Spontaneous hemodynamic improvement or stabilization and associated biopsy findings in patients with congestive cardiomyopathy

HANS R. FIGULLA, M.D., GÜNTHER RAHLF, M.D., MICHAEL NIEGER, M.D., HERIBERT LUIG, PH.D., AND HEINRICH KREUZER, M.D.

ABSTRACT The hemodynamic courses of 56 patients with congestive cardiomyopathy (CCM) were investigated. Fourteen patients died within 24 months after diagnosis. The hemodynamic courses of the remaining 42 patients were investigated in subsequent examinations by determination of left ventricular ejection fraction (LVEF), mean pulmonary arterial pressure at maximal workload, and peak systolic pressure/end-systolic volume index. During the study interval of 32.2 ± 20.0 months the conditions of 20 patients (48%) deteriorated, according to their hemodynamic status, and at least five of these died of terminal heart failure. Surprisingly, the conditions of 22 patients (52%) improved or stabilized. One of these died of leukemia. Seven patients in the latter group with initial LVEFs of 0.30 or less experienced an average increase from 0.22 to 0.51. Retrospectively consideration of age, alcohol intake, exercise capacity, and hemodynamic status were not helpful in predicting the course of the disease. In 38 patients endomyocardial biopsy samples could be obtained at the time of diagnosis. Reduced myofibril volume fraction (<60%) had prognostic significance for both hemodynamic deterioration and death (sensitivity 23/24 = 96%), while 14 of 15 patients whose conditions improved or stabilized had a myofibril volume fraction of 60% or more (specificity 14/15 or 93%, p < .002). A relationship between hemodynamic status and the myofibril volume fraction could not be found. Individual patients with CCM differ significantly with respect to course of the disease. A distinct separation of the patients by means of morphologic criteria is possible. This makes it more likely that the pathogenesis of the disease is not unique.

It is the purpose of this study to investigate the hemodynamic course of CCM reliably by use of semi-invasive methods in patients at rest and during exercise. We found that individual patients with CCM differ significantly with respect to hemodynamic course. This enabled us to investigate prognostic features.

Methods

Study protocol. The following diagnostic procedures were performed on entry of patients into the study. Left heart catheterization was performed in all patients and 38 patients underwent cardiac biopsy. Swan-Ganz thermodilution catheterization and simultaneous gated blood pool (GBP) scanning was also performed in 23 patients at rest and during exercise.

Reexaminations included Swan-Ganz catheterization/GBP scanning in all patients while at rest and during exercise. Also obtained in each patient at entry and on reexamination were a clinical workup, standard laboratory tests, a chest x-ray, an echocardiogram, and an electrocardiogram.

Techniques
Left heart catheterization. Left heart catheterization was performed according to the Sones technique. Biplane cineventriculograms and coronary angiograms were obtained according to standard techniques. The end-systolic and end-diastolic volume indexes (ESVI, EDVI) and the left ventricular ejection fraction (LVEF) during a normal cardiac cycle were evaluated according to the biplane area-length method of Dodge et al.20 Peak systolic pressure (PSP) and end-systolic pressure of the left ventricle were recorded through the fluid-filled lumen of the catheter. The ratio of PSP/ESVI was determined and used as an index of left ventricular contractility 20-22. Swan-Ganz catheterization. Swan-Ganz catheterization was performed through a right cubital vein with a No. 7F-Swan-Ganz thermodilution catheter. The mean of three consecutive measurements of cardiac output was considered to be representative. Mean pulmonary arterial pressure (PAP) and mean pulmonary wedge pressure (PWP) were measured through the fluid-filled catheter. A cuff sphygmomanometer was used at the left brachial artery to determine PSP at the point where two consecutive first Korotkoff sounds appeared.

