Infantine Dilated Cardiomyopathy
Relation of Outcome to Left Ventricular Mechanics, Hemodynamics, and Histology at the Time of Presentation

Abraham Mattiau, MD; Antonio Perez-Atayde, MD; Stephen P. Sanders, MD; Thierry Sluysmans, MD; Ira A. Parness, MD; Philip J. Spevak, MD; Steven D. Colan, MD, FACCC

Background  For patients with acute dilated cardiomyopathy, definition of prognosis and of clinical features predictive of outcome is particularly important due to the availability of cardiac transplantation and other innovative treatment strategies.

Methods and Results  We reviewed our experience with 24 children under 2 years of age with dilated congestive cardiomyopathy to determine outcome and potential predictive variables. Clinical, serological, ECG, echocardiographic, hemodynamic, and histological findings were analyzed. Idiopathic cardiomyopathy or myocarditis constituted 29% of the patients presenting with congestive heart failure without structural heart disease. Among these patients, 45% recovered completely, 25% survived with persistent left ventricular dysfunction, and 30% died. All except one of the deaths occurred during the first 2 months after presentation. Poorer outcome and higher mortality were associated with a more severely depressed left ventricular ejection fraction and/or a more spherical left ventricular shape at presentation. Histological evidence of myocardial inflammation was a favorable prognostic indicator, whereas histological evidence of endocardial fibroelastosis was associated with a poor outcome. During the recovery phase, diastolic volume fell rapidly. Ventricular mass was elevated from the earliest observations and fell more slowly, with persistent elevation of the mass-to-volume ratio up to 2 years. Function and contractility improved over the first several months in most patients who recovered, although in occasional patients continued improvement was seen for as long as 2 years after presentation.

Conclusions  Histological and echocardiographic features can be used to identify patients at particularly high risk for death. To have any impact on outcome, decisions about cardiac transplantation must be reached rapidly, since almost all deaths occurred within the first 2 months after presentation. Recovery of function is often rapid, but continued improvement may be seen for as long as 2 years. (Circulation. 1994;90:1310-1318.)

Key Words  • dilated cardiomyopathy • pediatrics • morbidity • mortality

Dilated cardiomyopathy (DCM) represents a heterogeneous group of diseases with multiple etiologies united by a common presentation of a dilated, poorly contractile heart, usually accompanied by heart failure. Although specific causes can be identified in some cases such as congenital heart disease or metabolic disease, most cases are idiopathic. At least some of these patients have myocarditis, although clinical diagnosis may be very difficult.1,2 The prognosis varies from complete recovery to death and has been reported to be better in patients who present before the age of 2 years.3,4 The availability of cardiac transplantation has increased the importance of accurate diagnosis and prognosis. We reviewed our young patients with DCM to identify prognostic factors from echocardiograms, hemodynamics, or histology to improve selection of patients for early transplantation instead of medical management.

Methods

Study Population

The study population was limited to patients with either idiopathic congestive cardiomyopathy or myocarditis who presented within the first 2 years of life. The specific study entrance criteria were presentation to Boston Children’s Hospital with congestive heart failure before 2 years of age between 1982 and 1990; dilated, hypococontractile left ventricle on echocardiogram (ejection fraction, <50%); absence of identifiable cause of ventricular dysfunction, including congenital heart disease (eg, left-sided obstructions and coronary artery anomalies), exposure to cardiotoxic agents (eg, antirhythmic agents), Kawasaki’s disease, chronic primary arrhythmias, bacterial sepsis, postischemic injury (asphyxia), and HIV infection. Case finding was performed by search of the computerized echocardiographic database.

Data Collection

The hospital records of each patient were reviewed. The ECG and chest radiograph at presentation, echocardiogram at presentation and during follow-up, hemodynamic data at earliest catheterization (if catheterization was done), results of tissue diagnosis (endomyocardial biopsy or postmortem examination), and clinical outcome were reviewed. From the catheterization records, the following data were obtained when available: mean right atrial pressure, mean pulmonary artery pressure, left ventricular (LV) end-diastolic pressure, and cardiac index (thermodilution or Fick method).

