, % | 48 | 49 | 47 | 1.000 |
| CHF at diagnosis, % | 37 | 42 | 26 | 0.072 |
| Family history of cardiomyopathy, % | 23 | 14 | 42 | 0.004 |
| Idiopathic, % | 88 | 93 | 77 | 0.008 |
| Left atrial enlargement, %* | 86 | 71 | 86 | 0.296 |
| Right atrial enlargement, %* | 72 | 62 | 72 | 0.556 |
| FS *z* score | −0.36±3.30 | −0.60±3.10 | 0.10±3.70 | 0.302 |
| LVED *z* score | −0.14±2.09 | −0.04±1.95 | −0.54±2.34 | 0.214 |
| PWT *z* score | 0.65±2.46 | 0.23±1.96 | 1.53±3.09 | 0.014 |
| IVS *z* score | 0.78±2.11 | 0.15±1.60 | 1.91±2.46 | <0.001 |
| LVM *z* score | 0.60±2.33 | 0.13±1.97 | 1.55±2.71 | 0.007 |

RCM indicates restrictive cardiomyopathy; HCM, hypertrophic cardiomyopathy; CHF, congestive heart failure; FS, fractional shortening; LVED, left ventricular end-diastolic dimension; PWT, posterior wall thickness; IVS, end-diastolic septal thickness; and LVM, left ventricular mass.

*Sample sizes for left and right atrial enlargement are 56, 35, and 21 for RCM, pure RCM, and RCM/HCM, respectively.

