Mildly dilated congestive cardiomyopathy

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ABSTRACT Five patients with only mildly dilated ventricles but other features typical of congestive cardiomyopathy underwent cardiac transplantation for class IV NYHA heart failure. The findings of clinical studies, cardiac catheterization, endomyocardial biopsy, and pathologic examination of the removed hearts in this group with mildly dilated congestive cardiomyopathy (MDCM) were compared with similar data in four patients with idiopathic restrictive cardiomyopathy (IRCM) and in 10 patients with typical dilated congestive cardiomyopathy (DCM). In comparison with the other groups, patients with MDCM had a higher incidence of familial cardiomyopathy (p = .02) and a shorter symptomatic period than patients with IRCM (p < .02). Patients with both MDCM and DCM had globular hearts (with predominant left ventricular dilatation), congestive hemodynamics and poor left ventricular contractility (ejection fraction 12% to 19%), and high incidence of ventricular thrombi. Patients with IRCM showed normal ventricular size, marked atrial dilatation, restrictive hemodynamics, mild-to-moderate decrease in left ventricular contractility (ejection fraction 29% to 55%), and absence of ventricular thrombi. Cardiac index, ventricular wall thickness, and light microscopic findings were similar in the three groups of patients. Electron microscopy showed no myofibrillar loss in patients with IRCM but mild (partial) or moderate-to-severe (almost total) myofibrillar loss in those with MDCM and DCM, respectively. We conclude that (1) end-stage congestive cardiomyopathy may occur without significant ventricular dilatation and (2) patients with MDCM have heart sizes intermediate between those found in IRCM and DCM but their clinical, hemodynamic, and pathologic findings are virtually identical to those of patients with typical DCM.


CONGESTIVE and restrictive cardiomyopathies represent distinct entities with different hemodynamic and morphologic features. Congestive cardiomyopathy is characterized by ventricular dilatation and poor systolic function with greatly reduced ejection fraction. Dilatation of the ventricles usually occurs earlier than heart failure and is considered the most important manifestation of the disease. For this reason, the terms “dilated” or “dilated congestive” cardiomyopathy are currently preferred. Light and electron microscopic assessment show major but nonspecific abnormal changes.

Restrictive cardiomyopathy is characterized by normal or near normal ventricular size and systolic function but compromised ventricular relaxation leading to distinctive hemodynamic findings. The term restrictive (nondilated) cardiomyopathy is preferred by some authors to emphasize the absence of ventricular dilatation. Infiltrative processes or endomyocardial fibrosis, with or without eosinophilia, usually represent its pathologic basis. Rarely has a primary or idiopathic form of the disease been reported in which histologic examination did not reveal specific changes.

This study presents the clinical and morphologic data of patients who underwent cardiac transplantation in whom the characteristic features of congestive cardiomyopathy occurred without significant ventricular dilatation. For better characterization of these patients, with what we tentatively term “mildly dilated” congestive cardiomyopathy (MDCM), the findings of this group were compared with those of heart transplant recipients with idiopathic restrictive cardiomyopathy (IRCM) and with typical dilated congestive cardiomyopathy (DCM).

Methods

Patients. Review of the pathologic findings in 103 consecutive patients with idiopathic cardiomyopathy who underwent cardiac transplantation revealed normal ventricular size or bor-
derline ventricular enlargement in 10 patients. Of these, eight patients were included in the study by fulfilling the following additional criteria: (1) normal or slightly enlarged left and right ventricular diameter (no more than 10% to 15% above normal range after correction for body surface area) on preoperative echocardiogram and/or angiogram, (2) well preserved recipient heart specimens suitable for current analysis, and (3) available preoperative clinical charts and catherization data. Based on data from clinical, hemodynamic, and echocardiographic studies and from the results of pericardial biopsy (two patients), the preoperative diagnosis was IRCM in three patients and congestive cardiomyopathy with mild ventricular dilatation (MDCM) in five. We also included a nonconsecutive patient who was recently admitted to the heart transplantation program and in whom angiography, echocardiography, right ventricular endomyocardial biopsy, and hemodynamic study proved the presence of IRCM. The clinical, hemodynamic, and pathologic data in these two categories of patients were compared with similar data recorded in 10 contemporaneous patients with typical DCM.