Echocardiographic data were collected using previously described methods.5-13 Subjects under 2 years of age were sedated with 50 to 100 mg/kg chloral hydrate. Sedation was used in older patients as needed. Complete Doppler and two-dimensional echocardiographic examinations were performed using a Diasonics Cardiovue 100, ATL Mark 600, Hewlett-Packard 77020, or Accuson 128 cardiac imager equipped with a transducer appropriate for body size and habitus and recorded on 0.5-in videotape. Standard short- and
long-axis views of the LV were recorded to assess regional wall motion and calculate LV mass and volume. In addition, in patients with a circular LV in short-axis views and no evidence of regional wall motion abnormalities, high-speed (100 mm/s) hard-copy two-dimensional echocardiographic-directed M-mode recording of the LV minor axis was obtained simultaneously with the ECG, phonocardiogram, indirect carotid pulse tracing (or axillary pulse tracing in patients <4 years of age), and peripheral blood pressure. Systolic and diastolic blood pressures were obtained as the average of three to six readings using a Dynamap 845 Vital Signs Monitor.

Data Analysis
Outcome Variables

Outcome was assessed in terms of late status with respect to survival and persistence of symptoms referable to the cardiovascular system and/or ventricular dysfunction. Patients who survived, who were symptom free, and in whom ventricular function (ejection fraction, >55%) had fully recovered were classified as having a “good” late outcome, whereas patients who died, had persistent ventricular dysfunction, or had persistent symptoms were classified as having “poor” outcome.

Echocardiographic Determination of LV Mass and Volume

Long-axis four-chamber images of the LV from apical or subxiphoid windows and short-axis images of the LV were digitized using an off-line video digitizing and analysis device (Dextra 200 Analysis System, Dextra Medical Inc). End-diastolic and end-systolic frames were defined as the frames showing the largest and the smallest LV silhouettes, respectively. After calibration, endocardial and epicardial borders of the LV were hand-digitized at end systole and end diastole. The LV mass, end-systolic volume (ESV), and end-diastolic volume (EDV) were calculated according to a modified biapical Simpson’s rule, using one long-axis and one short-axis view in orthogonal planes. LV mass was determined as total epicardial volume minus cavity volume multiplied by specific gravity of myocardium (1.04 g/mL). Ejection fraction was determined as (EDV – ESV)/EDV. The results for ventricular mass and volume were adjusted for body size by dividing by (body surface area)5–7.

M-Mode Measurements

The pulse tracing, the LV endocardial border of the septum, and the endocardial and epicardial borders of the LV posterior wall were hand-digitized using a microcomputer-based digitizing station with custom software. This system is programmed to adjust the tablet sampling rate to 200 Hz, which is adequate to obtain at least 50 nonaliased harmonics at heart rates of <120 beats per minute. The pulse transmission delay was corrected by electronically aligning the dicrotic notch of the pulse tracing with the first high-frequency component of the second heart sound of the phonocardiogram. End-systolic pressure was calculated from the calibrated pulse tracing as previously described.9–11 To obtain an estimate of LV shape, the LV long-axis dimension was measured from apical four-chamber two-dimensional echocardiographic images at end diastole and at end systole. From the digitized data, the following measurements were obtained endocardially by averaging these measurements by three to six cardiac cycles: LV short-axis diameter, LV posterior wall thickness, and LV pressure. End-systolic LV meridional wall stress (ESSm) was calculated according to the following15:

$$\text{ESSm} = \frac{P \cdot D \cdot (1.35)}{h \cdot [1+(h/D)] \cdot 4}$$

where P is pressure (mm Hg), D is short-axis dimension (cm), h is posterior wall thickness (cm), and 1.35 is the conversion factor (from mm Hg to g/cm²). End-systolic values were determined at the time of aortic valve closure, and end-diastolic values were determined at the time of maximum LV dimension. The LV fractional shortening was calculated as (EDD – ESD)/EDD, where EDD is end-diastolic short-axis dimension and ESD is end-systolic short-axis dimension. LV ejection time was measured from the pulse tracing and adjusted to a heart rate of 60 beats per minute by dividing by the square root of the RR interval on the ECG. The rate-adjusted mean velocity of shortening (VCFe) was calculated as fractional shortening divided by the rate-adjusted ejection time. The relation between VCFe and ESSm has been shown previously to be an index of contractility that is relatively independent of preload and incorporates afterload.17 The value of the afterload-adjusted VCFe (stress-velocity index [SVI]) for each patient was determined relative to the previously reported distribution of this index in healthy subjects aged 1 to 19 years and expressed as the normal deviate or Z score (the number of standard deviations from the population mean VCFe for the ESSm).