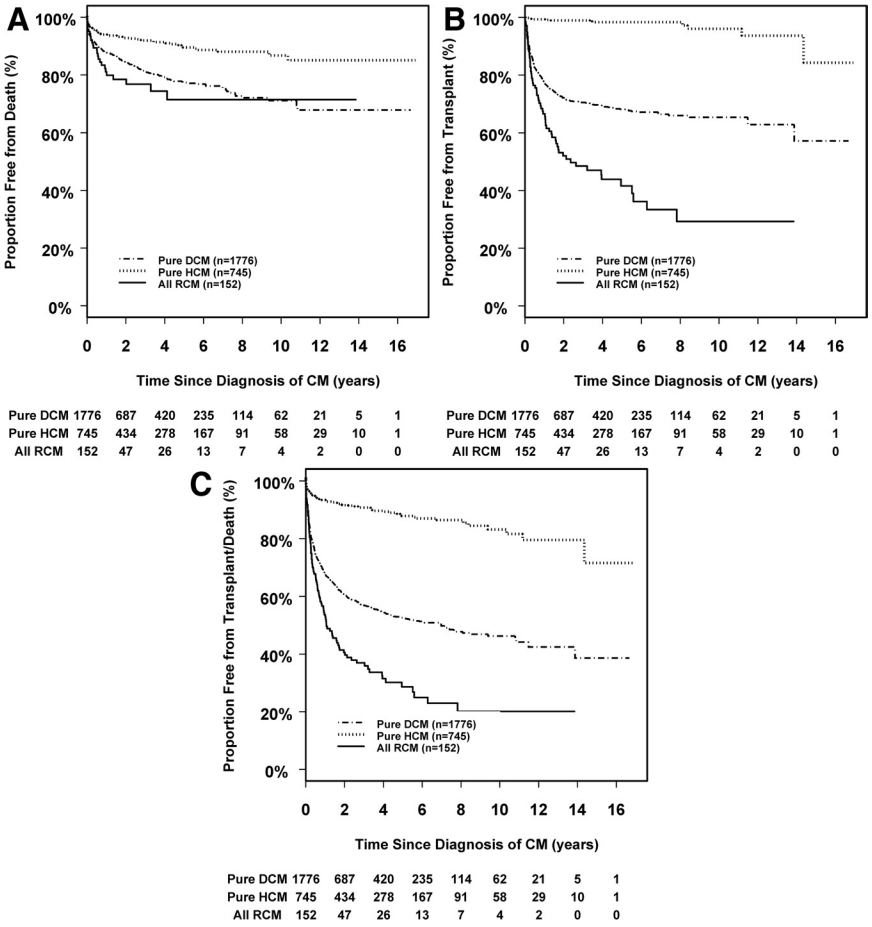


**Figure 1.** Probability of freedom from death (censored at transplantation) (**A**), transplantation (**B**), and death or transplantation (**C**) among 3375 children diagnosed with cardiomyopathy in the PCMR stratified by type of cardiomyopathy. CM indicates cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy; and PCMR, Pediatric Cardiomyopathy Registry.

receiving transplants was 2.0 (0.4, 11.2) months for the pure RCM group and 9.8 (1.1, 27.1) months postdiagnosis for the RCM/HCM group ($P=0.10$).

Because there are >2 possible outcomes at any given time, competing outcomes methodology was used to demonstrate the proportion of patients in 3 mutually exclusive groups at any time point after diagnosis. The mutually exclusive outcomes are death without transplant, alive without transplant, and transplanted. The cumulative incidence event rates estimated by the use of the competing risks methodology for patients in the pure RCM group and the mixed RCM/HCM group are shown in Figure 3. The cumulative incidence of death was similar for the pure RCM and the RCM/HCM groups ($P=0.27$). At 1, 2, and 5 years after diagnosis, the mortality rates were 14%, 15%, and 20% for the pure RCM group and 22%, 24%, and 28% for the RCM/HCM group. The cumulative incidence of transplantation at 1, 2, and 5 years after diagnosis was 38%, 51%, and 58% for the pure RCM group and 13%, 23%, and 30% for the RCM/HCM group.

## Causes of Death

The following causes for the 29 deaths were recorded: progressive heart failure (n=12), sudden (with or without documented arrhythmia) (n=6), stroke (n=1), cardiac tamponade secondary to pericardial effusion (n=2), and unknown (n=8). There were no differences between phenotypic subgroups. Among the 6 patients with sudden death, ventricular arrhythmias were documented in 3 (ventricular tachycardia in 2 and ventricular fibrillation in 1).

## Cerebrovascular Accidents and Antithrombotic Therapy Usage

There was no documentation of stroke at presentation or during follow-up visits, and no echocardiographic demonstration of intracardiac thrombus was recorded. One patient (see above) died with evidence of cerebral infarction. For the 61 RCM patients for whom medication usage was collected, 43% were reported to have received some form of anticoagulation/antithrombotic therapy during follow-up.

## Electrocardiographic Abnormalities and Arrhythmias at Presentation and During Follow-Up

Only limited long-term arrhythmia data were available. No patient was documented to have second- or third-degree atrioventricular block at presentation. Four of the 58 patients received a permanent pacemaker at diagnosis, which included defibrillator capability in 3. Three additional pacemakers were implanted during follow-up. Across all follow-up, 24-hour ambulatory monitor results were available in 23 cases and revealed supraventricular tachycardia in 4 cases and ventricular tachycardia in 3.