Gated blood pool (GBP) scanning. The equilibrium GBP scanning technique, without background correction, of Luig et al.21 was used. Results obtained with this technique demonstrated a very good correlation to our biplane cineangiographic results (r = .97), with the regression line LVEFGBP = 0.92 LVEFAngio + 0.07. Thus, the error in the determination of LVEFGBP was in the range of 0.008 to 0.042 (LVEFAngio = 0.20 to 0.60). The applied GBP scanning technique had a time resolution of 1 msec and was performed in list mode. By evaluating the scintigraphic data forward and backward in time relative to each central R wave electrocardiographic signal, the whole cardiac cycle could be described. By a two-parameter RR interval selection, patients with arrhythmias could be evaluated reliably. Human red blood cells labeled in vitro with 99mTc (10 mCi) were used as the imaging agent. A convergent collimator was used in the left lateral position (40 to 50 degrees) with additional cranial angulation (10 to 20 degrees) to the sagittal axis.

End-systolic volume (ESV) was determined with the formula

\[
ESV = \frac{SV}{LVEF_{GBP}} - SV
\]

where SV = stroke volume. Thus, PSP/ESVI could be determined either at the time of entry into the study or at reexamination. Since mitral regurgitation lowers the measured forward stroke volume, the PSP/ESVI ratio does decrease somewhat. Therefore, only PSP/ESVI changes exceeding 0.30 were considered significant.

Exercise testing. Exercise stress tests were performed by patients in the supine position on a electrical braked bicycle ergometer. The workload began at 153 kilopond-meters (kpm)/min (25 W) or 306 kpm/min (50 W), depending on the clinical status of the patient, and was increased in increments of 153 kpm/min or 306 kpm/min. Each level of exercise was sustained for 5 min unless one of the following end points was reached: dyspnea, fatigue, or PAP of greater than 50 mm Hg. Data acquisition for GBP scanning was performed at between 2.5 and 5 min at each increment, while PAP, PWP, heart rate, and cardiac output were measured at between 3 and 5 min.

Cardiac biopsy. Biopsy samples from the right ventricular septum (n = 20) or the left ventricular inferior wall segment (n = 18) were obtained with King’s College biopsome. Tissue samples were fixed by immersion with a 1.5% glutaraldehyde and 1.5% paraformaldehyde mixture in 0.2 mol/liter cacodylate buffer, postfixed in OSO4, and embedded in araldite. Light microscopic investigations including morphometry were performed on 0.3 μm semithin sections (four to eight per patient) that were stained with alkaline toluidine blue or alkaline toluidine blue and 3% paraphenylenediamine. Ultra thin sections were stained according to standard techniques.

The morphometric technique used was as follows. At a magnification of 160 x the volume fraction of the interstitial structured tissue was determined. For this purpose a area with 36 test points was projected on each section and the volume fraction was measured according to the point-counting methods of Weibel.24 At least four random test areas with 36 test points per area were used in three randomly chosen sections. Test points superimposed on interstitial structured tissue were related to all other points and this relationship was taken as the volume fraction of interstitial structured tissue.

The volume fraction of the myofibrils was evaluated by means of the same technique with oil immersion and phase contrast at a magnification of 1000 x (figure 1). Light-microscopic values for myofibril volume fraction have been shown by Mall et al.25 to correlate closely with electron microscopic values. Since light microscopy allows evaluation of a larger area of the biopsied tissue, this method was preferred to electron microscopy. According to Mall et al.25 the sampling variability in light microscopy is small, especially in the determination of the myofibril volume fraction and fiber diameter. Unfortunately the results of morphometric analysis in tissue obtained at biopsy cannot be compared with results in tissue obtained at autopsy, since autolysis of the latter effects the morphometric results. Mitochondrial and nucleus swelling reduces the relative tissue volume fraction of the myofibrils.

Fiber diameters of the myocardial cells were measured from 50 to 100 cross or oblique sections at a magnification of 420 x (oblique sections = short diameter of the section profile; cross sections = diameter of the cell at the level of the nucleus). All measurements were made without knowledge of the clinical data.