Myocardial Histological Analysis

A total of 19 endomyocardial biopsies were obtained in 16 children (2 patients had serial biopsies). The entire heart was examined in 4 children who underwent autopsy examination. When possible, 5 to 8 endomyocardial biopsies were obtained at the time of cardiac catheterization. In each of 16 cardiac catheterizations with endomyocardial biopsy, four to eight pieces of tissue were analyzed by light microscopy (median, 5.5 pieces); in 2 endomyocardial biopsy procedures, three pieces were available for histological evaluation; and in 1 biopsy, only one piece of tissue was obtained. In 15 children, one piece each was fixed immediately in 2.5% gluteraldehyde for electron microscopy, and another was embedded in OTC and kept frozen at –70°F. Sections taken for conventional light microscopic studies were stained with hematoxylin and eosin, PAS, and trichrome and elastic tissue stains. Tissue for electron microscopy was postfixed in 1% osmium tetroxide and embedded in Epon 812. Then, 1-µm-thick sections were made in each block and stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate and examined with a Phillips 300 electron microscope. All diagnostic interpretations were made after examination of routine histological slides, plastic embedded sections, and electron microscopy.

Criteria used for tissue classification were as follows:

Myocarditis. The Dallas criteria18 were used for diagnosis of myocarditis. Myocarditis was considered definite in the presence of an evident interstitial lymphocytic or lymphoplasmacytic infiltrate associated with interstitial edema and focal or diffuse myocyte degeneration and necrosis. Although myocyte hypertrophy and interstitial fibrosis were considered indicative of chronic disease, they were not present in any of these cases.

Borderline myocarditis. Following the Dallas criteria,18 a diagnosis of myocarditis was considered when interstitial edema and sparse lymphocytic infiltrate without myocyte degeneration or necrosis were present.

Endocardial fibroelastosis. This diagnosis was made when the light microscopic examination demonstrated a thick endocardium made up of excess fibrous tissue. In addition, in all cases, elastic tissue stains and electron microscopy revealed the presence of abundant elastic tissue scattered throughout the thickened endocardium. In no case was there any evidence of endocardial or myocardial inflammation, edema, or myocyte necrosis. In some cases, the excess in elastic tissue extended to myocardial interstitium.

Mild nonspecific changes. These cases included myocyte hypertrophy, focal interstitial fibrosis, and mild focal fibrous thickening of the endocardium without elastic tissue excess.

Statistical Analysis

Relation of cardiac structure and function at the time of presentation to survival and recovery of LV function was
examined using survival analysis (Wilcoxon statistic) and ANOVA. Serial data on recovery of function and rate of normalization of echocardiographic variables were analyzed with nonlinear curve-fitting techniques using an exponential decay model.

**Results**

There were a total of 82 patients less than 2 years of age with DCM by echocardiography without structural heart disease who presented during the study time period. The distribution of diagnoses was (1) ischemic damage (30.5%, 25 patients), related to perinatal asphyxia or postresuscitation for primary problems other than heart disease; (2) idiopathic cardiomyopathy or myocarditis (29%, 24 patients); (3) adriamycin cardiomyopathy (11%, 9 patients); (4) Kawasaki cardiomyopathy (8.5%, 7 patients); (5) AIDS (7.5%, 6 patients); (6) bacterial sepsis (6%, 5 patients); (7) chronic or recurrent atrial arrhythmia (5%, 4 patients); and (8) glycojen or mucopolysaccharide storage (2.5%, 2 patients).

There were 24 patients who met study entrance criteria for idiopathic cardiomyopathy and myocarditis (Table 1). Thirteen patients were boys and 11 were girls. The age at presentation ranged between 1 day and 1.67 years with a mean of 0.44±0.46 year and a median age of presentation of 0.34 year. All patients presented with clinical signs of congestive heart failure. No patients had a family history suggestive of familial cardiomyopathy. Five of 24 were febrile at presentation, 4 of whom had biopsy findings consistent with myocarditis. Of the 19 chest radiographs that were obtained at the time of presentation, 16 were interpreted as demonstrating moderate to severe cardiomegaly, and 3 were interpreted as demonstrating mild cardiomegaly. ECGs at the time of presentation were available in 22 of the patients, and all had abnormal repolarization patterns. Eight patients had left ventricular hypertrophy on ECG (3 with endocardial fibroelastosis [EFE] on myocardial biopsy, 4 with normal or nonspecific findings on biopsy, and 1 with no biopsy). Abnormally small QRS complexes were found in 2 patients, both of whom were believed to have myocarditis. Three patients had ventricular tachycardia during the first admission, 2 of

