Progressive Left Ventricular Dysfunction and Remodeling After Myocardial Infarction
Potential Mechanisms and Early Predictors

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Background. Left ventricular enlargement and the development of chronic heart failure are potent predictors of survival in patients after myocardial infarction. Prospective studies relating progressive ventricular enlargement in individual patients to global and regional cardiac dysfunction and the onset of late chronic heart failure are not available. It was the aim of this study to define the relation between left ventricular dilatation and global and regional cardiac dysfunction and to identify early predictors of enlargement and chronic heart failure in patients after myocardial infarction.

Methods and Results. Left ventricular volumes, regional area shrinkage fraction in 18 predefined sectors (gated single photon emission computed tomography), global ejection fraction, and hemodynamics at rest and during exercise (supine bicycle, 50 W, 4 minutes, Swan-Ganz catheter) were assessed prospectively 4 days, 4 weeks, 6 months, and 1.5 and 3 years after first myocardial infarction. Seventy patients were assigned to groups with progressive, limited, or no dilatation. Patients without dilatation (n = 38) maintained normal volumes and hemodynamics until 3 years. With limited dilatation (n = 18), left ventricular volume increased up to 4 weeks after infarction and stabilized thereafter; depressed stroke volume was restored 4 weeks after infarction and then remained stable at rest. Wedge pressure during exercise, however, progressively increased. With progressive dilatation (n = 14), depressed cardiac and stroke indexes were also restored by 4 weeks but progressively deteriorated thereafter. Area shrinkage fraction as an estimate of regional left ventricular function in normokinetic sectors at 4 days gradually deteriorated during 3 years, but hypokinetic and dyskinetic sectors remained unchanged. Global ejection fraction fell after 1.5 years, whereas right atrial pressure, wedge pressure, and systemic vascular resistance increased. By multivariate analysis, ejection fraction and stroke index at 4 days, ventriculographic infarct size, infarct location, and Thrombolysis in Myocardial Infarction trial grade of infarct artery perfusion were significant predictors of progressive ventricular enlargement and chronic dysfunction.

Conclusions. Almost 26% of patients may develop limited left ventricular dilatation within 4 weeks after first infarction, which helps to restore cardiac index and stroke index at rest and to preserve exercise performance and therefore remains compensatory. A somewhat smaller group (20%) develops progressive structural left ventricular dilatation, which is compensatory at first, then progresses to noncompensatory dilatation, and finally results in severe global left ventricular dysfunction. In these patients, depression of global ejection fraction probably results from impairment of function of initially normally contracting myocardium. Early predictors from multivariate analysis allow identification of patients at high risk for progressive left ventricular dilatation and chronic ventricular dysfunction within 4 weeks after acute infarction. (Circulation 1993;87:755-763)

Key Words • dilatation, ventricular • heart failure • hemodynamics • prognosis

The cumulative incidence of heart failure rises in the years after infarction, and its clinical manifestation is associated with an adverse prognosis.1 Dilatation of the left ventricle may play an important active role in the development of chronic heart failure,2-8 and left ventricular volume is the most powerful predictor of survival in patients with coronary heart disease.9-11 Deterioration of cardiac performance correlates with the degree of dilatation in experimental infarction,3 and left ventricular dilatation precedes deterioration of exercise performance in patients.8 However, the relation of left ventricular dilatation to chronic heart failure is based primarily on indirect evidence and has not been carefully studied in individual patients. Dilatation of infarcted and noninfarcted sections of the left ventricle has been observed.7 The time course and interaction of regional function of noninfarcted and infarcted myocardium and global left ventricular dysfunction have not been assessed in detail. One reason for lack of this information may be the chronicity of the process, which requires an observation time of several years.

Animal experiments have defined myocardial infarct size as a major determinant of left ventricular dilata-
tion, and recent clinical studies have confirmed this observation. Infarct size, prognosis, and ejection fraction are closely related; the latter has been used to select patients prone to ventricular dilatation. In patients, left ventricular dilatation appears to be the result of a long-term interactive process of multiple variables. Their relative importance for dilatation and heart failure has not been assessed, and no prospective criteria are available to identify individual patients who may be at high risk for progressive dilatation and chronic heart failure.