Study patients
Patient selection. Fifty-six patients were included in this study. Each demonstrated latent or manifest heart failure, arrhythmias, or left bundle branch block of unknown origin. A precise workup of the patients could not uncover an illness superimposed on the heart disease. Invasive diagnostic procedures demonstrated CCM according to the definition of the WHO/ISFC.26 The conditions of all patients included in this study were diagnosed between January 1979 and March 1983, and all patients were subsequently reinvestigated or died before reinvestigation.
of the heart muscle were not considered to have CCM and therefore were excluded from our study. The reinvestigation procedure was approved by the hospital ethical committee. Written informed consent of all patients was obtained for all left heart catheterization and biopsy procedures.

The study group consisted of 45 men (80%) and 11 women (20%). The mean age was 47.1 ± 9.7 (range 16 to 65) years. Severity of heart failure was classified according to the NYHA definition. Fourteen patients died within the first 24 months after diagnosis. The remaining 42 could be reexamined; six of these died after the reexamination.

Classification of patients. Patients were considered to have deteriorating CCM if in the time between the two examinations changes in two of three of the following parameters of cardiac performance exceeded the level of significance: LVEF (decrease > | 0.05 |), PAP<sub>max</sub> (increase > | 3 | mm Hg), and PSP/ESVI (decrease > | 0.30 | mm Hg·ml<sup>-1</sup>·m<sup>2</sup>).

Alcohol intake was graded on a scale of 0 to 3 (0 = no alcohol intake; + = alcohol on very rare occasions; ++ = <50 g alcohol per day; +++ = ≥50 g alcohol per day).

Therapy. The patients were treated, according to the degree of heart failure, with digitalis, diuretics, and vasodilators. The antiarrhythmics given were mexiletine, propafenone, and amiodarone. Dicumarol was given to 24 patients as an oral anticoagulant. No cardiac medications other than antiarrhythmics were given less than 16 hr before examinations.

Statistical analysis. Differences in hemodynamic courses or among groups were tested with the Wilcoxon test, since normal distribution could not be presumed because of the nonlinearity of the parameters. Based on the null hypothesis, which states that there is no difference between the groups or results, two-tailed tests were used. Probability values ≥0.05 were considered to indicate nonsignificant differences. If more than two groups were compared univariate analysis of variance was used. In the case of discrete variates fourfold tables were used in combination with the exact Fisher or chi-square test. In table 4 Student’s t test was used, since normal distribution could be presumed. Correlation coefficients were obtained with a standard formula.

Results

Hemodynamic course and survival. The hemodynamic courses of patients with CCM were determined in this study by means of the parameters of LVEF, PAP<sub>max</sub>, and PSP/ESVI. During the follow-up period of 32.2 ± 20.0 months from the entry examination until the last reexamination three groups of patients emerged (figure 2). (1) Fourteen patients died before reexamination or within 2 years after the initial diagnosis (group 1). (2)
FIGURE 3. Cumulative survival rate for 56 patients with CCM over 49 months. AML = acute myeloid leukemia.

In 20 patients left ventricular function deteriorated (group 2). Five of these later died as a result of increasing heart failure, and one patient underwent a heart transplant. (3) In 22 patients there was no hemodynamic deterioration (group 3), but one of these died of acute myeloid leukemia.

In figure 3 the curve of the cumulative survival rate is shown. The average yearly mortality rate amounted to 9%. Forty-two patients could be reexamined. In group 3 LVEF increased, on the average, from 0.386 to 0.651, PAP_max decreased from 38.6 to 28.9 mm Hg, and PSP/ESVI increased from 1.94 to 2.88 mm Hg·ml⁻¹·m⁻². In group 2, LVEF decreased from 0.392 to 0.282, PAP_max increased from 39.2 to 53.2 mm Hg, and PSP/ESVI decreased from 2.41 to 1.38 mm Hg·ml⁻¹·m⁻² (table 1). The individual changes and the mean parameter values in both groups are shown in figure 4. The mean hemodynamic changes in each of the 42 patients were nonsignificant.

Twenty-two patients in the study group were reexamined several times. In figure 5 the LVEFs of these patients in relation to time are shown. In most of the cases there was either a monotonic increase or decrease in the LVEF over time. Significant fluctuations in the LVEF, which would indicate a greater variability in the individual patient’s contractility, were rare (three instances).