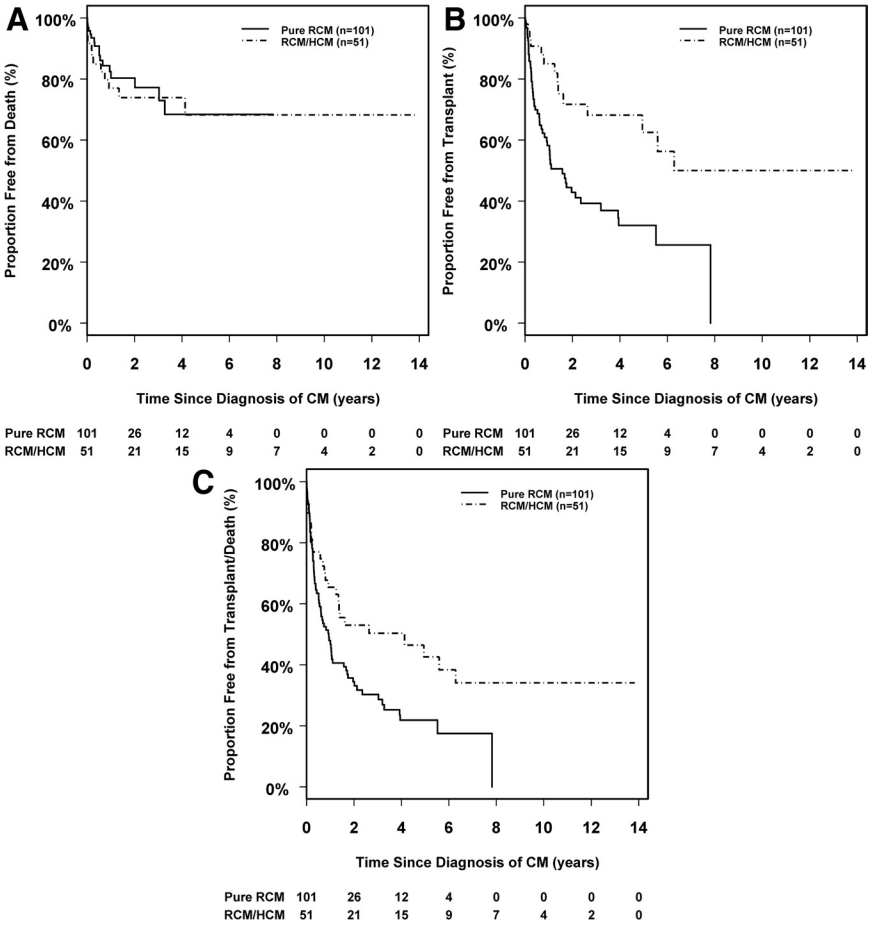


**Figure 2.** Probability of freedom from death (censored at transplantation) (**A**), transplantation (**B**), and death or transplantation (**C**) among 152 children with RCM stratified by phenotype (pure RCM versus mixed/overlapping phenotype RCM/HCM). CM indicates cardiomyopathy; HCM, hypertrophic cardiomyopathy; and RCM, restrictive cardiomyopathy.

## Risk Factors for Adverse Outcomes

Risk factors were sought for the outcomes of freedom from death and for the composite end point of freedom from death or transplantation. Risk factors for time to death (censored at transplantation) in the multivariable analysis are shown in Table 3. This shows that lower fractional shortening $z$ score at diagnosis, and, in the RCM/HCM group only (interaction $P=0.012$), increased end-diastolic posterior wall thickness at diagnosis are identified as independent risk factors for mortality. The presence of pure RCM is not a risk factor for death in comparison with the mixed RCM/HCM phenotype.

Significant risk factors in the multivariable analysis for the combined end point of time to death or transplantation are shown in Table 4. The final model identified the following at diagnosis to be independent risk factors for this end point: (a) congestive heart failure (hazard ratio, 2.20; $P=0.005$), (b) lower fractional shortening $z$ score (hazard ratio, 1.12 per 1 SD decrease in $z$ score, $P=0.014$), and (c) higher posterior wall thickness $z$ score in the RCM/HCM group only (hazard ratio, 1.32; $P<0.001$).

Hemodynamic variables were explored only in unadjusted models of risk factors for death, transplant, or death/transplantation because of the limited number of patients with available data. We did not collect catheterization data from 95 RCM patients. Only 24 of the remaining 57 RCM patients underwent cardiac catheterization studies. Mean left ventric-