The objectives of the present study were to determine hemodynamic consequences at rest and during exercise of progressive left ventricular dilatation, the time course of regional function of noninfarcted and infarcted myocardium from 4 days until 3 years after infarction, and whether variables that are likely to predict progressive left ventricular dilatation and chronic dysfunction can be identified early after infarction.

Methods

Patient Population and Group Assignment

Acute myocardial infarction was confirmed by ECG and creatine kinase enzymes in 193 patients admitted to our intensive care unit from January 1987 to September 1988. Of these, 99 matched our inclusion criteria, which were age ≤70 years, first infarction, and signed informed consent. Patients with clinical signs of heart failure or cardiogenic shock in the first week after myocardial infarction, unstable angina, life-limiting noncardiac disease, conditions precluding cardiac catheterization or exercise testing, or delayed (>6 days) hospital admission for acute infarction were excluded. Thirteen patients refused to participate in the study. Later, further exclusions were due to reinfarction (four patients) and death before the 3-year assessment (three patients); an additional nine patients did not adhere to the follow-up protocol. Patients received conventional drug therapy according to individual needs, which remained the responsibility of the attending physician. The currently prescribed drug therapy was monitored, and changes were analyzed over time within and between groups. Thrombolytic therapy was administered if not contraindicated according to currently accepted criteria. Patients were categorized according to the individual course of left ventricular end-diastolic volume index (EDVI). Patients in whom EDVI rose (>8% of preceding EDVI) with each subsequent examination were assigned to a group with “progressive dilatation.” Patients with a rise (>8%) of EDVI until 6 months but without further increase thereafter were assigned to a group with “limited dilatation.” A third group consisted of patients without any increase of EDVI beyond 8% from baseline (“no dilatation”).

Radionuclide Studies

Gated blood pool radionuclide ventriculograms were sequentially obtained in each patient as described in detail elsewhere. In brief, erythrocytes were labeled in vivo by 15–20 mCi 99mTc pertechnetate. The angiograms were acquired by a rotating camera (gated single photon emission computerized tomography [gated SPECT]) in 32 projections or 180°, respectively, from the right anterior oblique to the left posterior (280–300°/100–120°) view. Radionuclide counts were collected for 40 seconds per projection and cardiac cycle gated into eight frames triggered by ECG. Coronal tomograms in 90° position to the long axis of the left ventricle were reconstructed, which served to calculate left ventricular volumes by Simpson’s rule. Automatic edge finding of the left ventricle was used after application of a region of interest (PDP 1184 computer, Digital Equipment Co.). The region of interest was divided into 90–150 segments originating from its center of gravity and then transformed in a polar coordinate system. End-diastolic and end-systolic volumes were defined as maximum or minimum, respectively, of the sum of all coronal tomograms of the left ventricle and related to body surface area as EDVI and end-systolic volume index. Left ventricular volume measurements by gated SPECT were previously validated by contrast angiography. Normal values for left ventricular end-diastolic and end-systolic volumes obtained from 18 persons without cardiac disease were 75±3 and 29±2 mL/m², respectively. Immediately after the gated SPECT, planar radionuclide ventriculography was performed in a 30° ("best septal") left anterior oblique view for determination of global left ventricular ejection fraction according to standard techniques (16 frames per heart cycle, automatic region of interest detection for each frame of the cardiac cycle).