**Echocardiography.** Two-dimensional and M mode echocardiograms were obtained 2 to 80 days (32 ± 17 days) before surgery with a Hewlett-Packard model 77020A imaging system and a 2.5 or 3.5 MHz medium- or short-focused transducer. All studies included at least the standard parasternal, apical, and subcostal views. 10 Echocardiographic measurements were performed in a standard way. 11 The right ventricular and right atrial diameters were measured from the apical four-chamber view, as previously described. 10 Both M mode and two-dimensional echocardiographic measurements (corrected for body surface area) were compared with normal values obtained in our laboratory. 10, 12 The range of normal values (expressed in cm/m²) are: left ventricular diastolic diameter, 2.0 to 3.2; left atrial systolic diameter, 1.1 to 2.3; right ventricular diastolic minor axis, 1.0 to 2.8; right atrial systolic minor axis, 1.7 to 2.5. 10

**Cardiac catheterization and angiography.** Left and right heart catheterization were performed with standard transducers and fluid-filled catheters. Pressure tracings were specifically analyzed for presence or absence of restrictive patterns. 3, 4 Left ventricular angiograms were obtained in the 30 degree right anterior oblique projection. The parameters measured during these tests (table 1) represented the major preoperative criteria for classifying the patients into the groups with restrictive or congestive cardiomyopathy. The results of coronary arteriography were normal in all patients.

**Pathology.** Pathologic assessment included morphologic examination of the removed hearts and microscopic evaluation of preoperative and postoperative endomyocardial biopsy specimens. The presence of atrial thrombi and characteristics of the pericardium were evaluated during operation and, when indicated, pericardial biopsy specimens were taken.

**Collection of heart specimens.** Immediately after excision the recipient heart was collected, weighed, and photographed, and a gross description was made. Wall thickness measurements were made in the pulmonary outflow tract for the right ventricle (normal range 0.2 to 0.3 cm) and in the left ventricular wall opposite the caudal tip of the anterolateral papillary muscle (normal range 1 to 1.2 cm). The heart was then placed in 10% formalin for fixation. Because the atria are partially left within the patient, it was not possible to inflate the hearts; whenever possible, however, the ventricles were packed with wadding before fixation to maintain their shape. After fixation, the heart

### TABLE 1

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<th>Clinical and hemodynamic findings in all patients</th>
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<td>IRCM (n = 4)</td>
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<td>Age (yr)</td>
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<td>Family history</td>
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<td>Symptomatic period (mo)</td>
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<td>Atrial fibrillation</td>
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<td>LVFS (%)</td>
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<td>RAP (mean, mm Hg)</td>
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<td>PCWP (mean, mm Hg)</td>
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<td>LVDP (mm Hg)</td>
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<td>Ejection fraction (%)</td>
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<td>Cardiac index (l/min/m²)</td>
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AV = atrioventricular; LVFS = left ventricular fractional shortening; LASI = left atrial systolic index; LVDD = left ventricular diastolic index; LVDP = left ventricular end-diastolic pressure; LVSI = left ventricular systolic index; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; RASI = right atrial systolic index; RVDD = right ventricular diastolic index; RVDP = right ventricular end-diastolic pressure; VT/VF = ventricular tachyarrhythmia/ventricular fibrillation.

10Paroxysmal and/or chronic atrial fibrillation.

12Echocardiographic measurements of cavity sizes and left ventricular fractional shortening not performed in one patient with IRCM.

Statistically significant difference found as compared with mildly dilated cardiomyopathy (MDCM).
was opened and visual and photographic descriptions of the interior of the ventricles were made. The presence of thrombi and endocardial fibrosis was noted. The extent of endocardial fibrosis was analyzed in the three ventricular portions (inflow, outflow, and trabeculated area) and graded from 0 (no fibrosis found) to 3 (fibrosis present in all three ventricular portions).

Light microscopy. After fixation, sections were taken from the left and right ventricles and interventricular septum. These sections were embedded in paraffin, sectioned at 4 to 6 μm thickness, stained routinely with hematoxylin and eosin for cellular and nuclear morphologic examination, and stained with Masson’s trichrome for evaluation of fibrous tissue. The degree of myocyte hypertrophy was measured at a level that included the myocyte nucleus, in approximately 100 myocytes in random fields with a micrometer scale built into the microscope eyepiece. A mean myocyte width of less than 30 μm, between 30 and 50 μm, and greater than 50 μm was estimated for each sample. On hematoxylin and eosin sections, the myocyte nuclei were estimated visually for size, hyperchromaticity, and bizarre shape as compared with normal myocytes (figure 1). Fibrosis was assessed as present in a fine pattern or in coarse bands (figure 2). Morphometric estimations were not made.