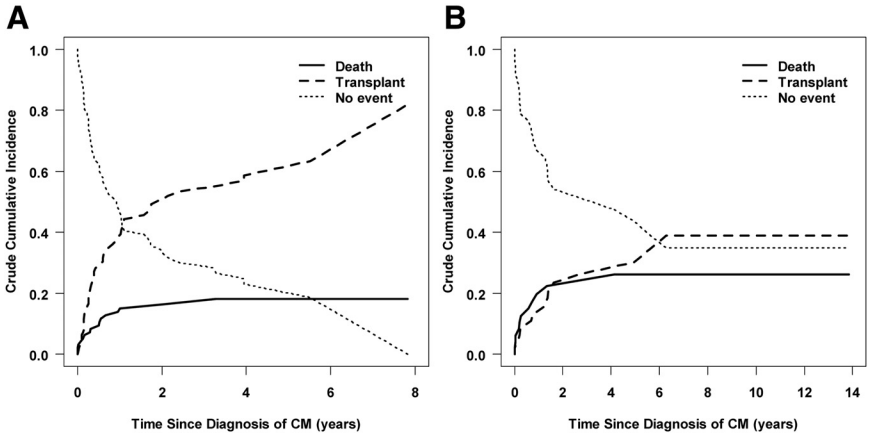


**Figure 3.** Competing outcomes analysis showing estimated proportion of patients in 3 mutually exclusive groups at all times after diagnosis (alive, transplanted, and died without transplant). Summation of proportions equals 1 at all time points. **A**, Patients with pure RCM. **B**, Patients with an RCM/HCM phenotype. CM indicates cardiomyopathy; HCM, hypertrophic cardiomyopathy; RCM, restrictive cardiomyopathy.

**Table 3. Results of The Multivariable Model* of Risk Factors for Time to Death (N=104)**

| Variable | Hazard Ratio (95% CI) | P |
|---|---|---|
| Lower FS *z* score | 1.17 (1.03, 1.33) | 0.016 |
| Pure RCM (yes vs no) | | 0.504 |
| PWT *z* score | | 0.012 |
| PWT *z* score by RCM group interaction | | 0.041 |
| Pure RCM:PWT *z* score | 0.93 (0.70, 1.24) | 0.626 |
| RCM/HCM:PWT *z* score | 1.39 (1.08, 1.79) | 0.012 |

FS indicates fractional shortening; CI, confidence interval; HCM, hypertrophic cardiomyopathy; PWT, end-diastolic posterior wall thickness; and RCM, restrictive cardiomyopathy.

*The follow-up time of cases undergoing transplant was censored at the time of transplant. An alternative model using transplant as a time-dependent covariate found it to be not significant ($P=0.97$), and the model had nearly identical hazard ratios for the other terms in the model.

ular end-diastolic pressure was 25 mm Hg and mean systolic and diastolic pulmonary artery pressures were 47 and 25 mm Hg, respectively. Mean pulmonary vascular resistance index was 4.1 IU. In unadjusted Cox regression models in the subset of patients who underwent catheterization, no hemodynamic measure at presentation predicted death, transplant, or death/transplant (4 deaths, 14 transplants) with the exception of pulmonary vascular resistance index at diagnosis, which was weakly predictive of transplant-free survival (hazard ratio, 1.18; 95% CI, 1.01–1.38; $P=0.039$).

## Discussion

This study represents the largest cohort of children with RCM reported to date. Previous case series have described very small numbers of patients,[2–8] reflecting the extreme rarity of this condition. Indeed, almost all single-institution studies report on <25 cases,[13] effectively precluding the ability to define risk factors for adverse outcomes. The PCMR contains data on some 3375 children with cardiomyopathy, and it has proven to be an essential tool for enhancing our knowledge about rare forms of cardiomyopathy. Earlier data from the PCMR, and findings from the National Australian Childhood Cardiomyopathy Study, suggest that RCM has an incidence of ≈0.03 to 0.04 cases/100 000 children and accounts for <5% of pediatric cardiomyopathy.[10,14] In the present analysis, we identified 152 cases, representing 4.5% of all cardiomyopathies in the PCMR. The baseline clinical and echocardiographic characteristics have been described in detail. There is equal sex distribution, with relatively young age of onset, but only about one sixth presenting in infancy. Interestingly, almost one fourth had a family history of cardiomyopathy, a higher incidence than has hitherto been described in the literature. This emphasizes the need for further genetic studies in this rare form of cardiomyopathy.