### Table 1. Summary of Data for Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, mon</th>
<th>ST-Wave Changes</th>
<th>LVH</th>
<th>QRS</th>
<th>Efp</th>
<th>RA, mm Hg</th>
<th>PA, mm Hg</th>
<th>ED, mm Hg</th>
<th>CI</th>
<th>Biopsy</th>
<th>Post-mor</th>
<th>Follow-up, y</th>
<th>Dead or Alive</th>
<th>EF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td>46</td>
<td>7</td>
<td>22</td>
<td>10</td>
<td>2.1</td>
<td>N</td>
<td>0.1</td>
<td>Alive 58</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>46</td>
<td>7</td>
<td>22</td>
<td>10</td>
<td>2.1</td>
<td>N</td>
<td>0.1</td>
<td>Alive 58</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.5</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>44</td>
<td>7</td>
<td>15</td>
<td>7</td>
<td>3.9</td>
<td>N</td>
<td>7</td>
<td>Alive 52</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7.5</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>24</td>
<td>1</td>
<td>18</td>
<td>12</td>
<td>3.6</td>
<td>E, H</td>
<td>4</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>42</td>
<td>0</td>
<td>12</td>
<td>6</td>
<td>1.9</td>
<td>C</td>
<td>3</td>
<td>Alive 67</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0.1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>4</td>
<td>12</td>
<td>15</td>
<td>8</td>
<td>2.5</td>
<td>C</td>
<td>5</td>
<td>Alive 42</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>14</td>
<td>6</td>
<td>15</td>
<td>8</td>
<td>2.5</td>
<td>C</td>
<td>5</td>
<td>Alive 42</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>0.3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>36</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>Alive 76</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>0.3</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>40</td>
<td>1</td>
<td>12</td>
<td>4</td>
<td>2.8</td>
<td>C</td>
<td>1</td>
<td>Alive 69</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>15</td>
<td>2</td>
<td>22</td>
<td>19</td>
<td>3.0</td>
<td>H</td>
<td>1.5</td>
<td>Alive 45</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>11</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>42</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>2.3</td>
<td>C</td>
<td>4</td>
<td>Alive 58</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>12</td>
<td>1</td>
<td>20</td>
<td>11</td>
<td>2.2</td>
<td>C</td>
<td>0.1</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>17</td>
<td>0</td>
<td>16</td>
<td>9</td>
<td>3.0</td>
<td>E, H</td>
<td>3</td>
<td>Alive</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>28</td>
<td>6</td>
<td>20</td>
<td>12</td>
<td>2.9</td>
<td></td>
<td>7.5</td>
<td>Alive 54</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4.5</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>44</td>
<td>2</td>
<td>18</td>
<td>10</td>
<td>3.2</td>
<td>H</td>
<td>3</td>
<td>Alive 55</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>5.5</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E</td>
<td>0</td>
<td>Dead</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>30</td>
<td>8</td>
<td>58</td>
<td>24</td>
<td>2.2</td>
<td>E, H</td>
<td>2</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4</td>
<td>LBBB</td>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>1</td>
<td>18</td>
<td>12</td>
<td>2.9</td>
<td>C</td>
<td>2</td>
<td>Alive 47</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>0.2</td>
<td>RBBB</td>
<td></td>
<td></td>
<td></td>
<td>17</td>
<td>10</td>
<td>22</td>
<td>15</td>
<td>1.8</td>
<td>C</td>
<td>2</td>
<td>Alive 59</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>6</td>
<td>+</td>
<td>+</td>
<td>−</td>
<td></td>
<td>19</td>
<td>3</td>
<td>10</td>
<td>7</td>
<td>2.2</td>
<td>NS</td>
<td>0.2</td>
<td>Dead</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>7.5</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>30</td>
<td>15</td>
<td>38</td>
<td>24</td>
<td>2.7</td>
<td>C</td>
<td>1.5</td>
<td>Alive 65</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>E</td>
<td>0</td>
<td>Dead</td>
</tr>
<tr>
<td>23</td>
<td>0.1</td>
<td>+</td>
<td>−</td>
<td>+</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7</td>
<td>Alive 63</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>12</td>
<td>+</td>
<td>−</td>
<td>−</td>
<td></td>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

*Age indicates age at presentation (mon); ST, ST-wave changes; LVH, ECG criteria for left ventricular hypertrophy; QRS, low-voltage QRS complex; Efp, ejection fraction at presentation; RA, right atrial pressure; PA, pulmonary artery pressure; ED, left ventricular end-diastolic pressure; CI, cardiac index at catheterization; Outcome, late status; LBBB, left bundle-branch block; RBBB, right bundle-branch block; N, normal histology; E, endocardial fibroelastosis on histology; H, hypertrophy on histology; C, histological findings consistent with carditis; and NS, nonspecific changes on histology.*
whom had myocarditis. One patient with myocarditis had supraventricular tachycardia. Complete left bundle-branch block was found in 1 patient with borderline myocarditis on biopsy, and complete right-bundle branch block was found in 1 patient with myocarditis. Sinus bradycardia with slow ventricular escape rhythm was found in 1 patient with myocarditis.

