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Recovery of Echocardiographic Function in Children With Idiopathic Dilated Cardiomyopathy

Results From the Pediatric Cardiomyopathy Registry

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Objectives This study sought to determine the incidence and predictors of recovery of normal echocardiographic function among children with idiopathic dilated cardiomyopathy (DCM).

Background Most children with idiopathic DCM have poor outcomes; however, some improve.

Methods We studied children <18 years of age from the Pediatric Cardiomyopathy Registry who had both depressed left ventricular (LV) function (fractional shortening or ejection fraction *z*-score <−2) and LV dilation (end-diastolic dimension [LVEDD] *z*-score >2) at diagnosis and who had at least 1 follow-up echocardiogram 30 days to 2 years from the initial echocardiogram. We estimated the cumulative incidence and predictors of normalization.

Results Among 868 children who met the inclusion criteria, 741 (85%) had both echocardiograms. At 2 years, 22% had recovered normal LV function and size; 51% had died or undergone heart transplantation (median, 3.2 months), and 27% had persistently abnormal echocardiograms. Younger age (hazard ratio [HR]: 0.92; 95% confidence interval [CI]: 0.88 to 0.97) and lower LVEDD *z*-score (HR: 0.78; 95% CI: 0.70 to 0.87) independently predicted normalization. Nine children (9%) with normal LV function and size within 2 years of diagnosis later underwent heart transplantation or died.

Conclusions Despite marked LV dilation and depressed function initially, children with idiopathic DCM can recover normal LV size and function, particularly those younger and with less LV dilation at diagnosis. Investigations related to predictors of recovery, such as genetic associations, serum markers, and the impact of medical therapy or ventricular unloading with assist devices are important next steps. Longer follow-up after normalization is warranted as cardiac failure can recur. (Pediatric Cardiomyopathy Registry; NCT00005391) (J Am Coll Cardiol 2014;63:1405–13) © 2014 by the American College of Cardiology Foundation

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Abbreviations and Acronyms

CI = confidence interval
DCM = dilated cardiomyopathy
EDD = end-diastolic dimension
EF = ejection fraction
ESD = end-systolic dimension
FS = fractional shortening
HR = hazard ratio
LV = left ventricular

Idiopathic dilated cardiomyopathy (DCM) is a disease of the heart muscle characterized by ventricular chamber enlargement and systolic dysfunction (1,2). The prognosis is usually poor, but some patients do recover normal cardiac function. Studies in both adults and children have reported recovery of cardiac function in 21% to 37% of patients, as indicated by serial echocardiograms (3–5). Survival of adults with idiopathic DCM has improved in recent decades, with more than half surviving for 10 years (5,6). Although risk factors for death or transplantation in children with idiopathic DCM are well-studied, predictors of normalization are largely unknown (7–10). With additional medical therapies being used for heart failure in children, as well as a marked increase in the use of ventricular assist devices, identifying predictors of recovering cardiac function is of particular importance.

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We studied children with idiopathic DCM who had echocardiographic data sufficient to assess recovery of normal LV function and size. We identified the proportion of these children who regained normal echocardiographic measurements in the large, multicenter, National Heart, Lung, and Blood Institute–funded Pediatric Cardiomyopathy Registry (PCMR) (11,12). We sought to identify the clinical characteristics at presentation that predict echocardiographic normalization within 2 years. Additionally, we report longer-term follow-up data in children whose LV function and size returned to normal within 2 years of diagnosis to examine the permanence of recovery.

Methods

Study design. The design and conduct of the PCMR are detailed elsewhere (13,14). Institutional review board approval of the PCMR protocol was obtained from all participating centers. From 1990 to 2012, the PCMR enrolled more than 3,000 children <18 years of age in whom cardiomyopathy was diagnosed at any of 98 pediatric cardiac centers in the United States and Canada. The data in the PCMR database current as of January 14, 2013, were analyzed.

Patient classification. The PCMR diagnostic criteria for pure DCM (13,14) are based on strict echocardiographic measurements related to left ventricular (LV) enlargement and depressed function; pathologic findings at autopsy or by endomyocardial biopsy; or clinical evidence from the diagnosing physician. We studied only children with *idiopathic DCM,* defined as DCM of unknown cause at the time of diagnosis (1,6,9). Children who were classified at presentation by the clinical investigators as having neuromuscular disease, familial cardiomyopathy, metabolic or mitochondrial disorder, or myocarditis on the basis of the presentation of new-onset cardiac symptoms and/or echocardiographic abnormalities developing after a history of recent infection with or without evidence of myocarditis on endomyocardial biopsy were excluded (4). Additionally, to examine recovery of normal LV function and size in a homogeneous group, the sample was restricted to children who had both LV dilation (i.e., LV end-diastolic dimension [EDD] >2 SD above normal for body surface area) and depressed LV systolic function (LV fractional shortening [FS] or LV ejection fraction [EF] >2 SD below normal for age) at diagnosis. Echocardiographic outcomes were determined only in children with echocardiographic data on function and size both at diagnosis and at follow-up within 2 years. A minimum interval of 30 days between the first and subsequent echocardiograms was used to classify children into 2 groups: 1) those with persistently abnormal echocardiograms; and 2) those who recovered normal LV size and function. Figure 1 details the composition of the analytic cohort. Echocardiographic data beyond 2 years was not sufficiently complete to uniformly assess a longer follow-up period for recovering normal echocardiographic function and size. However, long-term follow-up data regarding death or heart transplantation outside the 2-year window, where available, are reported for each group.

Data collection. Patient age, race, sex, weight, height, and body surface area were collected at diagnosis. Clinical evidence of congestive heart failure and echocardiographic measurements of LVEDD, left ventricular end-systolic dimension (LVESD), LVFS, LV septal and posterior wall thicknesses, and LV mass were also collected at diagnosis and annually thereafter. Values for LV measurements are expressed as *z*-scores to adjust for the effect of body size and age. The z-score is the number of SDs from the mean value at a given body surface area in a distribution of a large population of normal children. The *z*-score for the mean of this population distribution is 0, and the normal range is typically defined as −2 to +2 SD (10).

Statistical methods. The Data Coordinating Center at the New England Research Institutes, Watertown, Massachusetts, performed all data analyses. Summary statistics are presented as mean ± SD or as median and interquartile range for continuous variables and as percentages for categorical variables. Changes in echocardiographic measures obtained at diagnosis and follow-up were compared using a paired Student *t* test. Patient characteristics among the 3 groups were compared with analysis of variance or the Kruskal-Wallis test for continuous variables and a Fisher exact test for categorical variables.

We used nonparametric competing-risks methodology to estimate the cumulative incidence rates of echocardiographic normalization versus death or transplantation versus persistent abnormal LV size or function (15). Risk factors for the