**Table 4. Results of the Multivariable Model of Risk Factors for Time to Death or Transplantation (N=104)**

| Variable | Hazard Ratio (95% CI) | P |
|---|---|---|
| Pure RCM (yes vs no) | | 0.088 |
| CHF present at diagnosis | 2.20 (1.27, 3.80) | 0.005 |
| Lower FS *z* score | 1.12 (1.02, 1.22) | 0.014 |
| PWT *z* score by RCM group interaction | | 0.040 |
| Pure RCM:PWT *z* score | 1.06 (0.90, 1.24) | 0.485 |
| RCM/HCM:PWT *z* score | 1.32 (1.13, 1.54) | <0.001 |

CHF indicates congestive heart failure; CI, confidence interval; FS, fractional shortening; HCM, hypertrophic cardiomyopathy; PWT, end-diastolic posterior wall thickness; and RCM, restrictive cardiomyopathy.

One important characteristic of the PCMR is that site investigators were given the opportunity to classify patients as having more than 1 type of cardiomyopathy. This has enabled us to explore the phenomena of mixed or overlapping phenotypes, an increasingly recognized aspect of pediatric (and adult) cardiomyopathies. No hierarchy was required, ie, designation of a primary versus secondary diagnoses was not required. This avoids some of the semantic arguments as to whether one is dealing with a RCM with ventricular hypertrophy versus a HCM with restrictive physiology.[15] The relevance of such debates declines as we increase our understanding of the etiology of these entities. We now know that sarcomeric gene mutations cause some cases of RCM,[9,15] and that the same mutations may cause highly variable phenotypes, even within single families.[9] To date, RCM has been associated with mutations within the genes encoding troponin I, troponin T, beta myosin heavy chain, and alpha cardiac actin.[16–18] Several mutations within the desmin gene have also been associated with RCM.[19–21] The phenotype generally, although not invariably,[20] involves skeletal myopathy and conduction abnormalities. In adults, several mutations of the transthyretin gene have been associated with amyloid heart disease and RCM phenotype.[22,23] Although the PCMR has carefully defined the phenotype of RCM, the capability of genotype testing (and thus genotype–phenotype correlations) has only recently become available. More recently, in collaboration with the Children's Cardiomyopathy Foundation and the National Heart, Lung and Blood Institute of the National Institutes of Health, a blood and tissue repository has been established, the Pediatric Cardiomyopathy Specimen Repository (NHLBI R01 HL087000; J.A.T.) and a search for mutations in various candidate genes will be a priority for future studies. Newer technologies will also allow for broader genome-wide studies to help identify novel mutations that may cause RCM in childhood.

One important goal of the current study was to estimate outcome rates and identify risk factors. The primary outcome measures of interest were freedom from death, freedom from transplantation, and freedom from the composite end point of death or transplantation. Previous small studies have suggested that this disease carries a very poor prognosis with median survival after diagnosis often quoted at ≈2 years.[8,13] Early reports frequently spanned decades and included patients cared for before the modern era in which new therapies such as transplantation and automatic implantable cardiovertor-defibrillator implantation have emerged. The PCMR has given us the opportunity to evaluate outcomes for a contemporary large cohort of patients with RCM. We have shown that survival is inferior to that in both dilated and HCM. Comparison with older reports, however, is compli-