**Evidence of Viral Infection**

Viral cultures were taken in 18 patients. In 1 patient, Coxsackie B4 was isolated in the stools (this patient had no biopsy), 1 patient had a fourfold increase in Coxsackie A titers (this patient had a biopsy diagnosis of myocarditis), and 1 patient had aseptic meningitis, suggesting a viral etiology, although viral cultures were negative (this patient had a biopsy diagnosis of myocarditis).

**Serum Analysis**

In 11 patients, creatine phosphokinase (CPK) levels were available. In the 4 who had elevated CPK levels, myocardial tissue examination showed myocarditis in 2 patients and borderline myocarditis in 1 patient (1 had no biopsy). In the 7 patients with normal CPK levels, myocardial biopsies showed EFE in 4 patients, nonspecific findings in 2, and borderline myocarditis in 1. Blood carnitine levels had been obtained in 11 patients, and all were within normal limits. In 10 patients, organic acid profile was examined in the urine or in the blood, and no specific or diagnostic abnormalities were found. Abnormalities of serum glucose were excluded in the 21 patients surviving beyond initial presentation.

**Clinical Diagnosis of Myocarditis**

Several clinical criteria were found to be reasonably specific for the diagnosis of myocarditis. Myocarditis was noted in 4 of 5 patients with fever, 2 of 2 patients with low-voltage QRS complexes, 6 of 7 patients with conduction or rhythm abnormalities, and 3 of 4 patients with elevation of CPK. However, these same criteria were not very sensitive for the diagnosis, with fever present in only 4 of 9 patients with myocarditis, low-voltage QRS complexes in 2 of 9, rhythm or conduction abnormalities in 6 of 9, and CPK elevation in 3 of 9.

**Cardiac Catheterization**

Cardiac catheterization was performed in 18 of the 24 study patients. In most cases, catheterization was not done at presentation but only after a period of medical therapy, a median of 6 days after presentation. The average right atrial mean pressure was 6 mm Hg (range, 0 to 24 mm Hg); the average pulmonary artery systolic pressure was 21 mm Hg (range, 10 to 58 mm Hg); and the average LV end-diastolic pressure was 12 mm Hg (range, 4 to 24 mm Hg). The average cardiac index was 2.7 L · min⁻¹ · m⁻² (range, 1.8 to 3.9 L · min⁻¹ · m⁻²).

**Pathology**

Endomyocardial tissue was available in 20 of 24 patients. Sixteen were myocardial biopsies, and four were postmortem examinations. In 2 patients, three serial biopsies were performed. Biopsies were obtained from only the right ventricle in 9 children and from both the right and the left ventricles in 7. In the 4 children with postmortem tissue examination, previous endomyocardial biopsies had not been performed. In 7 of 16 children, the biopsies were believed to be diagnostic (4) or borderline (3) for myocarditis. Definitive myocarditis was diagnosed at autopsy in 2 children. In 6 children, EFE was observed: in 4 on biopsy material and in 2 at autopsy. When EFE was present, the LV was invariably involved, whereas the right ventricle was either not involved (2 patients) or involved only to a minor degree (4 patients) compared with the LV. Mild nonspecific changes were observed in the biopsies of 4 children: 3 had myocyte hypertrophy, and 1 had focal interstitial fibrosis. In 1 child, the biopsy showed no significant pathological changes. The electron microscopic findings were helpful in confirming the diagnosis of myocarditis and endomyocardial fibroelastosis in children with this diagnosis by light microscopy. In 2 cases of borderline myocarditis, myocyte degeneration was ultrastructurally observed in addition to the sparse interstitial lymphocytic infiltrate, again consistent with borderline myocarditis. Nonspecific changes with hypertrophy, mild mitochondrial pleomorphism, and interstitial fibrosis were observed in the majority of cases.

In the patients who had successive biopsies, 1 had a definite diagnosis of myocarditis in his first biopsy, whereas the second and third biopsies (3 and 7 months after the first biopsy) showed only nonspecific changes, including focal fibrosis and hypertrophic changes. In the other patient with serial biopsies, the first biopsy showed borderline myocarditis (myocardial edema and mild lymphocytic infiltrate but no myonecrosis), and later biopsies revealed only focal interstitial fibrosis (3 and 7 months after the first biopsy).

