Mildly Dilated Congestive Cardiomyopathy

Use of Prospective Diagnostic Criteria and Description of the Clinical Course Without Heart Transplantation

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Prognosis in classically described dilated congestive cardiomyopathy has been reported to be related to ventricular size. Mildly dilated congestive cardiomyopathy (MDCM) has been defined as end-stage heart failure of unknown etiology (New York Heart Association class IV, left ventricular ejection fraction less than 30%), occurring with neither typical hemodynamic signs of restrictive myopathy nor significant ventricular dilatation (less than 15% above normal range). The present study includes follow-up in 12 nontransplant patients. In the first 4 months after diagnosis, two patients improved and are living, and two showed cardiac dilation and clinical deterioration and died. Six of the remaining eight with persistent MDCM died (four with intractable heart failure and two, sudden deaths) without change in ventricular size before death, despite medical therapy over 20±8 months. Eight comparable transplanted patients with persistent MDCM demonstrated improved total survival by life table analysis (p<0.05). A family history of congestive cardiomyopathy was found in nine of 16 patients (56%) with persistent MDCM. Nontransplant patients were older (p<0.02), but other findings were similar in the two groups. Endomyocardial biopsies available in 14 of 16 cases showed little or no myofibrillar loss in spite of severe hemodynamic impairment. The degree of myofibrillar loss did not correlate with hemodynamic parameters but showed good correlation with left ventricular size, that is, five of six patients with no myofibrillar loss had normal ventricular size, whereas all eight patients with mild myofibrillar loss had mild cardiomegaly (p<0.002). Our current experience suggests a somewhat variable but negative prognosis after prospective diagnosis of MDCM, with poor survival in patients with persistence of the original diagnostic features during follow-up. Preservation of heart size in MDCM is probably related to lack of significant myofibrillar loss. Thus, irrespective of heart size or myofibrillar preservation on biopsy, heart transplantation should be strongly considered in MDCM if signs of severe cardiac dysfunction persist despite therapy. (Circulation 1990;81:506–517)

Ventricular dilation is considered the earliest and most distinguishing morphologic feature of congestive cardiomyopathy, which is often called “dilated cardiomyopathy.” Lack of significant ventricular dilation is typically found in hypertrophic and in restrictive cardiomyopathies. Restrictive cardiomyopathy has also been termed “nondilated cardiomyopathy” by some authors to emphasize its morphological appearance and differentiate it from dilated congestive cardiomyopathy. The prognosis in classical dilated congestive cardiomyopathy has been said to be negatively related to ventricular size. Prognosis also has been said to be better in patients with preserved myofibrils in endomyocardial biopsy. We have previously described an unusual, probably variant, form of dilated congestive cardiomyopathy termed “mildly dilated congestive cardiomyopathy” (MCDM), for lack of a better term. This was initially described in five heart transplant recipients with persistent clinical and hemodynamic features of end-stage congestive cardiomyopathy but with little or no left ventricular dilation. Additional unusual findings of MDCM were little or no myofibrillar loss on electron microscopy and a trend toward occurrence of dilated cardiomyopathy in other family members. These patients represented 5% of 102 consecutive patients with cardiomyopathy transplanted at Stanford University Hospital.

A second report involving this condition stressed its distinction from idiopathic restrictive cardiomyop-
Athry with the uniform finding of diffusely poor left ventricular contraction despite only mild or no left ventricular dilation, and the presence of nonrestrictive hemodynamics in MDCM. The hemodynamics and other findings were more consistent with this being a variant of congestive cardiomyopathy. Because of the association with the transplant program and the small number of patients, evaluated information about the natural history of the disease could not be obtained, and therefore, the clinical and pathologic features of MDCM had to be considered preliminary observations.

This report updates our knowledge about such patients gained at two institutions using identical methods of patient evaluation. The group not transplanted provided information about the natural course of the syndrome and permitted evaluation of the clinical usefulness and limitations of previously defined diagnostic criteria for this condition.