cated by the change in availability of transplantation for this condition.[24,25] Survival curves are censored at the time of transplantation, and the natural history of this condition is no longer discernable. Even more pronounced distinction from DCM and HCM is noted when one analyzes freedom from transplantation and freedom from the composite end point of death or transplantation. It is apparent that a much higher proportion of patients with this condition undergo transplantation in comparison with other forms of cardiomyopathy. There is insufficient information in this data set to know to what extent this trend reflects physician behavior (recommending early listing for transplantation) versus the development of severe symptoms. Transplantation outcomes have progressively improved, with median graft half-life of ≈12 years, and even higher (17 years) for infants.[26] It is clear that this exceeds the natural history of typical survival for RCM patients (for whom there is no proven medical therapy that will enhance survival) and suggests that listing early in the course of the disease is generally warranted.[8] A relatively low wait-list mortality in children with RCM was observed recently by Zangwill and colleagues (in an analysis of data from the Pediatric Heart Transplant Study),[25] and both their findings, and our own, suggest that improved survival in comparison with the historical literature reflects an aggressive approach to listing and early transplantation in the current era. The Pediatric Heart Transplant Study also documented that infant age, the need for inotropic agents, mechanical ventilation, and mechanical circulatory support are important risk factors for death while waiting.

Some patients are asymptomatic at the time of presentation, and this group of patients, especially if beyond infancy, poses special challenges for the treating physician and parents. These patients do not appear ill, yet the risk of sudden death is real. Based on current transplant outcomes, survival is likely to be prolonged by early transplantation, but the latter poses unique problems of its own and is palliative and not curative. Furthermore, the donor supply remains limited, and there is a clear need to direct donor organs to those patients who are sickest, or have high risk of early mortality. The sophistication of decision making about timing of transplantation would be improved if there were clearly identified risk factors for adverse outcomes, especially sudden death. The relatively large size of the current cohort has allowed us to investigate potential risk factors for death and death/transplantation. Unfortunately, we have defined only a few risk factors at presentation for subsequent death, namely, low fractional shortening $z$ score (all patients) and increased end-diastolic posterior wall thickness $z$ score (in the RCM/HCM subgroup only). For the composite end point of freedom from death or transplantation, there was significantly worse transplant-free survival in those with pure RCM, driven by a reduced freedom from transplantation. It is not possible to be entirely certain whether differences in outcome between phenotypic subgroups reflect natural history of heart disease or physician behavior; we did notice a trend to earlier listing for transplantation in patients with pure RCM versus those with RCM/HCM. For those with overlapping RCM/HCM phenotype, we found that the extent of posterior wall hypertrophy is a risk factor for both death and death/transplantation. Again, it cannot be determined how the degree of hypertrophy might influence physician behavior as to when to list for transplantation. As might be expected, the presence of congestive heart failure and poor systolic function at presentation were predictors of worse transplant-free survival. There was inadequate information on hemodynamics, including pulmonary vascular resistance, to enter these variables into the multivariate analyses.

Although this is the largest study of RCM in childhood, some limitations exist. The diagnosis was determined by the treating physician, and without central review of echocardiographic studies by the investigators. Furthermore, no echocardiographic assessment of diastolic function was captured, although hemodynamics were recorded when cardiac catheterization was performed. We chose to focus on risk factors at presentation, but it remains possible that analysis of serial data (eg, echocardiographic or hemodynamic) might have identified other clinically relevant risk factors that could aid in patient management. However, the PCMR collected only 1 measurement per year, and most deaths from RCM occurred in the first year. The study design was also not suitable for evaluating effectiveness of treatments. Finally, as discussed above, routine genetic investigations have not been part of the PCMR to date, but are planned for the future.

In conclusion, we have used the PCMR to identify a large cohort of children with RCM. Over 150 cases were identified over the 18 years of enrollment with approximately one-third having mixed/overlapping phenotype of RCM/HCM and approximately one fourth having a family history of cardiomyopathy. Overall, patients with pure RCM had the worse event-free survival and outcomes that are inferior to all other forms of cardiomyopathy in childhood. We identified congestive heart failure and lower fractional shortening $z$ score at presentation for all patients with RCM and higher posterior wall thickness z score in RCM/HCM patients as factors that independently predict adverse outcome. Genetic causes of RCM should be explored, along with genotype-phenotype correlations. Understanding the genetic basis for pediatric RCM should help delineate the molecular and cellular events of myocardial restriction and may identify potential therapeutic targets.