Electron microscopy. Tissue for ultrastructural evaluation was taken by endomyocardial biopsy from the right ventricular septum just before cardiac transplantation and/or from the beating heart within minutes of being explanted. The tissue fragments were minced to 1 to 3 mm and placed in a cold solution of 2% paraformaldehyde, 2.5% glutaraldehyde, and 0.1M sodium cacodylate buffer for fixation. The samples were then postfixed in 2% osmium tetroxide and stained with uranyl acetate en bloc. After dehydration and infiltration, in LX epoxy resin, thin sections were cut on an LKB III ultramicrotome, stained with lead citrate, and screened with a Phillips 201 electron microscope. At the ultrastructural level, myocyte hypertrophy and nuclear configuration were assessed and compared with normal (figure 3). Myofibrillar loss was assessed at both the 1 μm (thick plastic) sections as well as by ultrastructural examination of the tissue. Myofibrillar loss was assessed as partial (figure 4, A) or total (figure 4, B). All available tissue was screened (never fewer than five blocks) and electron micrographs were made of all the myocytes showing myofibrillar loss. Severe and diffuse myofibrillar loss (more than 20% of all the cells in five plastic blocks) was graded as 3+, many affected myocytes (10% to 15% of all myocytes in five plastic blocks) were graded 2+, and less than 10% of all myocytes affected in five plastic blocks was graded as 1+, similar to techniques used in grading anthracycline cardiotoxicity.13

Statistical analysis was performed by analysis of variance, chi square, and the two-tailed Student t test for equal and unequal variances where indicated.

Results

Some of the clinical and laboratory findings are summarized in table 1. All patients suffered from symptoms of congestive heart failure (class IV NYHA) and were free of systemic diseases, as required by the cardiac transplantation protocol.14 Symptoms of congestive heart failure occurred 2 months postpartum in a 28-year-old patient with MDCM. None of the patients

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**FIGURE 1.** A, Normal myocardium showing the normal width (arrows) of the myocytes, with normal shape and size of the nuclei (N). B, Myocardium showing myocyte hypertrophy (arrows), with large hyperchromic nuclei (N) and coarse interstitial fibrosis (F) from a patient with end-stage DCM. (Hematoxylin and eosin, original magnification × 320 [both panels].)
had a previous history of arterial hypertension or alcohol abuse. In all six patients with positive family history, the siblings suffered from typical DCM, although four of these six propositi had MDCM.

The physical findings were similar in the three groups except for the apical impulse, which was markedly displaced in patients with DCM. Left atrial lift was found in two patients with DCM. A third or fourth heart sound was present in all patients and a systolic murmur was found in 14 of 17 patients in whom a specific record was made of this finding.

The electrocardiogram showed nonspecific findings in all three groups of patients: ST-T wave changes, left ventricular hypertrophy, and left or bialtrial enlargement. Arrhythmias and conduction disturbances were found in all three groups of patients. Sustained ventricular tachycardia was documented in 10 of the 19 patients (52%), whereas ventricular fibrillation needing cardiopulmonary resuscitation was present in two of five patients with MDCM.

The preoperative chest roentgenograms were not available in all patients so we reviewed the original radiologists’ readings. These reports noted congestive heart failure and varying degrees of cardiac enlargement in all patients with MDCM and DCM. Mild cardiomegaly was read in three of the four patients with IRCM, and the fourth patient’s results were variably interpreted (see figure 5).

M mode and two-dimensional echocardiographic recordings were not available in one patient with IRCM. At the time of echocardiographic evaluation, six patients had atrial fibrillation and four patients had implanted ventricular pacemakers. The size of cardiac chambers and other data are summarized in table 1. Patients with MDCM and DCM showed globular hearts with preponderant left ventricular dilatation, whereas in patients with IRCM only dilatation of the atria was found. A left atrial/left ventricular diameter ratio was less than 0.8 in all patients with MDCM and DCM and was 1.0 or greater in all patients with IRCM. The percent systolic thickening of the interventricular septum was significantly higher in patients with IRCM (30.3 ± 12.0%) than in those with MDCM (2.5 ± 2.0%) or DCM (2.0 ± 0.8%; p < .001). The mitral valve E-point septal separation index[13] was normal in only one patient with IRCM, who had a 55% angiographic ejection fraction. Segmental wall motion analysis by both echocardiography and angiography dem-

FIGURE 2. A, Section of myocardium from a patient with IRCM showing fine perimyocytic fibrosis (arrows, darker areas). B, Section from a patient with DCM showing a coarse fibrosis (arrows, bracket, F). (Both panels Masson’s trichrome, original magnification × 100).
Figure 3. A. Electron micrograph showing normal myocyte width (arrows) and normal nucleus (N). B. Section from a patient with DCM showing a hypertrophied myocyte (edges beyond the border of this field) with a large nucleus (N). (Both panels original magnification × 4500.)