Table 2 represents a retrospective comparison of the historical and clinical features of the patients in groups 1, 2, and 3. Groups 1 and 2 include the patients with progressive CCM. A comparison of these two groups with the group 3 patients showed they did not differ significantly with respect to the occurrence of left bundle branch block, age, NYHA classification, exercise tolerance, alcohol intake, duration of prediagnostic symptoms, or heart dimension as determined by chest x-ray and echocardiography.

In table 3 the hemodynamic characteristics of the patients are compared. Again no significant difference at the time of diagnosis could be detected, a finding that might be of prognostic significance.

In figure 6 data on the hemodynamic courses of 18 patients with LVEFs of 0.30 or less at the time of diagnosis are illustrated. Eleven of these deteriorated or died, while seven improved. Although 34 of the 56 patients studied died or their conditions deteriorated,

### TABLE 1

<table>
<thead>
<tr>
<th>LVEF</th>
<th>PAP_max (mm Hg)</th>
<th>PSP/ESVI (mm Hg · ml⁻¹ · m⁻²)</th>
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<tbody>
<tr>
<td><em>EX₀</em></td>
<td><em>EX₆</em></td>
<td>Mean change</td>
</tr>
<tr>
<td>0.392</td>
<td>0.282</td>
<td>-0.110</td>
</tr>
<tr>
<td>0.083</td>
<td>0.102</td>
<td>0.095</td>
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</table>

<table>
<thead>
<tr>
<th>Group 2</th>
<th>(n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>0.392</td>
<td>0.083</td>
</tr>
<tr>
<td>0.083</td>
<td>0.102</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group 3</th>
<th>(n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>0.386</td>
<td>0.139</td>
</tr>
<tr>
<td>0.130</td>
<td>0.131</td>
</tr>
</tbody>
</table>

p value:

- group 3 vs group 2: NS⁺⁺, .001⁺⁺, NS⁺⁺⁺, .001⁺⁺⁺, NS⁺⁺⁺⁺, .001⁺⁺⁺⁺

**EX₀** = examination at the time of entry into the study; **EX₆** = time of last reexamination.

⁺By paired Wilcoxon range test; ⁺by unpaired Wilcoxon range test; ⁺⁺by Student’s t test.
only 11 of these had LVEFs of 0.30 or less at the time of diagnosis.

LVEF of 0.30 or less used as an indication of deterioration had a sensitivity of only 11/34 (29%). The specificity was 15/22 (68%), and therefore the predictive value was 11/18 (61%; \( \chi^2 = 1.64; p > .1 \)). Therefore, the deduction of a prognosis from the degree of left ventricular dysfunction at the time of diagnosis is neither sensitive nor specific.

Results of biopsies. In 38 patients endomyocardial biopsy samples could be obtained at the entrance examination. None of the samples showed any evidence of myocarditis or classified myocardial diseases. In 33 samples evaluation of the volume fraction of myofibrils could be performed by means of histologic morphometry and 18 of these showed myofibril volume fractions of less than 60%, while 15 showed myofibril fractions of 60% or greater.

Data on the hemodynamic courses of the surviving patients with myofibril volume fractions of 60% or greater (\( n = 25 \)) and with myofibril volume fractions of less than 60% are illustrated in figure 7. Compared with LVEF and PSP/ESVI at the time of diagnosis, there was a significant increase in these parameters in the patients with volume fractions of 60% or greater, and a decrease in these parameters in patients in the less than 60% group within 31.2 ± 16.0 months. The change in \( \Delta \text{PAP}_{\text{max}} \) was not significant in either group. However, nine of 10 patients whose conditions deteriorated had myofibril volume fractions of less than 60% (sensitivity 9/10 or 90%). Fourteen of 15 patients whose conditions improved or stabilized had myofibril volume fractions of 60% or greater (specificity 14/15 or 93%; \( p < .002 \)).

The myofibril volume fractions of all patients who died before the first reexamination were less than 60% (\( n = 8 \)). Thus, a myofibril volume fraction of less than 60% appears to be an appropriate prognostic index of hemodynamic deterioration or death. The probability that a patient with CCM and a myofibril volume fraction in this range will deteriorate or die is 93% (prevalence = 0.6).