## Sources of Funding

This work was supported by the National Heart Lung and Blood Institute (NHLBI R01 HL53392) and the Children's Cardiomyopathy Foundation. The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of the National Heart, Lung, and Blood Institute.

## Disclosures

None.

## References

1. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, Moss AJ, Seidman CE, Young JB; American Heart Association; Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; Council on Epidemiology and Prevention. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement. *Circulation.* 2006;1113:1807–1816.

2. Lewis AB. Clinical profile and outcome of restrictive cardiomyopathy in children. *Am Heart J*. 1992;123:1589–1593.
3. Cetta F, O'Leary PW, Seward JB, Driscoll DJ. Idiopathic restrictive cardiomyopathy in childhood: diagnostic features and clinical course. *Mayo Clin Proc*. 1995;70:634–40.
4. Denfield SW, Rosenthal G, Gajarski RJ, Bricker JT, Schowengerdt KO, Price JK, Towbin JA. Restrictive cardiomyopathies in childhood– etiologies and natural history. *Tex Heart Inst J*. 1997;24:38–44.
5. Chen S, Balfour IC, Jureidini S. Clinical spectrum of restrictive cardiomyopathy in children. *J Heart Lung Transplant*. 2001;20:90–92.
6. Weller RJ, Weintraub R, Addonizio LJ, Chrisant MRK, Gersony WM, Hsu DT. Outcome of idiopathic restrictive cardiomyopathy in children. *Am J Cardiol*. 2002;90:501–506.
7. Russo LM, Webber SA. Idiopathic restrictive cardiomyopathy in children. *Heart*. 2005;91:1199–1202.
8. Rivenes SM, Kearney DL, O'Brian Smith E, Towbin JA, Denfield SW. Sudden death and cardiovascular collapse in children with restrictive cardiomyopathy. *Circulation*. 2000;102:876–882.
9. Mogensen J, Kubo T, Duque M, Uribe W, Shaw A, Murphy R, Gimeno JR, Elliott P, McKenna WJ. Idiopathic restrictive cardiomyopathy is part of the clinical expression of cardiac troponin I mutations. *J Clin Invest*. 2003;111:209–216.
10. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, Lurie PR, McCoy KL, McDonald MA, Messere JE, Colan SD. The incidence of cardiomyopathy in two regions of the United States. *N Engl J Med*. 2003;348:1647–1655.
11. Sluysmans T, Colan SD. Theoretical and empirical derivation of cardiovascular allometric relationships in children. *J Appl Physiol*. 2005;99:445–457.
12. McGriffin DC, Naftel DC, Kirklin JK. Depicting time-related events after cardiac surgery: Kaplan-Meier or competing risk? *Asia Pacific Heart J*. 1998;7:98–102.
13. Webber SA. Primary restrictive cardiomyopathy in childhood. *Prog Pediatr Cardiol*. 2008;25:85–90.
14. Nugent AW, Daubeney P, Chondros P, Carlin JB, Colan SD, Cheung M, Davis AM, Chow CW, Weintraub RG; National Australian Childhood Cardiomyopathy Study. The epidemiology of childhood cardiomyopathy in Australia. *N Eng J Med.* 2003;348:1639–1646.
15. Kubo T, Gimeno JR, Bahl A, Steffensen U, Steffensen M, Osman E, Thaman R, Mogensen J, Elliott PM, Doi Y, McKenna WJ. Prevalence, clinical significance, and genetic basis of hypertrophic cardiomyopathy with restrictive phenotype. *J Am Coll Cardiol*. 2007;49:2419–2426.
16. Peddy SB, Vricella LA, Crosson JE, Oswald GL, Cohn RD, Cameron DE, Valle D, Loeys BL. Infantile restrictive cardiomyopathy resulting from a mutation in the cardiac troponin T gene. *Pediatrics*. 2006;117:1830–1833.
