

EDITORIAL COMMENT

# Normalization of Function in Pediatric Dilated Cardiomyopathy



## Recovery or Remission?\*

Alan B. Lewis, MD

Los Angeles, California

Dilated cardiomyopathy (DCM) is the final common phenotypic pathway for multiple pathological processes that are characterized by left ventricular (LV) chamber dilation and systolic dysfunction, and clinically manifested by congestive heart failure (1). Etiologies may include antecedent viral myocarditis and generalized myopathies, along with a broad spectrum of sarcomeric, sarcolemmal, cytoskeletal, or nuclear protein abnormalities. However, etiology remains idiopathic in approximately two-thirds of cases (2). Epidemiological studies have estimated the incidence of newly diagnosed DCM to be between 0.57 and 0.73 cases per 100,000 per year among infants and children <18 years of age (3,4). Despite advances in the medical management of congestive heart failure, the prognosis of children with DCM remains poor, with a 5-year transplantation-free survival of approximately 50% (5). Nonetheless, normalization of LV size and systolic function on serial echocardiography has been reported in 25% to 37% of children (6) and adults (7). The factors associated with echocardiographic reverse remodeling in idiopathic DCM have been elusive, often because smaller, single-center series have been insufficiently powered to identify these factors, but younger age at presentation has been recognized previously (6).

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In this issue of the *Journal*, Everitt et al. (8) report the findings of the multicenter Pediatric Cardiomyopathy Registry (PCMR) in 741 children under 18 years of age who had both LV dilation (LV end-diastolic dimension [EDD] z-score >2) and LV systolic dysfunction (fractional shortening or ejection fraction z-score <-2) at presentation

and who had undergone at least 1 follow-up echocardiogram 30 days to 2 years after presentation. Patients with clinical and/or pathological (biopsy or autopsy) evidence of myocarditis were excluded. The authors found that 22% of patients surviving to 2 years had normalized LV echocardiographic parameters, with a median time to recovery of 9.5 months, whereas 27% continued to have abnormal LV dimension and function, and 51% had died or undergone cardiac transplantation. The incidence of normalization of LV size and function was highest in younger-age children at their initial presentation; 24% in children <1 year of age and 26% in children between 1 and 10 years of age. Conversely, only 10% of children >10 years of age at presentation demonstrated normalization of LV size and function on echocardiography. These data are similar to those from an earlier single-institution study in which 25% of patients had normalized LV function at a mean follow-up interval of 4.5 years (6). Patients whose echocardiograms returned to normal were younger ( $2.1 \pm 1.8$  years) at presentation compared with children with persistently abnormal LV size and function ( $4.5 \pm 5.9$  years). It is possible that additional patients in the study by Everitt et al. (8) may have ultimately crossed over into the normalized group because the cutoff for the follow-up interval was only 2 years, and the curve for the cumulative incidence rate of recovery continued to increase while the proportion with persistently abnormal function continued to decline during the final months before study closure. Indeed, the recent publication by Alexander et al. (9) of the long-term follow-up of 175 children in the National Australian Childhood Cardiomyopathy Study reported normalization of LV function in 33% of all patients and in 69% of survivors 15 years following diagnosis. Normalization in the Australian study was related to greater baseline LV fractional shortening, but the study population included children with endomyocardial biopsy-confirmed myocarditis.

In addition to younger age at presentation, Everitt et al. (8) identified less LV dilation, that is, a lower LVEDD z-score by multivariate analysis, as an additional factor independently associated with restoration of normal size and function on echocardiography. For each 1-year decrease in age, there was a 1.1-fold increase in the likelihood of recovery, whereas each 1-unit decrement in LVEDD z-score resulted in a 1.3-fold increase in recovery of normal LV size and function. Overall, normalization was achieved in 30% of children with LVEDD z-scores in the lowest tertile ( $\leq 4.29$ ) but in only 13% in the highest tertile ( $\geq 6.29$ ). These observations provide new insight that was previously unavailable because earlier smaller, single-center studies were inadequately powered to identify the contribution of LV dimension at diagnosis to the potential for echocardiographic normalization.

These positive observations are tempered, however, by the finding that 9 of 96 children who achieved normal LV size and function within 2 years of diagnosis subsequently

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From the Division of Cardiology, Children's Hospital Los Angeles, Los Angeles, California. Dr. Lewis has reported that he has no relationships relevant to the contents of this paper to disclose.

underwent heart transplantation or died. Because their analysis was limited to a 2-year time frame, the authors did not report how many of the surviving normalized patients developed late secondary deterioration in LVEDD and function. Many questions, therefore, remain unanswered and await further investigation. In addition to initial LVEDD and age at presentation, what factors could help to identify patients likely to exhibit recovery of normal LV size and function? Identification of novel biomarkers (10), systematic evaluation of echocardiographic measures of LV diastolic function and/or systolic strain, and investigation of genetic variation may aid in prognostication and in differentiating those children with the potential for recovery of function from those at high risk for death/transplantation or persistent LV dysfunction. For example, the level of N-terminal pro-B-type natriuretic peptide at 3 months after initial diagnosis may be predictive of the long-term adverse outcome of severe LV dysfunction or death (11). Moreover, within the “recovered” group, it is essential to understand the risks and mechanisms for later secondary decompensation without which withdrawal of anti-heart failure medications is both premature and imprudent. How can we differentiate patients with long-term recovery from those with only short-term, temporary reverse remodeling? Cardiac magnetic resonance imaging with late gadolinium enhancement for the identification of focal myocardial fibrosis and inflammation or T<sub>1</sub> mapping (12) for the quantification of extracellular volume and diffuse myocardial fibrosis may further inform our understanding of the biomechanics of reverse remodeling. Such studies may also aid in differentiating patients with “permanent” recovery of LV function, in whom discontinuation of medical treatment with anti-heart failure agents is appropriate, from those who may have achieved only temporary remission. Finally, new antifibrosis and myocellular therapeutic strategies are needed to increase the proportion of patients with pediatric DCM who undergo reverse remodeling and long-term recovery of LV size and function. The study by Everitt et al. (8) raises

these provocative questions and opens avenues for further investigation.

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**Reprint requests and correspondence:** Dr. Alan B. Lewis, Division of Cardiology, MS#34, Children’s Hospital Los Angeles, 4650 Sunset Boulevard, Los Angeles, California 90027. E-mail: [alewis@chla.usc.edu](mailto:alewis@chla.usc.edu).

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