**Methods**

**Patients**

MDCM was arbitrarily defined in patients with 1) idiopathic cardiomyopathy, exhibiting severe heart failure, 2) in the presence of decreased left ventricular contraction (left ventricular ejection fraction less than 30%), but 3) without early diastolic dip and plateau pressure patterns or equalization of right and left ventricular diastolic pressures typical of restrictive myopathy, and 4) which occurred with no or only mild ventricular dilation (less than 15% above normal range corrected for body surface area). Patients with an associated systemic illness that could influence survival were excluded from the study. No patient had a previous history of alcohol abuse. The heart transplant protocol age limit was 55 years. In the nontransplant group, we included patients 65 years old or younger if the absence of coronary artery disease was documented by coronary arteriography.

Twenty patients with the initial diagnosis of MDCM by these criteria were identified from the heart transplant program at Stanford University Hospital, Stanford, California, and from the general patient population at Bikur Cholim Hospital, Jerusalem, Israel. Eight patients (including five previously reported) received cardiac allografts and are called the transplant group. The nontransplant group included 12 patients who initially fulfilled the diagnostic criteria for MDCM and of whom nine had endomyocardial biopsy performed. Within 6 months of follow-up, four of the patients in this group no longer fulfilled the criteria for MDCM. The remaining eight patients with persistent MDCM were considered most similar to the clinical presentation and subsequent clinical course of the transplant group before surgery and these two groups of eight patients each were most directly compared.

**Echocardiography**

Two-dimensional and M-mode echocardiograms were obtained at both institutions with a phased array Hewlett-Packard 77020 ultrasonograph (Hewlett-Packard Co., Andover, Massachusetts) using 2.5 or 3.5 MHz medium- and short-focused transducers. All studies included the parasternal, apical, and subcostal views, and nine patients also had Doppler echocardiographic evaluation. Echocardiographic measurements were performed as recommended by the American Society of Echocardiography. The mitral valve E-point to septal separation index was measured as reported by Massie et al. Measurements of right ventricular diastolic minor axis and right atrial systolic minor axis were performed as previously described. Measurements corrected for body surface area were compared with previously published normal values. The upper limits of normal were as follows (cm/m²): left ventricular diastolic diameter, 3.2; left atrial systolic diameter, 2.3; right ventricular diastolic minor axis, 2.8; and right atrial systolic minor axis, 2.5. Mitral regurgitation was graded qualitatively using a combination of pulsed and continuous wave Doppler as well as color flow velocity mapping. Echocardiographic studies were performed every 3 months in the nontransplant group, and for data analysis, the last study was recorded.

**Cardiac Catheterization and Angiography**

Left and right heart catheterization was performed with fluid-filled catheters and low-volume displacement transducers (P50, Gould Electronics, Cupertino, California). Pressure tracings were specifically analyzed for the presence of a restrictive pattern of hemodynamics with a characteristic early diastolic dip and subsequent rapid plateau in both ventricular pressure curves, with abnormal elevation in ventricular pressure achieved with the rapid filling wave and near equalization (within 5 mm Hg) of early pressures. Left ventricular angiography was performed in the 30° right anterior oblique projection and wall motion abnormalities were analyzed qualitatively (nontransplant group) or with the help of a computerized system (transplant group). Mitral regurgitation, if present, was graded during left ventriculography from the visualization of dye in the left atrium as mild (dye just visible), moderate (dye weakly opacifying the atrium but clearing within one or two beats after the end of the injection), or severe (sustained dense opacification of the atrium). Coronary arteriograms were within normal limits in all patients.

**Nuclear Angiography**

All patients in the nontransplant group had equilibrium radionuclide angiography after in vivo labeling of red blood cells by 20 mCi technetium 99m. A multicrystal gamma camera with a parallel-holes collimator was used. Data acquisition was performed in anterior and left anterior oblique views that best separated the right and left ventricles in the plane of the interventricular septum. The processing of the left ventricular ejection fraction was performed from the left anterior oblique view using the standard commercially supplied semiautomated edge detec-
tion program. The normal range of left ventricular ejection fraction is 55–70%. The processing of right ventricular ejection fraction was performed according to the technique described by Maddahi et al.\textsuperscript{22} The normal range of right ventricular ejection fraction is 40–55%. In the transplant group, nuclear angiographic left ventricular ejection fraction was available from the original site of referral in six of eight patients. In both groups, the most recent ejection fraction was recorded for data analysis, whether it was by radionuclide or contrast angiography.