Regional Wall Motion

Regional left ventricular wall motion was assessed by gated SPECT using area shrinkage fraction in 18 predefined regions of interest of the left ventricle. The difference between end-diastolic and end-systolic area of each region was calculated and expressed as the percentage of end-diastolic area. To define these regions, the 30° right anterior oblique plane of the left ventricle was divided clockwise from 0° to 360° into 18 equidistant radial sectors originating from the center of gravity. The position of 0° was determined by Fourier analysis as the angle from atrial to ventricular phase of contraction. Normal values for wall motion were derived from measurements in 18 patients without cardiac disease. Normokinetic or abnormally contracting segments of patients of the present study were defined as sectors with area shrinkage fraction values within or outside 2 SD of the normal population, respectively. To account for variation in magnitude of normal wall motion in different regions and to allow comparisons between different regions of the same heart and between different hearts, the extent of wall motion abnormality in abnormally contracting segments was standardized by means of a regional area shrinkage fraction score. This score relates area shrinkage fraction of sectors with abnormal wall motion (ASF) to the mean value for this sector (ASFₙ) and its variability (standard deviation, SDₙ) in the normal population: Score = (ASF - ASFₙ)/SDₙ. Area shrinkage fractions and score values of sectors defined as “normokinetic” or “abnormally contracting segments” at 4 days were averaged and followed sequentially until 3 years after infarction in patients with progressive, limited, or no left ventricular dilatation.
Cardiac Catheterization

In all patients, left and right heart catheterization was performed 3–5 weeks after myocardial infarction. The right brachial artery and a concomitant vein were exposed after local anesthesia, and coronary angiography in multiple views and biplane left ventricular angiography were performed by use of a Sones catheter. Infarct size was quantified as the percentage of akinetic and dyskinetic segment length of the total end-diastolic circumference of the biplane contrast left ventriculogram obtained 4 weeks after infarction. The presence of a left ventricular aneurysm was assessed during cineangiography and defined as a paradoxical systolic expansion of a portion of the ventricular wall with or without protrusion during diastole. Perfusion of the infarct region by the infarct-related coronary artery was assessed according to the criteria of the Thrombolysis in Myocardial Infarction (TIMI) trial. A grade of 0 indicated no flow of contrast beyond the point of occlusion; 1, penetration with minimal perfusion; 2, partial perfusion; and 3, complete perfusion. These measurements were performed by an operator blinded for the other measurements.

Right heart catheterizations at 4 days, 6 months, and 1.5 and 3 years were performed from a transcutaneous right or left cubital access by standard Seldinger techniques and a Swan-Ganz thermol dilution catheter (7F Edwards). A Siemens Sirecust 404-I A cardiac output computer calibrated for 10.0 ml iced injectate was applied. At each time point, three measurements (coefficient of variation, 7.0±2.9%) were obtained, and the average was calculated. Left ventricular stroke volume was calculated by division of cardiac output by heart rate and related to body surface area and expressed as stroke volume index.

Protocol

Four days (2–6 days), 4 weeks (3–5 weeks), 6 months (5–8 months), 1.5 years (16–20 months), and 3 years (34–38 months) after admission for acute infarction, gated SPECT, planar radionuclide ventriculography, and right heart catheterization were performed simultaneously at rest. At 4 weeks, 6 months, and 1.5 and 3 years, right heart catheterization was repeated during supine bicycle exercise. Left ventricular ejection fraction, pulmonary capillary wedge pressure, and cardiac output were measured after baseline resting parameters had been obtained and during steady-state conditions after 4 minutes at an exercise level of 50 W. In addition, 4 weeks after admission, coronary angiography and biplane cineangiography were performed in all patients. No attempt was made to control medical or any other therapy. Patients were fasting the night before and off medication for the previous 24 hours. This protocol was approved by our interdisciplinary University Ethics Committee.