**Clinical Outcome**

There were seven deaths (29%), with all except one occurring less than 2 months after presentation. In three cases (patients 1, 22, and 24), death occurred within hours of presentation, and this included both patients with carditis who died. The three early deaths occurred in patients from the immediate area, whereas 9 of 21 of the other patients were from geographically remote locations. This implies that selection bias is likely, such that the patients included in this study were already selected for longer survival. Three of the 4 patients who died more than 1 week after presentation (patients 12, 16, 17, and 20) had a tissue diagnosis of EFE. In 2 patients, an LV thrombus was documented by echocardiography during the acute phase of the disease. In no instance was there clinical evidence of embolic phenomena. In the 17 survivors followed for 1 to 7.5 years, 11 regained normal LV function (LV ejection fraction, >51%), 4 have persistent LV dysfunction (LV ejection fraction, <47%), and 2 are asymptomatic. Follow-up ejection fraction was not available in the 2 survivors with a tissue diagnosis of EFE, but both are asymptomatic.

**Relation of Outcome to Pathology**

The relation of tissue diagnosis to outcome is displayed in Table 2. Tissue diagnosis of EFE was associated with poorer survival, with death in 4 of the 6 patients with EFE. Of the 8 patients with tissue diagnosis of myocarditis (6 patients with definite and 2 with borderline myocarditis on biopsy), 2 died. Four of the patients (3 with definite and 1 with borderline myocarditis by biopsy) were treated with immunosuppressive drugs (steroids, cyclosporine, immun, and immunoglobulin
infusion), and all recovered. Survival analysis demonstrated significantly poorer survival in patients with EFE (P<.02). When considered as a group, myocarditis was not significantly related to survival. However, when analysis was restricted to the subgroup of patients who survived long enough to initiate medical therapy (ie, beyond the first hours of presentation), patients with myocarditis had significantly better survival (P<.01).

Relation of Outcome to Echocardiographic Data at Presentation

LV Ejection Fraction

The magnitude of depression of LV ejection fraction at presentation was related to outcome. The 10 patients who had good outcome (patients who regained normal LV function) had a mean LV ejection fraction of 35±10% at presentation, whereas the 9 with poor outcome (patients who died or in whom LV dysfunction persisted) had an initial LV ejection fraction of 17±7% (Fig 1, P=.0004). When examined with respect to survival, the mean LV ejection fraction of the 15 survivors was 29±11%, whereas the LV ejection fraction in the 6 who died was 16±8% (P=.02). There was considerable overlap in the two groups, but all patients with an initial ejection fraction of >35% survived.

LV Shape

LV shape (short axis–to–long axis ratio [SA/LA]) at the time of presentation was also found to have prognostic value, with a more spherical shape associated with a higher risk of death. The 10 patients who had good outcome had a mean SA/LA ratio of 0.74±0.09, whereas the 9 who had a poor outcome had a ratio of 0.83±0.1 (P=.027). When analyzed with respect to survival, the 15 survivors had a SA/LA ratio of 0.74±0.08, and those who died had a ratio of 0.86±0.1 (Fig 2, P=.013). Again, there was considerable overlap in the two groups, but all patients with an initial SA/LA ratio below 0.75 survived.

Relation of Outcome to Hemodynamic Data

Of the 18 patients who had cardiac catheterization, 3 died and 15 survived. None of the hemodynamic variables were predictive of outcome with respect to either survival or recovery of function (Table 3).

Patterns of Recovery of LV Function

For 24 patients, a total of 68 echocardiograms were available at various times following presentation that had adequate data for analysis of LV function by two-dimensional echocardiography, M-mode, or both. The data (from two to five echocardiograms per patient) were pooled to examine the trends in LV size, function, and contractility over time. These trends are illustrated in Figs 3 through 6. Body surface area–adjusted EDV fell rapidly over the first several months of observation,

<table>
<thead>
<tr>
<th>Pathology</th>
<th>EFE</th>
<th>Carditis</th>
<th>Other</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>6</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Alive</td>
<td>2</td>
<td>7</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Normal LV function</td>
<td>?</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

EFE indicates endocardial fibroelastosis; NA, not available; and LV, left ventricular.

Fig 1. Plots of relation between left ventricular ejection fraction (%) at presentation and outcome in infants with dilated cardiomyopathy. The ejection fraction was significantly lower in patients with a poor outcome versus those with a good outcome (P=.0004) and was higher in survivors than in nonsurvivors (P=.02), although there was considerable overlap in both cases.