Pathologic Evaluation

Pathologic evaluation was performed without knowledge of the echocardiographic findings. The technique used in the transplant group has been previously described in detail\textsuperscript{14} and includes 1) gross morphologic assessment of explanted heart specimens, 2) light microscopic assessment of endomyocardial biopsies and right and left ventricular sections of explanted hearts, and 3) electron microscopic evaluation of endomyocardial biopsies taken from the right ventricular septum before heart transplantation and from the heart within minutes of being explanted. In the nontransplant group, special care was taken to follow the previously used protocol\textsuperscript{14} for light and electron microscopic evaluation of right ventricular endomyocardial biopsies.

Heart Collection

After excision, the removed heart was weighed, and the gross description was made. Ventricular wall thickness and the anulus circumference of atrioventricular valves were measured. The heart was then placed in 10% formalin. After fixation, the heart was opened and evaluation of the interior of the ventricles was made. Endocardial changes and the presence or absence of thrombi were noted.

Light Microscopy

Myocardial tissue was embedded in paraffin, sectioned at 4–6-mm thicknesses. Sections stained with hematoxylin and eosin were assessed for myocyte hypertrophy and myocyte nuclear abnormalities. Fibrosis was judged from sections stained with Masson’s trichrome.

Electron Microscopy

Right ventricular endomyocardial biopsies obtained in both groups were prepared and evaluated as previously described.\textsuperscript{14} The samples were minced to 1–3 mm; fixed in 2% paraformaldehyde, 2.5% glutaraldehyde, and 0.1 mol/l sodium cacodylate; postfixed in 2% osmium tetroxide; and stained initially en block with uranyl acetate and, after dehydration and infiltration in epoxy-embedding resin, stained again with lead nitrate. Electron microscopic screening was performed for myocyte appearance and nuclear configuration. Myofibrillar loss was carefully assessed and graded in at least five plastic blocks as no myofibrillar loss (grade 0), less than 10% of myocytes affected (grade 1), 10–20% of myocytes affected (grade 2), and more than 20% of myocytes affected (grade 3).\textsuperscript{23} Patients without cardiac pathology show no myofibrillar loss (grade 0), whereas grade 2 or 3 myofibrillar loss is usually seen in patients with advanced stages of dilated congestive cardiomyopathy.\textsuperscript{8,14,23}

Statistics

Statistical analysis was performed using $\chi^2$ and two-tailed unpaired Student’s $t$ test where indicated. Cumulative mortality rate over time between the transplant and the nontransplant group was described by Kaplan-Meier curves,\textsuperscript{24} and the differences between curves were assessed by the Cox-Mantel test using a BMDP-1L computer program.\textsuperscript{25}

Results

Patient Distribution and Follow-up

Clinical follow-up of the MDCM nontransplant group. The nontransplant group included 12 patients who fulfilled the above criteria for MDCM on initial presentation (Figure 1). Four of these patients showed changes during clinical follow-up over 6 months that violated the criteria for MDCM. In two patients (17%) without either suggestive clinical history or myocardial biopsy signs of myocarditis, left ventricular diameter slightly decreased and ejection fraction increased from 19% to 28% to 39% and 46%, respectively, over 4 months without change in therapy. One of these patients had an ejection fraction of 57% at 16 months after the original study. The other of these patients had extensive follow-up 2 years after initial presentation. She was asymptomatic for cardiac failure off all medications and had only mild noncardiac chest pain, left ventricular diastolic diameter of 6.1 cm (left ventricular diastolic index, 3.5 cm/m\textsuperscript{2}), and ejection fraction of 55%. She gave informed consent for repeat catheterization and biopsy, which showed persistence of myocyte hypertrophy, bizarre-shaped nuclei, interstitial fibrosis, and no myofibrillar loss. There was no difference between this biopsy and the one performed on presentation when she was in severe congestive heart
failure. The remaining two patients with changes during follow-up had progressive ventricular dilation over the initial 3–4 months, then showing the typical picture of dilated cardiomyopathy, and both died (Figure 1).