Myocyte fiber diameter could not be related to the course of the disease. The volume fraction of the interstitial structured tissue was elevated in the case of hemodynamic deterioration, but this difference barely reached the level of significance (table 4).

Although patients in groups 1, 2, and 3 differed with respect to the amount of myofibrils present, no major distinctions could be made in their clinical or hemodynamic status at the time of the initial diagnosis. When the correlations between the myofibril volume fraction and LVEF or PSP/ESVI were plotted (figure 8), the correlation was poor (\( r = .25, r = .29 \)).

**FIGURE 4.** The changes in LVEF, \( \Delta \text{PAP}_{\text{max}} \), and PSP/ESVI over the study interval of 33.2 ± 20.0 months. If there was significant deterioration of two of the three parameters of cardiac performance the patient was classified as having progressive disease (DET; 20 patients) and if not, he or she was classified as having the nonprogressive form of the disease (NOT; 22 patients). On the average, LVEF increased in the latter group by 0.165, PSP/ESVI increased by 0.96 mm Hg·mL\(^{-1}\)·m\(^{-2}\), and \( \Delta \text{PAP}_{\text{max}} \) decreased by 11 mm Hg, while in the former group LVEF decreased by 0.110, PSP/ESVI decreased by 1.14 mm Hg·mL\(^{-1}\)·m\(^{-2}\), and \( \Delta \text{PAP}_{\text{max}} \) increased by 14 mm Hg. \( \Delta \) LVEF = change in LVEF at rest over the study interval; \( \Delta \text{PAP}_{\text{max}} \) = change in \( \text{PAP}_{\text{max}} \) over the study interval; \( \Delta \text{PSP/ESVI} \) = change in this index at rest over the study interval.

**FIGURE 5.** The course of the LVEF in the 22 patients reexamined several times. Note that the within-patient trend in the LVEF course was the same at subsequent examinations.
### TABLE 2
Historical and clinical features of the patients at the time of diagnosis

<table>
<thead>
<tr>
<th>Group 1</th>
<th>NYHA class (n = 14)</th>
<th>Alcohol intake (n in each class)</th>
<th>Age (yr)</th>
<th>W_max (kpm/min)</th>
<th>X-ray/CT ratio</th>
<th>Echo. (mm)</th>
<th>Duration of symptoms (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>LBBB</td>
<td>1, 2;</td>
<td>0, 2;</td>
<td>48.4 ± 13.1</td>
<td>0.580 ± 0.060</td>
<td>69 ± 8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 0;</td>
<td>+, 5;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>III, 10;</td>
<td>+, +, 0;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IV, 2</td>
<td>+++, 6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>(n = 20)</td>
<td>18</td>
<td>7</td>
<td>1, 2;</td>
<td>0, 3;</td>
<td>47.5 ± 6.5</td>
<td>375 ± 126</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>II, 8;</td>
<td>+, 6;</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>III, 9;</td>
<td>+++, 4;</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>IV, 1</td>
<td>+++, 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>(n = 22)</td>
<td>16</td>
<td>5</td>
<td>1, 5;</td>
<td>0, 4;</td>
<td>46.9 ± 10.3</td>
<td>405 ± 195</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>II, 10;</td>
<td>+, 4;</td>
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<td></td>
<td></td>
<td></td>
<td>III, 5;</td>
<td>+++, 7;</td>
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<td></td>
<td></td>
<td></td>
<td>IV, 2</td>
<td>+++, 7</td>
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**p value, group 3 vs group 1 and 2**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>NS*, NS*, NS*, NS*, NS*, NS*</th>
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**p value, group 3 vs group 2**

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**Plus or minus** values are mean ± SD.

LBBB = left bundle branch block; W_max = maximal workload (kpm/min); CT ratio = cardiothoracic ratio; Echo. = left ventricular end-diastolic diameter (mm) by means of echocardiography.

AUnits are arbitrary units grading intake from 0 to +++. 