**TABLE 3. Relation of Hemodynamics to Outcome**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Dead</th>
<th>Dysfunction</th>
<th>Normal Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>3</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Mean RA pressure, mm Hg</td>
<td>4±3</td>
<td>3±2</td>
<td>9±7</td>
</tr>
<tr>
<td>Mean PA pressure, mm Hg</td>
<td>29±21</td>
<td>18±3</td>
<td>21±8</td>
</tr>
<tr>
<td>LV EDP, mm Hg</td>
<td>14±7</td>
<td>12±5</td>
<td>12±6</td>
</tr>
<tr>
<td>Cardiac output, L·min⁻¹·m⁻²</td>
<td>2.3±2</td>
<td>3.0±1</td>
<td>2.5±0.5</td>
</tr>
</tbody>
</table>

LV EDP indicates left ventricular end-diastolic pressure; RA, right atrium; and PA, pulmonary artery.
with little change thereafter (Fig 3). LV mass (adjusted for body surface area), which was generally elevated from the earliest observations, followed a similar pattern although the rate of fall was more gradual (Fig 4). As a result, the mass-to-volume ratio (normally 1.0) was elevated in most patients even at the time of first observation and fell gradually to the normal range over the first 2 years after presentation before a plateau was attained (Fig 5). Ejection fraction returned to normal within days to weeks in some individuals, but for the group it improved more gradually, with a plateau in the recovery after about 2 years (Fig 6). Contractility, assessed as the SVI (Fig 7), was noted to follow a trend similar to the pattern for ejection fraction, demonstrating a stable range after about 2 years. Thus, although EDV fell rapidly after presentation, perhaps in part due to medical therapy, mass, systolic function, and contractility normalized more slowly.

Discussion

In this review of patients with DCM presenting before 2 years of age, tissue evidence of myocarditis was found in 45% and was associated with a better prognosis, whereas tissue evidence of EFE, present in 25%, carried a worse prognosis. Overall, outcome in this study was death in 30%, residual LV dysfunction in 20%, and complete recovery in 50%. We found clinical data to be relatively unreliable in diagnosing myocarditis. Death or recovery of function usually occurred in the first month after presentation, although some individuals experienced further improvement of ventricular function for as long as 2 years. Echocardiographic predictors of a worse outcome included the severity of ventricular dysfunction and a more spherical LV configuration. In those who recovered, the first event was a reduction in EDV with a rise in the mass-to-volume ratio and subsequent improvement in ejection fraction and contractility with normalization of mass and mass-to-volume ratio.

Myocarditis

In this group of young patients with idiopathic congestive cardiomyopathy, all presented with clinical signs

\[
\text{EDVI} = 65(2.6 \times \text{Time}) + 111
\]

\[
\text{EF} = 3.7 \times \ln(\text{Time}) + 46
\]
Histological Predictors of Outcome

Predictors of outcome in DCM in children and infants vary in different reports. Although previous reports examining the utility of biopsy have occasionally included infants, to our knowledge, this is the first series to systematically examine the relation of outcome to histology in this age group. Factors that have been reported to be indicative of a poor prognosis include severity of ventricular dysfunction assessed angiographically or echocardiographically; the presence of dysrhythmias; age at presentation, with some reports indicating a better prognosis for patients presenting who are <2 years old; familial cardiomyopathy; and pathological findings of EFE. The predictive variables have varied substantially among studies, in part due to differences in study selection criteria. Some studies have excluded patients with “myocarditis” determined by clinical criteria or have excluded patients with transient myocardial dysfunction. We observed some patients with rapid recovery of function who by biopsy and other criteria had definite myocarditis. Other authors have analyzed patients with the diagnosis of EFE, only one of whom had tissue confirmation. We included all patients with DCM for whom a primary cause other than myocarditis could not be established and used tissue diagnosis as the means of classification. Strictly speaking, since the causative organism remains unknown even in patients with tissue evidence of inflammation, this group constitutes the spectrum of idiopathic DCM.

We found that histological evidence of EFE implies a worse prognosis than pathological finding of myocarditis or inflammation, a result previously noted by others. The pathological finding of EFE has been believed to be either a primary abnormality, as seen occasionally in infantile congestive cardiomyopathy, or secondary to congenital heart disease, mainly left-sided obstructive lesions. In a recent review, Lurie hypothesized that EFE may never be a primary disease, always representing a secondary response by the infantile myocardium to some myocardial stress. Regardless of the pathophysiological basis, the diagnosis of EFE has been believed to imply severe and irreversible myocardial damage. Although we found this to be generally true, we did observe two instances of biopsy-proven EFE with full functional recovery and long-term survival. The therapeutic implications of the difference in prognosis with EFE relate to long- versus short-term management. Several alternatives such as immunotherapy, extracorporeal membrane oxygenation, or ventricular assist device, which are clearly justified in patients with potentially reversible disease, should almost certainly be bypassed in favor of cardiac transplantation in the patient with EFE who fails to respond rapidly to medical support.