Statistical Analysis

To test for differences between two groups, an unpaired t test was used. To test for significant changes of variables over time (4 days, 4 weeks, 6 months, 1.5 years, 3 years) within each study group (progressive dilatation, limited dilatation, no dilatation), one-way ANOVA and, if significant, multiple comparison procedures were performed. One-way ANOVA and appropriate multiple comparison procedures were performed at 4 days, 4 weeks, 6 months, 1.5 years, and 3 years to test for differences between the three study groups. To test for differences in discrete variables, a X² statistic was applied. Variables were subjected to multivariate discriminant analysis based on the stepwise addition of the variable that contributed the largest increase in the “Rao V” value. These computations were performed by the programs of the Statistical Package for the Social Sciences (SPSS Inc., Chicago). Analyzed variables included sex, age, body weight, ventriculographic infarct size, infarct location, TIMI grade of infarct-related artery perfusion, hypertension, diabetes mellitus, drug therapy, coronary bypass surgery, percutaneous coronary angioplasty, ejection fraction, stroke volume index, left ventricular end-diastolic and end-systolic volume index on day 4 and at 4 weeks, and the change of ejection fraction, stroke volume index, left ventricular EDVI and end-systolic volume index from 4 days to 4 weeks after infarction. The factors that had significant but statistically independent relations to the three study groups were then weighted to construct the discriminant function that best maximized the multivariate F ratio and minimized the Wilks’ lambda value. Using these weights, it was possible to place each patient along the unidimensional discriminant function by multiplying any factor the patient possessed by the appropriate weight. By use of the unstandardized canonical discriminant function coefficients, the discriminant score for each patient was calculated. This score was obtained by multiplying the coefficients (B) by the values for the selected variables (X), summing these products, and adding the constant (B0). Score = B0 + B1X1 + B2X2 + ... + BpXp. For each study group (progressive dilatation, limited dilatation, no dilatation), the mean score and its 95% confidence interval were calculated. Statistical significance was assumed at p<0.05. Only two-sided p values were used. Results are presented as mean±SEM.

Results

Study Groups and Baseline Patient Data

Baseline data are shown for the individual groups in Table 1. Of 70 patients, 38 had stable left ventricular volumes, 18 had limited dilatation, and 14 had progressive left ventricular dilatation up to 3 years after myocardial infarction. Anterior infarct location was more common in patients with progressive or limited dilatation. Ventriculographic infarct size was larger in patients with progressive than in those with limited dilatation and in patients with limited than in patients without dilatation. In addition, the TIMI grade, which assesses the arteriographic contrast flow in the infarct artery, was reduced in patients with progressive dilatation, who also had a higher fraction of left ventricular aneurysms.

Left Ventricular Volumes and Hemodynamic Measurements at Rest

Time course of left ventricular volume index, ejection fraction, systemic vascular resistance, right atrial pressure, and mean arterial pressure is shown in Figure 1. By definition, left ventricular volume indexes were stable throughout the study in patients with no dilata-
Hypertension, TIMI Thrombolysis, Infarct location with given Aneurysm in years.

In this group, Patients with no or limited dilatation had stable ejection fractions, systemic vascular resistance indexes, and mean atrial and systemic arterial pressures. Left ventricular ejection fraction was already reduced early after infarction in the group with progressive dilatation, and a further decrease of ejection fraction was observed at 1.5–3 years after infarction. Concomitantly, systemic vascular resistance index and right atrial pressure rose.

**Regional Area Shrinkage Fraction**

Normokinetic or abnormally contracting segments did not change from 4 days until 3 years in patients without or with limited left ventricular dilatation and are, therefore, not shown. Figure 2 shows the time course of radionuclide area shrinkage fraction in segments that were normokinetic and of area shrinkage fraction scores of abnormally contracting segments 4 days after acute infarction in patients with progressive left ventricular dilatation. Area shrinkage fraction scores of segments defined as abnormal at day 4 were similar at each reexamination, and the number of abnormally contracting segments did not change (5.4±2 at 4 days and 5.3±2 at 3 years). In contrast, segments that were normokinetic 4 days after infarction remained unchanged until 4 weeks but then gradually deteriorated until 3 years. Since these segments remained within the confidence interval of the normal population, they were not abnormally contracting segments by definition. Area shrinkage fractions instead of score values are therefore given.

**FIGURE 1.** Line graphs indicate course of left ventricular end-diastolic and end-systolic volume indexes, ejection fraction, systemic vascular resistance index, and mean right atrial and systemic arterial pressures in patients with progressive (○), limited (▲), and no (●) left ventricular dilatation from 4 days until 3 years after myocardial infarction. Values are given as mean±SEM; p<0.05, * vs. limited dilatation; † vs. no dilatation; ‡ vs. 4 days; § vs. 4 weeks; ¶ vs. 4 days, 4 weeks, and 6 months; ‖ vs. 1.5 years.