Figure 4. A. Electron micrograph showing a myocyte from a patient with MDCM with only partial myofibrillar loss (arrows). (Original magnification × 4000). B. Myocyte (M) from a patient with DCM with severe, almost total, myofibrillar loss (represented by the pale area). Only peripheral Z-bands (large arrows) remain. See text for explanation of grading. C = capillary; m = mitochondria. (Original magnification × 6500.)
PATHOPHYSIOLOGY AND NATURAL HISTORY—CARDIOMYOPATHY

FIGURE 5. Longitudinally sectioned cardiac specimens removed at transplantation, fixed in the physiologic shape (see text), and photographed at equal scale from our patients with IRCM (A), MDCM (B), and DCM (C). The specimen in panel A is the smallest heart in the series, but the shape and size of the specimens in panels B and C are typical of their respective categories. Note the apical thrombi (Th) in the hearts in panels B and C. The majority of the atria are absent because of our surgical technique of transplantation. apm = anterolateral papillary muscle; laa = left atrial appendage; LV = left ventricle; RV = right ventricle.

onstated diffuse mild-to-moderate hypokinesis in patients with IRCM, whereas the patients with MDCM and DCM had severe hypokinesis or akinesis.

Hemodynamic findings also are summarized in table 1. All patients had increased end-diastolic pressure, but a square root sign and equalization of right and left ventricular diastolic pressures were present only in patients with IRCM. The pulmonary arterial pressures and pulmonic and systemic vascular resistances were similar in the three groups of patients. Mitral regurgitation was present in 14 patients; its degree was mild to moderate in those IRCM and MDCM and mild to severe in those with DCM.

Pathologic findings are summarized in table 2 and

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<td>Myofibrillar loss</td>
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LVW = left ventricular wall; RVW = right ventricular wall.
AMacroscopic evaluation not performed in one patient with IRCM.
BFor types of changes, see text.
CStatistically significant difference as compared with MDCM.
Figures 1 to 5. Macroscopic evaluation of the heart specimens showed increased interventricular wall thickness in all patients with IRCM examined, three of five with MDCM, and six of 10 with DCM. Patchy or diffuse left ventricular endocardial fibrosis was present in all patients. Endocardial fibrosis scores were similar in patients with IRCM (1.67 ± 0.58) and MDCM (1.2 ± 0.5) (see Methods). The extent of fibrosis in patients with DCM (2.4 ± 0.3) was significantly higher than that found in patients with IRCM (p < .05) or MDCM (p < .001). Right ventricular endocardial fibrosis was found in all patients with IRCM but in only two of five with MDCM and three of 10 with DCM. When present, the fibrosis was patchy in patients with MDCM and DCM and more diffuse in those with IRCM. Pathologic pericardial thickening was not found in any of the patients. Light microscopic assessment of endomyocardial biopsy specimens showed similar findings in the three groups of patients. All patients had myocyte hypertrophy (mostly in the range of 30 to 50 μm), bizarre-shaped nuclei, and hyperchromatism (figure 1, B). Fine, perimyocytic fibrosis (figure 2, A) was found in all patients with IRCM and MDCM and in eight of 10 with DCM. Coarse interstitial fibrosis (figures 1, B, and 2, B) was present in the remaining two patients with DCM. Coarse fibrosis was found in addition to the fine fibrosis in one patient with IRCM and two with MDCM.

Electron microscopy showed myocyte hypertrophy in all patients (figure 3, B). Myofibrillar loss was not detected in any patient with IRCM and in only one with MDCM. Four of the five patients with MDCM showed partial myofibrillar loss (graded +1, or mild form of cardiomyopathy) (figure 4, A). Five of 10 patients with DCM showed predominantly partial myofibrillar loss (graded +2, or moderate form of cardiomyopathy) and the other five had predominantly total myofibrillar loss (graded +3, or severe form of cardiomyopathy) (figure 4, B). Compared with MDCM, the degree of myofibrillar loss was significantly higher in patients with DCM (p < .001).

Discussion

We have described five patients in whom clinical, hemodynamic, and morphologic features typical of DCM occurred in the absence of significant ventricular dilatation (10% to 15% above normal range corrected for body surface area). In describing these patients we have used the term MDCM based on the findings discussed below.