Eight patients showed persistent criteria of MDCM and were symptomatic for 18–62 months with clinical and echocardiographic follow-up every 3 months after diagnosis. These patients were compared with the eight transplanted patients who all showed persistent criteria of MDCM for at least 6 months before transplantation (Table 1 and Figure 2). Therapy included digoxin, diuretics, and vasodilators in all patients, angiotensin converting enzyme inhibitors (five patients), antiarrhythmic drugs (three patients), and chronic anticoagulants (four patients). Metoprolol, up to 100 mg/day, was administered in one patient. During the follow-up period, four of these eight patients died of intractable heart failure while hospitalized, and two patients died suddenly. Echocardiograms performed 36 hours to 65 days before death in four of them showed left ventricular diastolic indexes in the range of 3.2–3.6 cm/m² (left ventricular diastolic diameters of 5.6–6.4 cm). One of the surviving patients has extremely severe heart failure and recurrent episodes of ventricular tachycardia. The other survivor is remarkable because of an initial 24-month period of stable New York Heart Association (NYHA) class III heart failure with a left ventricular diastolic diameter of 5.3 cm, ejection fraction of 22%, and a heart rate of more than 100 beats/min on conventional therapy. After addition of metoprolol, her symptoms improved to NYHA class II, with no change in ejection fraction (25%) or left ventricular diameter (5.5 cm), but significant decrease in heart rate over 38 more months of observation.

Clinical follow-up of the MDCM transplant group. The eight patients eventually transplanted had a history of severe congestive heart failure and little or no ventricular dilation persistent for 7–74 months before transplantation. Two of these patients underwent emergency surgery during episodes of cardiogenic shock and did not survive the perioperative period. Two patients died from infection 26 and 38 months after transplantation and four patients are alive and well 2.5–6.9 years postoperatively.

Comparative Analysis of Transplant and Nontransplant MDCM Groups

Clinical findings. The two patients who improved and the two patients who developed dilated hearts and died present groups of insufficient size for further analysis. The clinical findings in the two groups of persistent MDCM patients are presented in Table 1. Patients from the nontransplant group were older (p<0.02), as expected by selection criteria, but no other parameters were different between the two groups. Combined analysis of clinical data in the two groups showed a female gender predominance (female/male ratio 2.2/1) and congestive cardiomyopathy in another family member in nine of 16 patients (56%). Two patients had originally become symptomatic in the early postpartum period in the transplant group and a history of previous viral illness was present in two other patients in each group.

The physical findings were similar in the two groups. The apical impulse was recorded as displaced in only 10 of 15 patients with information available. A

![Figure 2. Plot of survival estimate versus time for two groups with persistent mildly diluted congestive cardiomyopathy, using Kaplan-Meier analysis (Reference 24). Survival of transplant group is significantly different by Cox-Mantel test (p<0.05).](http://circ.ahajournals.org/)

### TABLE 1. Clinical Findings in Patients With Persistent Mildly Dilated Congestive Cardiomyopathy

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Nontransplant group (n=8)</th>
<th>Transplant group (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>45.4±12.5</td>
<td>28.0±14.0*</td>
</tr>
<tr>
<td>Range (yr)</td>
<td>30–65</td>
<td>16–55</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Family history</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Symptomatic period (mo)</td>
<td>29.3±14.3</td>
<td>25.0±24.0</td>
</tr>
<tr>
<td>Range (mo)</td>
<td>18–62</td>
<td>7–74</td>
</tr>
<tr>
<td>Follow-up period† (mo)</td>
<td>19.5±8.2</td>
<td>44.7±21.3</td>
</tr>
<tr>
<td>Systemic emboli</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Systolic murmur</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Third and/or fourth heart sound</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Atrial fibrillation‡</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Complete atrioventricular block</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Ventricular tachycardia/ fibrillation</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Cardiothoracic ratio</td>
<td>&gt;55%</td>
<td></td>
</tr>
</tbody>
</table>

* p<0.02 as compared with nontransplant group.
† Includes only period after presentation at Bikur Cholim or Stanford; transplant group includes posttransplant period.
‡ Paroxysmal or chronic atrial fibrillation.
third or fourth heart sound was recorded in all cases during the follow-up. A systolic apical murmur compatible with mitral regurgitation was found in nine of the 16 patients. Mitral regurgitation was mild to moderate in eight patients by Doppler ultrasound, angiographic criteria, or both.

The electrocardiogram was abnormal in all patients and most commonly showed diffuse ST-T wave changes, left ventricular hypertrophy, atrial enlargement, conduction abnormalities, and rhythm disturbances. Ventricular tachycardia and fibrillation that required cardiopulmonary resuscitation occurred in three patients.