<p>| Table 1. Assignment to Study Groups and Baseline Patient Data |</p>
<table>
<thead>
<tr>
<th>Study group</th>
<th>Progressive dilatation</th>
<th>Limited dilatation</th>
<th>No dilatation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>14</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>13/1</td>
<td>17/1</td>
<td>24/4</td>
</tr>
<tr>
<td>Age (years)</td>
<td>58±3</td>
<td>53±2</td>
<td>56±1</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>6 (43)</td>
<td>10 (56)</td>
<td>10 (26)</td>
</tr>
<tr>
<td>Infarction location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior, n (%)</td>
<td>8* (57)</td>
<td>11* (61)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Inferior, n (%)</td>
<td>6 (43)</td>
<td>7 (39)</td>
<td>26 (68)</td>
</tr>
<tr>
<td>Infarction size (%)</td>
<td>20±3†</td>
<td>15±3†</td>
<td>7±1</td>
</tr>
<tr>
<td>Thrombolysis, n (%)</td>
<td>9 (64)</td>
<td>12 (67)</td>
<td>22 (58)</td>
</tr>
<tr>
<td>TIMI grade</td>
<td>1.3±0.3†</td>
<td>2.1±0.2</td>
<td>2.2±0.2</td>
</tr>
<tr>
<td>Aneurysm</td>
<td>10 (71)†</td>
<td>13 (72)†</td>
<td>10 (26)</td>
</tr>
</tbody>
</table>

TIMI, Thrombolysis in Myocardial Infarction trial. Values are given as mean±SEM.

* p<0.05 vs. no dilatation; †p<0.05 vs. limited dilatation.

tion, increased during 4 weeks and stabilized thereafter in patients with limited dilatation, and increased progressively in patients with progressive dilatation. Volumes tended to be larger at the beginning in patients with dilatation, but these differences were statistically not significant. From 4 weeks on, left ventricular volume indexes were larger in patients with progressive dilatation. In patients with limited dilatation, EDVI decreased after 6 months. End-systolic volume stabilized...
Clinical Events

Except for the development of the New York Heart Association (NYHA) functional class, no differences were observed with regard to clinical events. At 3 years, NYHA class I was registered less and class III more often in patients with progressive dilatation than in the other study groups (Table 2).

Drug Therapy

Table 3 shows that nitrates were taken less often in all groups after 3 years compared with 4 days after infarction. The percentage of patients with angiotensin converting enzyme inhibitors increased and with β-blockers decreased in the group with progressive dilatation. Digitalis was taken more often by patients with limited and progressive dilatation at 3 years compared with 4 days after infarction.

Multivariate Discriminant Analysis: Estimation of Risk for Progressive Left Ventricular Dilatation

Variables that were selected by multivariate discriminant analysis are listed in Table 4 according to decreasing statistical significance. Ejection fraction on day 4, ventriculographic infarct size (percent akinesis and dyskinesia of end-diastolic left ventricular circumference), infarct location, stroke index at day 4, and the rate of arteriographic contrast flow in the infarct artery (TIMI grade) were significant predictors of development of progressive, limited, or no left ventricular dilatation. These variables classified 89% of the patients correctly. Using the discriminant coefficients listed in Table 4, a “risk equation” can be provided: Score = -2.593 + 0.595 × (infarct size) + 0.142 × (stroke index) + 0.156 × (TIMI grade). For each patient, the discriminant score value was calculated and averaged for each study group. As shown in Table 5, there is no overlap of the 95% confidence intervals of the score means, and the differences among the groups are highly significant.