Characteristic features. The major findings in patients with MDCM were: (1) severe clinical congestive heart failure (class IV NYHA), (2) mild left ventricular dilatation associated with similar or lesser degree of enlargement of the other cardiac chambers (globular heart), (3) lack of the square root sign or diastolic pressure equalization and presence of diffusely poor left ventricular contractile motion (ejection fraction 12% to 19%), and (4) nonspecific changes on light microscopic examination and only partial myofibrillar loss documented in the hearts of four of five patients examined by electron microscopy. The groups with MDCM with DCM could not be well segregated by most of the variables included in tables 1 and 2. However, the degree of myofibrillar loss was greater (p < .001) in patients with DCM. Left ventricular endocardial fibrosis was present in all patients with DCM and MDCM, but it was scored as more extensive in patients with DCM as compared to those with MDCM (p < .001) or with IRCM (p < .05). Some clinical, hemodynamic, and morphologic criteria showed significant differences between patients with MDCM and those with IRCM. Patients with IRCM showed a longer symptomatic period, smaller (normal sized) and only mild-to-moderately hypokontractile left ventricles, atrial dilatation, restrictive hemodynamic pattern, more extensive right ventricular endocardial fibrosis, and lack of myofibrillar loss. In contrast to patients with MDCM, none of those with IRCM and only two of 10 with DCM had a positive family history of cardiomyopathy.

Restrictive or congestive cardiomyopathy? Congestive cardiomyopathy may represent the “final common path of many differing conditions that insult the ventricular myocardium.” Therefore it is debatable whether MDCM represents one of the final stages of IRCM. This hypothesis cannot be discarded with certainty. Given the rarity of IRCM, very little is known about the natural history. The small number of cases reported in the literature and our four cases seem to suggest that patients with end-stage IRCM usually retain the characteristic restrictive hemodynamic pattern with or without associated impairment of left ventricular contractility. Tei et al. recently described a type of “minimally dilated cardiomyopathy” of alcoholic etiology, in which severe decrease in left ventricular contractility was associated with typical restrictive hemodynamics. Until more data are accumulated about the natural history of IRCM, the inclusion of our patients among other “atypical” types of congestive cardiomyopathy seems justified.

Correlation between length of survival and degree of ventricular dilatation. Most previous studies reported a negative correlation or inverse relationship between the
degree of ventricular dilatation and length of survival of patients with congestive cardiomyopathy, but some failed to find such a correlation.  

Benjamin et al. examined the hearts of 30 patients with DCM at necropsy. The authors state that all hearts had “biventricular enlargement,” although left ventricular diameters ranged 3.5 to 8.0 cm. The degree of left ventricular dilatation was similar in short- and long-term survivors, but long-term survivors had more hypertrophy in proportion to dilatation. Two-thirds of these patients died from causes other than congestive heart failure. Roberts and Ferrans also noted among patients with dilated cardiomyopathy that “some have relatively thick ventricular walls and only mildly dilated cavities.” Because the attention in these previous studies was not focused specifically on patients with mildly dilated ventricles, the degree of functional impairment, hemodynamic findings, and cause of death were not specified.

The value and limitations of pathologic evaluation. This study supports previous observations attesting to the lack of specificity of pathologic findings in patients with DCM and IRCM and the lack of correlation between the degree of hemodynamic impairment and extent of pathologic changes. Except for size and individual heart weight, inspection of the removed hearts and light microscopic examination did not reveal major differences among these different types of cardiomyopathy. Findings described in patients with IRCM, such as increased wall thickness and fine endocardial and interstitial fibrosis, also were documented in patients with mildly or grossly dilated congestive cardiomyopathy. The presence of myofibrillar loss in patients with congestive cardiomyopathy and its absence, even in advanced forms of IRCM, suggest a correlation between ventricular dilatation and myofibrillar loss. This finding can be considered an interesting preliminary observation that needs future confirmation. Evaluation at the structural and ultrastructural levels are important, however, to exclude specific etiologies in patients with restrictive and congestive cardiomyopathy.

Conclusions. Congestive cardiomyopathy is an “enigmatic disease” in which, usually, “the size of the left ventricular cavity appears to be roughly proportional to the severity and duration of symptomatic congestive heart failure.” We call attention to a group of patients with end-stage heart disease, not an “early” form of cardiomyopathy, whose hearts are only mildly dilated and who display nonrestrictive hemodynamics. Such patients either have not been noted or have been given only passing acknowledgment in prior series.

The ultrastructural features in these cases are interesting, and there is an intriguing trend toward finding a family member with DCM.

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