Chest x-rays showed normal cardiothoracic ratios in two of 16 patients and variable degrees of pulmonary congestion in all patients. In three patients with radiographic cardiomegaly, there was normal ventricular size but additional mild-to-moderate pericardial effusion by echocardiography.

**Presenting symptoms and initial diagnosis.** Fatigue, dyspnea, and cough were the most frequent presenting symptoms (Table 2). Pulmonary edema associated with fever or with the postpartum period was the next most common patient presentation. The initial suspected diagnosis in these patients could be clearly documented from previous charts or echocardiographic requests in 14 of 16 patients. The diagnosis of cardiomyopathy was correctly suspected from the onset of symptoms in only five of these 14 patients. These were usually young patients who had either pulmonary edema or signs of severe congestive heart failure of unknown etiology at the time of their first evaluation. Chest pain, usually not typical for angina, and electrocardiographic changes in the presence of virtually normal cardiac size led to the erroneous initial diagnosis of ischemic heart disease or pericarditis in four patients. Two patients (one presenting in the postpartum period) received antibiotics because of unremitting cough and “pulmonary infiltrates” until development of frank pulmonary edema led to hospitalization and recognition of the cardiomyopathy.

**Laboratory and pathology findings.** The laboratory and pathology findings are summarized in Table 3.

### Table 2. Presenting Symptoms and Initial Diagnosis in Patients With Persistent Mildly Dilated Congestive Cardiomyopathy

<table>
<thead>
<tr>
<th>Presenting symptoms</th>
<th>Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue, dyspnea, cough</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>3</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3</td>
</tr>
<tr>
<td>Palpitations</td>
<td>1</td>
</tr>
<tr>
<td>Initial suspected diagnosis*</td>
<td></td>
</tr>
<tr>
<td>Cardiomyopathy</td>
<td>5</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>4</td>
</tr>
<tr>
<td>Mitral regurgitation</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary infection</td>
<td>2</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
<td>1</td>
</tr>
</tbody>
</table>

*Data available in 14 patients.

### Table 3. Laboratory Findings in Patients With Persistent Mildly Dilated Congestive Cardiomyopathy

<table>
<thead>
<tr>
<th></th>
<th>Nontransplant group (n=8)</th>
<th>Transplant group (n=8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.7±0.2</td>
<td>1.7±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVDD (cm/m²)</td>
<td>3.2±0.3</td>
<td>3.2±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>LVID (cm/m²)</td>
<td>2.8±0.4</td>
<td>3.0±0.2</td>
<td>NS</td>
</tr>
<tr>
<td>LASI/LVIDI</td>
<td>0.7±0.09</td>
<td>0.7±0.04</td>
<td>NS</td>
</tr>
<tr>
<td>RVDD/LVIDI</td>
<td>0.6±0.1</td>
<td>0.7±0.13</td>
<td>NS</td>
</tr>
<tr>
<td>FS (%)</td>
<td>14.0±4.5</td>
<td>10.1±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>EPSS (cm)</td>
<td>1.9±0.3</td>
<td>2.1±0.1</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Catheterization</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>12.1±3.8</td>
<td>14.8±5.3</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>23.6±7.7</td>
<td>26.7±6.0</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>20.7±5.2</td>
<td>18.8±4.3</td>
<td>NS</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.9±0.35</td>
<td>1.5±0.4</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Pathology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myofibrillar loss</td>
<td>(grade 0–1)</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

LVDD, left ventricular diastolic index; LVID, left ventricular systolic index; LASI, left atrial systolic index; RVDD, right ventricular diastolic index; FS, fractional shortening; EPSS, mitral valve E-point septal separation; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; CI, cardiac index.

**Echocardiography.** Body surface area and echocardiographic parameters were similar in the two groups. Left ventricular diastolic size was within normal limits in five of 16 patients. Patients with and without absolute left ventricular enlargement showed left ventricular size larger than that of other cardiac chambers. (The ratio of left atrial or right ventricular diameter to left ventricular diameter was 0.8 or less in all patients.) M-mode echocardiographic contractility parameters were severely decreased in all patients (Table 3). Left ventricular thrombi were identified in three patients from each group, and additional right ventricular thrombi were found in two of them.