Ventricular Configuration and Function

We found that the severity of LV dysfunction at presentation was predictive of outcome, although there were patients with very poor function who recovered. In addition, the patients who died were those in whom there was no improvement in ventricular function, and most died very early after presentation. In those who survived and regained normal LV function, most did so
in the first few months after presentation. A second predictive indicator was the shape of the LV at presentation. Similar to previous studies in adults with DCM, patients with a more spherical ventricle at the time of presentation were found to have a poorer prognosis.32 This phenomenon has also been described in myocardial injury secondary to prolonged volume overload, where the failure of the ventricular to maintain an ellipsoidal configuration with dilation is found in association with more severely depressed contractility.33,34 In a prior study of patients with volume-overloaded LV due to tricuspid atresia and other forms of single LV, we found that the transition to a more spherical ventricular shape was temporally associated with development of impaired contractility34 and with altered myocardial fiber orientation and similarly implied irreversibility of the myocardial injury.

**Ventricular Mass-to-Volume Ratio**

Prior clinical studies in adults with DCM have indicated that sustained ventricular hypertrophy with a more normal mass-to-volume ratio is associated with improved survival.28-35-37 For example, in one angiographic study, a mass-to-volume ratio <0.9 was found to be associated with higher mortality.38 The patients in this study had a nearly normal mass-to-volume ratio even at the time of first presentation, in contrast to the reduced mass-to-volume and thickness-to-dimension ratio that are typical of adults with DCM.29 It is known from animal and human studies that the immature myocardium has an enhanced hypertrophic capacity in response to increased wall stress.39-41 It is possible that this property, whether it represents hyperplasia or true hypertrophy, could contribute to the apparently better survival in DCM in the infant and young child.

**Hemodynamic Variables**

In our study, hemodynamic parameters such as right atrial pressure, pulmonary artery pressure, LV end-diastolic pressure, and cardiac index were not predictive of outcome. However, these hemodynamic variables were measured in only 3 of the 7 patients who died. Perhaps more important, the hemodynamic data were obtained at a median of 6 days after presentation. Therapeutic interventions had been undertaken in all, and it is likely that the administration of cardiotonic agents and vasodilators would have substantially altered these hemodynamic parameters.

**Recovery of Ventricular Function**

Improvement was rapid in many patients and followed a pattern of improved function, reduced diastolic volume, but slower reduction in ventricular mass with a consequent rise in the mass-to-volume ratio. The time course of recovery was usually within 1 or 2 months, although there were two instances of sustained recovery for as long as 2 years after presentation. However, even in these latter cases, there was some improvement in function within the first 2 months. In those instances where measures of contractility could be obtained, improvement in contractility followed a parallel but somewhat delayed course and never preceded the reduction in EDV or improved systolic function.

**Conclusions**

In children <2 years of age presenting with DCM cardiomyopathy of unknown cause, (1) the overall mortality is about 30%; patients with inflammatory changes on biopsy have a better outcome than do those with histological evidence of EFE; (2) the clinical diagnosis of myocarditis is unreliable and EFE is primarily a histological diagnosis, underscoring the need for biopsy; (3) death or recovery usually occurs early after presentation; (4) indicators of a poor prognosis at presentation include severe ventricular dysfunction, more spherical ventricular configuration, and evidence of EFE on histology; (5) in contrast to older patients, most had a normal mass-to-volume ratio, even at first presentation; and (6) with recovery, the rate of decrease in volume exceeds the reduction in mass, and although function returns to normal usually after a few months, the mass-to-volume ratio can remain high for more than 1 year, returning more slowly to normal.

**References**


15. Wyatt HL, Heng MK, Meerbaum S, Gueret P, Hestenes J, Dula E, Corday E. Cross-sectional echocardiography, II: analysis of math-
Infantile dilated cardiomyopathy. Relation of outcome to left ventricular mechanics, hemodynamics, and histology at the time of presentation.
A Matitiau, A Perez-Atayde, S P Sanders, T Sluysmans, I A Parness, P J Spevak and S D Colan

_Circulation_. 1994;90:1310-1318
doi: 10.1161/01.CIR.90.3.1310

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/90/3/1310

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ 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_ is online at:
http://circ.ahajournals.org//subscriptions/