BBy chi-square test; C by Wilcoxon test.

### TABLE 3
Hemodynamic features at the time of diagnosis

<table>
<thead>
<tr>
<th>HR (min⁻¹)</th>
<th>PSP (mm Hg)</th>
<th>LVEDVI (ml · m⁻²)</th>
<th>LVESVI (ml · m⁻²)</th>
<th>MR</th>
<th>LVEF</th>
<th>PAP_max (mm Hg)</th>
<th>PSP/ESVI (mm Hg ml⁻¹ · m⁻²)</th>
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<tbody>
<tr>
<td>Group 1 (n = 14)</td>
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</tr>
<tr>
<td>Mean</td>
<td>107</td>
<td>102</td>
<td>144</td>
<td>111</td>
<td>9</td>
<td>0.248</td>
<td>33.6</td>
</tr>
<tr>
<td>SD</td>
<td>26</td>
<td>18</td>
<td>61</td>
<td>54</td>
<td>13</td>
<td>0.113</td>
<td>8.3</td>
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<tr>
<td>n</td>
<td>14</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Group 2 (n = 20)</td>
<td></td>
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</tr>
<tr>
<td>Mean</td>
<td>85</td>
<td>117</td>
<td>107</td>
<td>67</td>
<td>5</td>
<td>0.392</td>
<td>40.4</td>
</tr>
<tr>
<td>SD</td>
<td>25</td>
<td>18</td>
<td>42</td>
<td>29</td>
<td>10</td>
<td>0.081</td>
<td>9.4</td>
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<tr>
<td>n</td>
<td>20</td>
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<td>20</td>
<td>20</td>
<td>10</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Group 3 (n = 22)</td>
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<tr>
<td>Mean</td>
<td>81</td>
<td>116</td>
<td>119</td>
<td>77</td>
<td>12</td>
<td>0.386</td>
<td>38.8</td>
</tr>
<tr>
<td>SD</td>
<td>24</td>
<td>22</td>
<td>39</td>
<td>40</td>
<td>18</td>
<td>0.139</td>
<td>9.0</td>
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<td>21</td>
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<td>18</td>
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</table>

**p value, group 3 vs group 2**

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>NS*, NS*, NS*, NS*, NS*, NS*</th>
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<tbody>
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**p value, group 3 vs groups 1 and 2**

<table>
<thead>
<tr>
<th>Group 1</th>
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<th>Group 3</th>
<th>NS*, NS*, NS*, NS*, NS*, NS*</th>
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**HR = heart rate; PSP = peak systolic pressure; LVEDVI = left ventricular end-diastolic volume index; LVESVI = left ventricular end-systolic volume index; MR = mitral regurgitation.**

*Fourfold table, Fisher test.

By Wilcoxon test.
FIGURE 6. The course of LVEF over time in 18 patients with initial LVEFs of 0.30 or less is shown. In 11 patients deterioration or death ensued, and seven patients improved.

Discussion

The course of CCM. In this study the course of illness of 56 patients with CCM was investigated. Left ventricular function was determined at subsequent examinations at rest and during exercise by means of ejection phase (LVEF) and pressure indexes (PAP) and the PSP/ESVI, the last of which was interpolated to zero and is said to be a sensitive parameter of left ventricular contractility and to be especially sensitive in the LVEF range above 0.50.20-22 These three parameters allowed us to reliably evaluate and define the hemodynamic courses of our patients.

It was the aim of this study to observe the hemodynamic courses of patients with CCM over an extended time period. Consequently patients with minor left ventricular dysfunction were also included in the study

FIGURE 7. Hemodynamic courses, as determined by the parameters LVEF, PAP<sub>max</sub>, and PSP/ESVI in the patients with myofibril volume fractions of less than 60% and those with fractions greater than or equal to 60%. The patients with myofibril volume fractions of less than 60% experienced a significant decrease in LVEF and PSP/ESVI over the study interval, and the opposite was true in patients with myofibril volume fractions of 60% or more. EX<sub>n</sub> = time of diagnosis; EX<sub>x</sub> = time of reexamination.