**Catheterization and angiographic results.** Right atrial and pulmonary capillary wedge pressures were elevated in all cases, showing the typical pattern of congestive cardiomyopathy with significantly higher left (as compared with right) ventricular diastolic pressure. No patient showed restrictive hemodynamics as defined in the methods section. Left ventricular ejection fraction was 20% or less in 12 of 16 cases and in the range of 15–28% in the nontransplant and 12–26% in the transplant group. Nuclear angiographic right ventricular ejection fraction was evaluated in six of eight nontransplant patients and in the range of 14–27%. The cardiac index of the transplant group was lower than that of the nontransplant group, with borderline statistical significance (p=0.05).

**Pathology results.** Light microscopy showed nonspecific myocyte hypertrophy, hyperchromatic and bizarre-shaped nuclei, and interstitial fibrosis in all 14 patients so evaluated. Electron microscopy (Fig-
ures 3 and 4) showed no myofibrillar loss (grade 0) in six patients and only partial myofibrillar loss (grade 1) in eight patients. In three cases with familial congestive cardiomyopathy, electron microscopy showed the “thumbprint” appearance of stacked mitochondrial cristae previously described in patients typical of familial dilated cardiomyopathy. Comparison of echocardiographic and catheterization parameters of the eight patients with some and six patients without any myofibrillar loss (Table 4) showed similar hemodynamics and ejection fractions. The left ventricular diastolic index of patients with no myofibrillar loss was less than that of patients with myofibrillar loss by a small (0.4 cm/m²) but statistically significant amount (p<0.002).

Discussion

The diagnostic criteria of MDCM were defined previously in a selected population of heart transplant candidates. In these patients, either the diagnosis was reached retrospectively or the prospective follow-up after diagnosis was limited by heart transplantation. The extension of our previous observations in heart transplant patients to the present nontransplant group suggests the ability to prospectively define such patients with mildly dilated cardiomyopathy initially presenting with heart failure. Four of 12 (33%) of these patients, however, did not fulfill the defined criteria during the initial 6 months of observation.

Some of the patients in this series actually had cardiac dimensions within normal limits. The initial presentation of these patients highlights the diagnostic difficulties encountered because of the small heart size in the face of severe clinical symptoms. An abnormal electrocardiogram was uniformly present but did not have specific features. The chest x-ray generally was not helpful in the diagnosis of this condition, and in fact, pericardial effusion can give the erroneous impression of cardiomegaly in some cases. The electrocardiogram, echocardiogram, hemodynamic and pathological studies in the original five patients reported, and the subsequent patients added in this report are very similar. Advanced heart failure in patients younger than 40 years old can more often suggest primary myocardial disease, whereas in those older, can suggest underlying ischemic heart disease with secondary heart failure.

Natural History of Mildly Dilated Cardiomyopathy

Four of the 12 patients who initially met the criteria for mildly dilated congestive cardiomyopathy showed changes that took them out of this diagnostic category over the follow-up period. Two patterns were seen. In two patients, progressive left ventricular dilation developed within 3–4 months, and these patients, then, were indistinguishable from typical dilated cardiomyopathy. Both patients died during the follow-up. A second pattern, improvement in function, was seen in two patients. These patients originally fulfilled the diagnostic criteria for MDCM, and myocarditis was excluded by clinical criteria and endomyocardial biopsy findings. During the next 4–6 months, however, the left ventricular ejection fraction increased from 28% to 46% and from 19% to 39% without significant change in medical therapy. Ejection fraction rose to more than 55% after 24 and 15 months in these patients. Although it is important to note the natural history of these four patients, they were not directly compared with the rest of the nontransplant group because they would have been reclassified over a short period of time as either typical dilated cardiomyopathy or as questionable cardiomyopathy if they had not been seen early and studied extensively.

The severe hemodynamic impairment in the presence of only a mildly dilated heart is pronounced in MDCM and differentiates this condition from that usually seen in early phases of dilated cardiomyopathy. It can be argued that once so labeled, such patients might retain the diagnosis of MDCM even if spontaneous improvement in hemodynamic parameters or cardiac dilation occurs (if myocarditis is excluded by clinical and endomyocardial biopsy criteria). Spontaneous clinical and hemodynamic improvement have been described in patients with typical dilated cardiomyopathy. We arbitrarily chose to compare patients with persistent MDCM with transplanted patients who also had persistent criteria of MDCM before surgery (Table 1). In this context, it might be appropriate to extend the definition of this condition to include persistence of the diagnostic criteria over the ensuing months despite therapy.