Discussion

Progressive Dilatation and Development of Global Chronic Cardiac Dysfunction

This study demonstrates that progressive left ventricular dilatation is associated with progressive global cardiac dysfunction. Previous studies provide indirect evidence that cardiac dysfunction may be linked to ventricular dilatation. For example, wedge pressure and pulmonary artery pressure tend to rise within 1 year of ventricular dilatation, and exercise duration is reduced in patients with excessive distortion of left ventricular shape. Ejection fraction decreases with dilatation at 4 weeks after infarction but then remains constant in the subsequent 5 months of dilatation, whereas stroke index does not decrease. In contrast, in the present study, direct hemodynamic evidence is provided in individual patients that chronic cardiac dysfunction develops insidiously in close relation to progressive dilatation within 3 years after infarction. Dilatation of the left ventricle precedes any detectable deterioration of global cardiac performance at rest by 6 months. In fact, between 4 days and 4 weeks after myocardial infarction, cardiac index and stroke index
Progressive, significant increases in pulmonary capillary wedge pressure (right panel) until 3 years after myocardial infarction. Measurements of patients with progressive, limited, and no dilatation are given in the upper, middle, and lower part of each panel, respectively. Mean values and standard errors for measurements at rest are indicated by the base (open boxes) and during supine bicycle exercise at 50 W by the top (filled boxes) of each column. Except for stroke index in patients with progressive dilatation at 1.5 and 3 years, all values were significantly higher during exercise than measurements at rest. \( p<0.05, * \) vs. limited dilatation; + vs. no dilatation; \( \# \) vs. 4 days; \$ vs. 4 weeks; \( \| \) vs. 4 days, 4 weeks, and 6 months; \# vs. 6 months; \('\) vs. 1.5 years; n.s. denotes no statistical significance between rest and exercise.

Progressive rise of wedge pressure in patients with limited dilatation suggests that activation of Frank-Starling compensation is required to maintain stroke index during exercise. In patients with progressive dilatation, cardiac index and stroke index deteriorate gradually after 6 months, and wedge pressure increases, first during exercise and later at rest. Elevation of systemic vascular resistance index, reduced stroke index, and reduced ejection fraction concurrent with 3 years of progressive dilatation indicate severe cardiac dysfunction at rest. Elevated right and left ventricular filling pressures may indicate transition to congestive dysfunction consistent with a shift of patients to higher NYHA functional classes. These measurements support the concept that dilatation is a cause rather than a consequence of further decline of pump function. It was not until 1.5 years after myocardial infarction that clear hemodynamic signs of left ventricular dysfunction became apparent at rest. Recent studies show that development of heart failure may be postponed by therapy with angiotensin converting enzyme inhibitors.\textsuperscript{22,23} In accordance with the present study, the survival advantage provided by an angiotensin converting enzyme

**TABLE 2. Clinical Events**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Total No.</th>
<th>Progressive LV dilatation (n=14)</th>
<th>Limited LV dilatation (n=18)</th>
<th>No LV dilatation (n=38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACVB</td>
<td>13</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>PTCA</td>
<td>6</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>NYHA (4 weeks/3 years)</td>
<td></td>
<td>4/0</td>
<td>1/3</td>
<td>20/18</td>
</tr>
<tr>
<td>I</td>
<td>9/6</td>
<td>1/7</td>
<td>1/3</td>
<td>16/20</td>
</tr>
<tr>
<td>II</td>
<td>1/3</td>
<td>2/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>III</td>
<td>0/1</td>
<td></td>
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</tbody>
</table>

LV, left ventricular; ACVB, aortocoronary bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; NYHA, New York Heart Association functional class.
Progressive Dilatation and Development of Regional Cardiac Dysfunction

Progressive deterioration of global left ventricular ejection fraction in patients with progressive dilatation was most likely due to deterioration of function of regions with wall motion classified as normal by radionuclide area shrinkage fraction at 4 days. Regions with hypokinesia, akinnesia, and dyskinesia showed no significant changes of area shrinkage fraction over time. The mechanism of deteriorating function in regions with initially normal wall motion remains unclear. It may be speculated that systolic or diastolic dysfunction of non-infarcted myocardium as sequelae of regional hypertrophy may have occurred. Contractile function in cardiac muscle with experimental hypertrophy eventually dete-