TABLE 4
Histomorphometric findings in relation to hemodynamic course

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean (μm)</th>
<th>SD</th>
<th>n</th>
<th>Myocytes</th>
<th>Interstitial</th>
<th>Myofibrils</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>19.3</td>
<td>4.1</td>
<td>9</td>
<td>14</td>
<td>46.6</td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td>20.0</td>
<td>3.3</td>
<td>12</td>
<td>25.6</td>
<td>55.2</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>17.2</td>
<td>4.6</td>
<td>16</td>
<td>19.6</td>
<td>64.2</td>
<td></td>
</tr>
</tbody>
</table>

p value, group 3 vs group 2<sup>a</sup> NS <.05 <.001
p value, group 3 vs groups 1 and 2<sup>a</sup> NS NS <.0001

<sup>a</sup>By Student’s t test.

(in particular, those with LVEFs less than 0.55 and EDVIs or ESVIs greater than 100 or 40 ml·m<sup>-2</sup>, respectively). Although the entry criteria permitted inclusion of very “early” cardiomyopathies, two patients with LVEFs greater than 0.50 at the time of diagnosis died from progressive heart failure. The hemodynamic courses (about 61% deteriorated and the mortality rate (9% a year) for our patients are similar to those in other studies,1-3,7,8 so we believe that these entry criteria were appropriate. The hemodynamic courses of individuals differed significantly, allowing us to deduce prognostic parameters.

Most longitudinal studies of CCM attempted to correlate the course of the disease with the cumulative survival rates1,3 or with the hemodynamic findings at rest (mainly chest x-ray) and clinical status.1,3,7,8 Yet to determine hemodynamic status solely by chest x-ray and clinical criteria (NYHA classification) is inadequate. Benge et al.18 showed that 50% of the patients with LVEFs of 0.30 or less at rest exhibited a normal cardiothoracic ratio on chest x-rays and had normal exercise capacity. These latter observations were confirmed by Litchfield et al.,16 who elucidated the mechanisms by which these patients were able to tolerate normal levels of exercise despite severe left ventricular dysfunction. Franciosa et al.17 pointed out that maximal exercise testing was preferable in the grading of symptomatic severity of congestive heart failure.

Since chest x-ray and clinical status alone are inad-
FIGURE 8. Correlation of the myofibril volume fraction (myo) with LVEF (top) and PSP/ESVI (bottom). Note that there is only a poor correlation between the parameters of left ventricular function and myo.

equate methods for determining the hemodynamic status of patients, and survival is not strictly related to the hemodynamic course of the disease, the direct relationship of “hemodynamic course” to prognostic features might be obscured in some studies.

Most longitudinal studies have demonstrated a cumulative death rate of between 5% and 10% per year²⁻⁵ and have stressed the correlation between the severity of hemodynamic manifestations at the time of diagnosis of CCM and the overall death rate. As shown in table 3, the survivors with progressive and those with nonprogressive disease did not differ with respect to hemodynamic features such as heart rate, peak systolic pressure, left ventricular EDVI, left ventricular ESVI, LVEF, and PSP/ESVI at rest. Even in the patient with an LVEF of 0.30 or less tremendous improvement of left ventricular function is possible (figure 6). The predictive value of an LVEF less than or equal to 0.30 for further deterioration or death is only 61% and a relationship between LVEF in this range at the time of diagnosis and deterioration of the condition of the patient does not exist ($\chi^2 = 1.64; p > .1$). Thus, hemodynamic status at the time of diagnosis alone has no prognostic significance.

Twenty-two patients in our study group were reex
amined several times and it appeared that improvements in left ventricular function were sustained (figure 5).

In patients with CCM the prognostic significance of the following variables can be ruled out: age, sex, left bundle branch block, alcohol consumption, heart rate, systolic blood pressure, left ventricular end-diastolic volume, LVEF at rest, PAP, and the index of left ventricular contractility PSP/ESVI (tables 2 and 3).

The prognostic significance of left ventricular hypertrophy, which reduces wall stress,¹²,²⁴ and the significance of levels of plasma catecholamines,²⁹ were not investigated.