Four of the eight nontransplant patients with persistent MDCM died of intractable heart failure, and two died suddenly at 18 and 36 months, respectively. None of these six patients showed further cardiac dilation before death. One of the surviving patients showed regression of symptoms on β-blocker therapy without a change in ejection fraction or heart size. The other patient remains in severe congestive heart failure 24 months after the onset of symptoms. An unusually high incidence (56%) of familial occurrence of dilated cardiomyopathy was found in our patients with persistent MDCM.

Correlation Between Degree of Myofibrillar Loss, Cardiomegaly, and Prognosis

These data suggest that myofibrillar loss correlates more with heart size than with hemodynamics or severity of congestive heart failure, as opposed to previous suggestions in the literature.

Several investigators have assessed possible associations between histologic changes on endomyocardial biopsy and hemodynamic data or survival in patients with dilated cardiomyopathy. Many parameters, including the degree of myocyte hypertrophy, interstitial fibrosis, and myofibrillar loss, have been assessed. Some authors found histologic changes correlated with left ventricular hemodynamics and predicted survival. Others could not correlate
pathological features with left ventricular ejection fraction\textsuperscript{13,36,37} or prognosis.\textsuperscript{37–39}

In a recent report, Figulla et al\textsuperscript{13} found no correlation between the severity of myofibrillar loss and the hemodynamic status of patients with dilated cardiomyopathy. They observed 23 of 24 patients (96\%) with a myofibril volume fraction of less than 60\% who deteriorated or died, whereas 14 of 15 patients (93\%) whose condition stabilized or improved had a myofibril volume fraction of 60\% or more. They concluded, “Heart transplants should not be performed in patients with myofibril volume fractions of 60\% or more, since the prognosis for these patients is good.”\textsuperscript{13} This conclusion does not seem valid in patients with persistent MDCM because the majority (six of eight), who were not transplanted, died despite little or no myofibrillar loss.

In the selected group of patients with persistent MDCM and biopsy or explanted heart histology reported here, having rather uniform hemodynamic findings, five of six patients with no myofibrillar loss had normal ventricular size, whereas all eight patients with mild myofibrillar loss (grade 1) had mild cardiomegaly ($p<0.002$). Moreover, in a previous study, there were no differences between transplant recipients with typical dilated cardiomyopathy and those with MDCM, regarding hemodynamics, wall thickness, myocyte hypertrophy, or perimyocyte fibrosis. But those with dilated cardiomyopathy had significantly more myofibrillar loss as compared with the MDCM patients.\textsuperscript{14} Thus, the degree of myofibrillar loss seems not to correlate with hemodynamic parameters or the degree of clinical functional impairment; however, myofibrils might have an important role in preservation of cardiac size in MDCM.

In dilated cardiomyopathy, the degree of cardiomegaly seems generally related to prognosis.\textsuperscript{1,3,9,11,12}
although some studies have failed to show such a correlation. The current cases of persistent MDCM negate the clinical impression that "... even if a patient is seemingly in pre-terminal heart failure, he may be rescued if the left ventricle is only modestly dilated." In patients with persistent MDCM, the poor prognosis seems to relate to the severe hemodynamic impairment that occurs despite preserved heart size. The results of the present study indicate that, irrespective of heart size or myofibrillar preservation on biopsy, heart transplantation should be strongly considered in MDCM if signs of severe cardiac dysfunction persist despite therapy. Survival after transplantation currently is approximately 85% at 1 year and about 65% at 5 years. In this group, it was only 50% at 5 years, but combined pretransplantation and posttransplantation survival was significantly beyond that seen in the comparable patients not transplanted ($p<0.05$) (Figure 2).