17. Ware SM, Quinn ME, Ballard ET, Miller E, Uzark K, Spicer RL. Pediatric restrictive cardiomyopathy associated with a mutation in beta-myosin heavy chain. *Clin Genet*. 2008;73:165–170.
18. Kaski JP, Syrris P, Burch M, Tomé-Esteban MT, Fenton M, Christiansen M, Andersen PS, Sebire N, Ashworth M, Deanfield JE, McKenna WJ, Elliott PM. Idiopathic restrictive cardiomyopathy in children is caused by mutations in cardiac sarcomeric proteins. *Heart*. 2008;94:1478–1484.
19. Dalakas MC, Park KY, Semino-Mora C, Lee HS, Sivakumar K, Goldfarb LG. Desmin myopathy, a skeletal myopathy with cardiomyopathy caused by mutations in the desmin gene. *N Eng J Med*. 2000;342:770–780.
20. Arbustini E, Pasotti M, Pilotto A, Pellegrini C, Grasso M, Previtali S, Repetto A, Bellini O, Azan G, Scaffino M, Campana C, Piccolo G, Viganò M, Tavazzi L. Desmin accumulation restrictive cardiomyopathy and atrioventricular block associated with desmin gene defects. *Eur J Heart Fail*. 2006;8:477–483.
21. Zhang J, Kumar A, Stalker HJ, Virdi G, Ferrans VJ, Horiba K, Fricker FJ, Wallace MR. Clinical and molecular studies of a large family with desmin-associated restrictive cardiomyopathy. *Clin Genet*. 2001;59:248–256.
22. Jacobson DR, Pastore RD, Yaghoubian R Kane I, Gallo G, Buck FS, Buxbaum JN. Variant-sequence transthyretin (isoleucine 122) in late-onset cardiac amyloidosis in black Americans. *N Engl J Med*. 1997;336:466–473.
23. Falk RH, Dubrey SW. Amyloid heart disease. *Prog Cardiovasc Dis*. 2010;52:347–361.
24. Bograd AJ, Mital S, Schwarzenberger JC, Mosca RS, Quaegebeur JM, Addonizio LJ, Hsu DT, Lamour JM, Chen JM. Twenty year experience with heart transplantation for infants and children with restrictive cardiomyopathy: 1986–006. *Am J Transplant*. 2008;8:201–207.
25. Zangwill SD, Naftel D, L'Ecuyer T, Rosenthal D, Robinson B, Kirklin JK, Stendahl G, Dipchand AI; Pediatric Heart Transplant Study Investigators. Outcomes of children with restrictive cardiomyopathy listed for heart transplant: a multi-institutional study. *J Heart Lung Transplant.* 2009;28:1335–1340.
26. Kirk R, Edwards LB, Aurora P, Taylor DO, Christie JD, Dobbels F, Kucheryavaya AY, Rahmel AO, Stehlik J, Hertz MI. Registry of the International Society for Heart and Lung Transplantation: Twelfth Official Pediatric Heart Transplantation Report-2009. *J Heart Lung Transplant*. 2009;28:993–1006.

## CLINICAL PERSPECTIVE

Restrictive cardiomyopathy is a rare form of cardiomyopathy in childhood with a few risk factors identified for death or transplantation. This analysis from the Pediatric Cardiomyopathy Registry identified 152 cases of restrictive cardiomyopathy among 3375 children with cardiomyopathy (4.5%), approximately one-third of whom had a mixed restrictive/hypertrophic phenotype. Survival did not differ between those with pure and mixed phenotypes, but transplant-free survival was inferior in the pure restrictive cardiomyopathy group. Overall outcomes were worse than for all other forms of cardiomyopathy in the Pediatric Cardiomyopathy Registry. Clinical and echocardiographic risk factors at presentation for worse outcome were identified and should aid the clinician in risk stratification.