Table 3. Medications Given Patients at Various Time Points

<table>
<thead>
<tr>
<th></th>
<th>4 Days</th>
<th></th>
<th></th>
<th>4 Weeks</th>
<th></th>
<th></th>
<th>3 Years</th>
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<tr>
<td></td>
<td>P</td>
<td>L</td>
<td>N</td>
<td>P</td>
<td>L</td>
<td>N</td>
<td>P</td>
<td>L</td>
</tr>
<tr>
<td>Nitrates</td>
<td>72</td>
<td>65</td>
<td>65</td>
<td>39</td>
<td>45</td>
<td>28</td>
<td>33*</td>
<td>20*</td>
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<tr>
<td>ACE inhibitors</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>3</td>
<td>17*</td>
<td>5</td>
</tr>
<tr>
<td>Ca antagonists</td>
<td>33</td>
<td>65</td>
<td>34</td>
<td>39</td>
<td>40</td>
<td>21</td>
<td>11</td>
<td>20</td>
</tr>
<tr>
<td>Digitalis</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>0</td>
<td>0</td>
<td>22*</td>
<td>10*</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>17</td>
<td>30</td>
<td>20</td>
<td>22</td>
<td>15</td>
<td>7</td>
<td>5*</td>
<td>20</td>
</tr>
<tr>
<td>Diuretics</td>
<td>28</td>
<td>10</td>
<td>17</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>28</td>
<td>5</td>
</tr>
</tbody>
</table>

Numbers give percentage of patients receiving respective medication. P, progressive dilatation; L, limited dilatation; N, no dilatation; ACE, angiotensin converting enzyme; Ca, calcium.

*p<0.05 vs. 4 days.

inhibitor in postinfarction patients does not become apparent until 1 year after infarction.\textsuperscript{22}

However, dilatation of the left ventricle after infarction is not necessarily progressive and does not necessarily portend a poor outcome. In patients of the present study, left ventricular dilatation occurred in 46% and was progressive in only 20%. This is in accordance with previous studies in which dilatation occurred in about 42%\textsuperscript{,6,8,21,24} but was progressive within 6 months after infarction in only 16%.\textsuperscript{25} An acutely depressed stroke index at rest was restored to normal within 2–4 weeks after infarction with early dilatation in the present and in previous studies\textsuperscript{,6,8,21,24} and therefore has been named “compensatory dilatation.”\textsuperscript{8} However, sequential hemodynamic and volumetric observations beyond 6 months have not been available previous to this report.

Table 4. Risk Factors for Left Ventricular Dilatation Identified by Multivariate Analysis and Univariate Relations Among the Study Groups

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Multivariate analysis</th>
<th>Univariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Significance level</td>
<td>Discriminant-function coefficient*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venticulographic infarct size (%)</td>
<td>p&lt;0.00001</td>
<td>0.132</td>
</tr>
<tr>
<td>Ejection fraction day 4 (%)</td>
<td>p&lt;0.00001</td>
<td>0.0427</td>
</tr>
<tr>
<td>Infarct location (% anterior)</td>
<td>p&lt;0.00001</td>
<td>0.595</td>
</tr>
<tr>
<td>Stroke index day 4 (mL/m²)</td>
<td>p=0.001</td>
<td>0.142</td>
</tr>
<tr>
<td>TIMI grade</td>
<td>p=0.044</td>
<td>0.156</td>
</tr>
</tbody>
</table>

*Unstandardized canonical discriminant function coefficients.
†Confidence interval in parentheses.
\*p<0.05 vs. limited dilatation; \$p<0.05 vs. no dilatation.

Potential Determinants and Early Predictors of Progression to Failure

Several variables have been identified that predict an increase in left ventricular volume after myocardial dilatation. Increased preload (wedge pressure) should improve the force of contraction by recruitment of Frank-Starling mechanism. However, increased afterload (systemic vascular resistance and left ventricular dilatation) in the presence of limited preload reserve could cause afterload mismatch and thereby depression of cardiac performance.\textsuperscript{27} In the recent Study of Left Ventricular Dysfunction (SOLVD), neurohumoral activity was already elevated in patients with asymptomatic or minimally symptomatic left ventricular dysfunction.\textsuperscript{28} Thus, systemic vasoconstriction may be the result of very early compensatory neurohumoral activation to maintain blood pressure in view of reduced myocardial function, stroke volume, and cardiac index. Further studies are needed to analyze the interaction of contractility and diastolic function of residual myocardium, global hemodynamics, and neurohumoral activity in the years after myocardial infarction.