**Limitations**

The patients reported on here are the results of a diligent search at two institutions and a highly selective process. Bikur Cholim Hospital is a primary-care innercity hospital with secondary referrals from clinics in neighboring cities. Stanford University Medical Center is a tertiary referral center for an international population. It is possible that undefined predisposing factors might be different in the two centers; however, both groups were truly multiethnic in population, and no clear genetic link within dilated cardiomyopathies or within nationalities has been identified. Nevertheless, the prevalence of dilated cardiomyopathy in at least one family member of patients with persistent MDCM was unusually high (56%), and therefore, genetic factors might be operative.

The prevalence of this condition within large populations of patients with congestive heart failure cannot be assessed from this series. Observation of such patients less clinically disabled, but fulfilling the hemodynamic and ventricular size criteria for MDCM, could be important for further understanding of the natural history of patients apparently presenting with this condition.
Keren et al Mildly Dilated Congestive Cardiomyopathy

FIGURE 4. Electronmicrographic patterns found in the current patients with mildly dilated congestive cardiomyopathy. Panel A: No myofibrillar (MF) loss. Compared with findings in Figure 2 (Panel A), note presence of myocyte hypertrophy with intercalated disc (ID) between myocytes, large, bizarre-shaped nucleus (N), and presence of lipochrome pigments (LC) (magnification, ×3,000). Panel B: Mild myofibrillar loss (ML) (grade 1) with remnants of sarcoplasmic reticulum (SR) and remnants of Z-bands (ZB) in localized area of myofibrillar loss. Normal contractile elements with myofibrils (MF) bracket area of myofibrillar loss. Area of fibrous tissue (F) is present (magnification, ×3,000). Compare with Figure 2 (Panel B). Panel C: Stacked mitochondrial cristae (CR) which give “thumbprint” appearance (some marked with arrows). In this patient, no myofibrillar loss was present (magnification, ×7,125).

Differentiation From Other Conditions

We suggest that persistent MDCM is an unusual subtype of dilated or congestive cardiomyopathy in which the patients otherwise have similar clinical, hemodynamic, and echocardiographic and electrocardiographic findings as well as similar prognoses. It is believed that persistent MDCM can be differentiated from other forms of cardiomyopathy with preserved left ventricular size. Latent cardiomyopathy described by Kuhn et al includes asymptomatic patients with normal heart size and resting hemodynamics but who showed left bundle branch block, exercise-induced elevation of left ventricular end-diastolic pressure, or histologic abnormalities. It can be easily differentiated from MDCM by its clinical presentation. Early forms of dilated cardiomyopathy show better hemodynamics. Patients with alcoholic (restrictive) cardiomyopathy that improves with abstention present with clinical congestive heart failure and a small left ventricle by imaging studies. This entity, however, is also characterized by restrictive hemodynamics that negate the diagnosis of MDCM. Patients with primary involvement of the

TABLE 4. Correlation Between Myofibrillar Loss and Hemodynamic Patterns in Patients With Persistent Mildly Dilated Congestive Cardiomyopathy

<table>
<thead>
<tr>
<th>Myofibrillar loss</th>
<th>Absent (n=6)</th>
<th>Present* (n=8)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVDI (cm/m²)</td>
<td>3.0±0.2</td>
<td>3.4±0.1</td>
<td>&lt;0.002</td>
</tr>
<tr>
<td>RAP (mm Hg)</td>
<td>14.5±4.6</td>
<td>12.8±5.8</td>
<td>NS</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>26.2±6.4</td>
<td>23.4±6.4</td>
<td>NS</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>20.7±3.3</td>
<td>19.1±5.2</td>
<td>NS</td>
</tr>
<tr>
<td>CI (l/min/m²)</td>
<td>1.9±0.4</td>
<td>1.8±0.4</td>
<td>NS</td>
</tr>
</tbody>
</table>

LVDI, left ventricular diastolic index; RAP, right atrial pressure; PCWP, pulmonary capillary wedge pressure; LVEF, left ventricular ejection fraction; CI, cardiac index.

*Grade 1.
right ventricle with cardiomyopathy\textsuperscript{5,6} can be differentiated from MDCM by echocardiography.

Several clinical or autopsy series of dilated cardiomyopathy include some patients with normal or borderline left ventricular size or cardiothoracic ratio in their tables\textsuperscript{8,43,47} but there is no discussion of these patients. Perhaps some of these patients fulfilled the proposed criteria for MDCM. This report might stimulate others to look for examples of MDCM to further our understanding of its prevalence and natural history.

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