Myocardial biopsy. In our study we examined 38 biopsy samples. In 33 specimens the volume fraction of the myofibrils could be determined and was found to be significantly reduced in groups 1 and 2 (table 4). The hemodynamic courses of the patients with myofibril volume fractions of less than 60% vs those in patients with fractions of 60% or greater are illustrated in figure 7. A clear separation can be seen. A myofibril volume fraction of less than 60% served as an appropriate prognostic index for hemodynamic deterioration or death in our study group ($p < .002$, sensitivity 90%, specificity 93%).

Other histomorphometric findings in the biopsy samples, such as myocyte fiber diameter and the volume fraction of interstitial structured tissue, could not be related to the course of the disease. Mall et al.,²⁵ found that sampling variability with endomyocardial biopsy was low for determination of fiber diameter and volume fraction of myofibrils when compared with variability in determination of volume fraction of interstitial structured tissue. This leads us to the conclusion that small endomyocardial biopsy samples are highly representative with respect to fiber diameter and myofibril volume fraction and are less representative with respect to interstitial fibrosis. Unfortunately, validation of the histomorphometric biopsy findings cannot be performed ad exitum at autopsy, since autolysis of myocardium will greatly affect the results.

We used light microscopy to determine the volume fraction of myofibrils to reduce the sampling error, which is naturally higher with electron microscopy. A strong correlation between light and electron microscopic findings was demonstrated by Mall et al.,²⁵

The determination of the myofibril volume fraction by light microscopy is only an integrative method, because it cannot be used to distinguish between mitochondrial swelling, mitochondrial accumulation, and degeneration of myofibrils. All of these events can reduce the relative volume fraction of the myofibrils.
The histologic picture of CCM is nonspecific and nonpathognomonic.\textsuperscript{30-32} The results of various studies show that the three diagnostic groups — "ordinary" hypertrophy, hypertrophic cardiomyopathy, and CCM — overlap.\textsuperscript{30-32} The question remains as to whether such nonspecific tissue disorders can be related to hemodynamic performance and the hemodynamic courses of patients. Kuhn et al.\textsuperscript{6} used a morphologic score and demonstrated a higher mortality rate in patients with extended ultrastructural myocardial lesions. Mall et al.\textsuperscript{25} and Kunkel et al.\textsuperscript{32, 34} confirmed the latter results, and they were also able to correlate LVEF with the amount of the myofibril volume fraction. In another study it was found that in patients with aortic stenosis the myofibril volume fraction (contractile mass) correlated with LVEF.\textsuperscript{31} In contrast, Baandrup et al.\textsuperscript{30, 35} could not confirm the relationship between morphologic changes and the functional status of patients or their prognosis. However, these authors did not assess the hemodynamic course by semi-invasive means.

In this study a highly significant relationship between myofibril volume fraction and hemodynamic course was found. Other histologic parameters could not be related to hemodynamic course.

In agreement with the results of Baandrup et al.,\textsuperscript{30, 35} we did not find any correlation between left ventricular function and the myofibril volume fraction (figure 8). Therefore, the possibility that reduced myofibril volume fraction is only a nonspecific phenomena related to reduced left ventricular function could be excluded.

Our results demonstrate that there are two groups of patients with CCM that differ with respect to their hemodynamic courses and morphologic features. This makes it more likely that the pathogenesis of the disease is not unique, and if it is not, the entity CCM can be divided into a progressive and nonprogressive form. Our present findings suggest that temporally depressed left ventricular function of unknown cause and without morphometric expression can exist. Use of experimental therapies suggested for CCM, e.g., \(\beta\)-blocker therapy,\textsuperscript{11, 12, 36} should be restricted to the homogeneous group of patients with reduced myofibrils because spontaneous improvement in the others might interfere with therapeutic effects.

In the future prospective evaluation of the courses of individual patients should be possible by determination of myofibril volume fraction. The prognosis should not be determined from the contractile status. Heart transplants should not be performed in patients with myofibril volume fractions of 60% or more, since the prognosis for these patients is good.

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