It is unlikely that hemodynamic deterioration was due to additional loss of contractile myocardium or progression of coronary artery disease, since patients with reinfarction were excluded, those with critical stenoses received coronary bypass surgery or angioplasty, and serial exercise ECGs were negative. Analysis of therapeutic interventions indicates that neither cardiac depressant drugs (e.g., β-adrenergic blockers) nor revascularization procedures account for the remodeling. Of interest, β-blockers were frequently stopped and vasodilators instituted in the group with progressive dilatation.
Table 5. Average Discriminant for Study Groups

<table>
<thead>
<tr>
<th>Study group</th>
<th>n</th>
<th>Mean</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive dilatation</td>
<td>14</td>
<td>-1.963*†</td>
<td>-2.596, -1.130</td>
</tr>
<tr>
<td>Limited dilatation</td>
<td>18</td>
<td>-0.219†</td>
<td>-0.739, 0.300</td>
</tr>
<tr>
<td>No dilatation</td>
<td>38</td>
<td>+1.169*</td>
<td>+0.871, 1.466</td>
</tr>
</tbody>
</table>

*p<0.00001 vs. limited dilatation; †p<0.00001 vs. no dilatation.

infarction. These include infarct size21,29 and the location (anterior) of the infarct. A patent infarct-related artery is also associated with a smaller left ventricular volume30 and better survival in patients after myocardial infarction.31,32 But their relative importance and predictive value in identifying patients at high risk for progressive dilatation and heart failure are not known. Multivariate analysis of the present data identifies variables that significantly and independently correlate with progressive dilatation and chronic ventricular dysfunction. Values for these variables and their discriminant coefficients listed in Table 4 may be entered into a risk equation. By this, a score value can be calculated for a single patient. This allows one to estimate the probability that a patient will develop one of our three post-myocardial infarction patterns. Since the variability of the score mean for the groups in the present study is small (no overlap of 95% confidence interval in Table 5), the likelihood of belonging to a certain group is very high if the score value of a patient is close to the mean value of the respective group. If applied to the population of the present study, 89% of the patients were classified correctly by the selected variables. Although left ventricular volumes at 4 weeks are highly significantly correlated (p<0.001) with the percentage of akinesis and dyskinesis, neither end-systolic nor end-diastolic ventricular volume at 4 days nor the change of these volumes from 4 days to 4 weeks is a significant predictor of late progressive dilatation and heart failure in the population of the present study. This may be because even patients with considerable dilatation within 6 months after infarction may eventually demonstrate only limited dilatation. If ventriculographic infarct size and TIMI grade, which may not be routinely available in many institutions, were omitted from multivariate analysis, only 71% of the patients could be classified correctly, and there was considerable overlap of the confidence intervals of the score means among the groups. Thus, the predictive value of the variables listed in Table 4 is highest if they all are used together. Multivariate discriminant analysis has been successfully applied in various clinical problems. It is important to note that variables and coefficients selected by multivariate discriminant analysis must be validated by prospective application, and conclusions from this study should be applied only to populations similar to the present study. Recent preventive studies show that ventricular dilatation and progression to symptomatic congestive heart failure can be reduced in patients with chronic hemodynamic dysfunction, and survival may be improved in patients after infarction by an angiotensin converting enzyme inhibitor. However, many patients who are not destined to have progressive disease have been treated to prevent adverse outcomes in the subgroup at risk. The predictive variables identified in the present study may be used to select patients at high risk for late cardiac failure for early intervention after infarction. By this approach, unnecessary preventive therapy may be avoided in the 80% of patients with low probability of development of chronic heart failure. Multivariate analysis of the present study suggests that progression from dilatation to dysfunction is multifactorial. Therefore, early multifactorial interventions might be necessary to arrest the process of myocardial remodeling before left ventricular dilatation has occurred.

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