Multivariate analysis of angiographic, histologic, and electrocardiographic data in patients with coronary heart disease

Willem Flameng, M.D., Luc Wouters, Paul Sergeant, M.D., Paul Lewi, Marcel Borgers, Dr. Sc., Fred Thone, and Raf Suy, M.D.

ABSTRACT In 61 consecutive patients undergoing aortocoronary bypass grafting, angiographic and electrocardiographic (ECG) changes were studied. Histologic delineation of myocardium was obtained by analysis of transmural biopsy specimens acquired at the time of surgery. The use of principal-component analysis revealed three definite groups of patients. Group I comprised patients with histologic findings associated with severe left anterior descending coronary artery (LAD) stenosis, without abnormal wall motion or ejection fraction. ECG abnormalities were limited to ST changes. Group II comprised patients with severe myocardial cell degeneration with only modest fibrosis associated with severe LAD stenosis and severely impaired wall motion. The incidence of infarction on the ECG was low. Group III patients had important myocardial cell degeneration with severe fibrosis associated with severe LAD stenosis, severely depressed wall motion, and significantly impaired ejection fraction. In this group there was a high incidence of infarction apparent on the ECG. Postoperative follow-up (24 months) showed a total survival of 94.4% in group I, 92.8% in group II, and only 72.7% in group III. This identification of subtypes of coronary artery disease seems to be helpful in estimating patient prognosis after coronary surgery.

Circulation 70, No. 1, 7–17, 1984.

This study deals with the histologic and ultrastructural changes in the myocardia of patients with coronary artery disease and compromised left ventricular function. Using intraoperative transmural biopsy samples, we made a correlation in vivo between the morphologic status of the myocardium and parameter values available before surgery (ejection fraction, wall motion, electrocardiographic [ECG] abnormalities, and degree of coronary stenosis). Based on these morphologic, angiographic, and ECG variables, a multivariate statistical technique was used to obtain insight into the phenomenon of obstructive coronary artery disease and to classify patients with this disease in terms of specific histologic and functional properties of the myocardium. Postoperative follow-up (2 years) was done to assess the prognostic value of this type of classification.

Patients and methods

Patients. Sixty-one consecutive surgical patients with obstructive coronary artery disease were included in the study. The patients (four women and 57 men) were 37 to 65 years old and all underwent aortocoronary bypass grafting. All patients had ventriculographic and coronary arteriographic examinations within 8 weeks before surgery and none had had an acute event between cardiac catheterization and operation. All patients gave their informed consent.

Catheterization. No premedication was used. In each patient, after measurement of left ventricular pressure, a biplane left ventriculographic examination in the 30 degree right anterior oblique projection was performed. Thereafter a coronary arteriographic examination was carried out with the Sones technique. Calibration of the ventricular image size was made with a grid filmed at the level of the left ventricular cavity. Wall motion was measured from the frontal end-diastolic and end-systolic outlines of the left ventricle. The long axis was divided into four equal parts and three perpendicular lines were constructed. Each hemiaxis (from the long axis to the endocardial surface) was measured and the percent of shortening was determined as the end-diastolic minus end-systolic hemiaxis divided by the end-diastolic hemiaxis times 100. The individual values for the two distal hemiaxes and the apical fourth of the long axis were averaged to obtain a representative measurement of regional motion of the myocardium distal to the obstructed left anterior descending coronary artery (LAD). Ejection fraction was calculated and the degree of LAD stenosis was estimated and graded as follows: none (0%), slight (<70%), moderate (70% to 80%), severe (>80%), or total occlusion (100%).

Biopsies. Two transmural needle biopsy specimens measur-
ing 1.5 mm in diameter (Tru-Cut biopsy needle, Travenol Laboratories) were obtained from the center of the area perfused by the LAD. These specimens were obtained when the patients were on cardiopulmonary bypass but before any of the distal or proximal anastomoses were performed. Each specimen was divided into a subepicardial and a subendocardial sample and was fixed in 3% glutaraldehyde, buffered to pH 7.4 with 0.009M potassium oxalate, for use in light and electron microscopic studies.

Light microscopy-morphometry. In an attempt to quantify the degree of cell degeneration in the different layers of myocardium, 100 myocardial cells that were sectioned through the nucleus were examined. This was done on semithick toluidine blue-stained sections of the subepicardial and subendocardial parts of the biopsy samples. The percentage of normal cells and of cells that had lost contractile material was calculated.

The degree of myocardial fibrosis was graded according to the system of Stinson and Billingham3 as follows: grade I, normal myocardium; grade II, mild-to-moderate myocardial fibrosis; grade III, moderate-to-severe fibrosis; grade IV, total replacement with fibrosis.

Electron microscopy. For electron microscopic examination, the blocks were fixed with 3% distilled glutaraldehyde in 0.09M potassium oxalate brought to pH 7.4 with normal potassium hydroxide for 2 hr at 4°C. After fixation they were thoroughly washed in the same buffer supplemented with 0.22M sucrose. Postfixation was done in 1% osmic acid, buffered to pH 7.4 with 0.05M veronal acetate containing 0.093M sucrose for 1 hr at 4°C. After a rinse in the buffer, the blocks were dehydrated in graded series of ethanol and routinely embedded in epon. Ultrathin sections were examined in a Philips EM 300 microscope after staining with uranyl acetate and lead citrate. Ultrastructural changes in the myocytes were observed in several electron micrographs that were taken at random for both areas (subepicardial and subendocardial). No attempt was made to quantify the degree of subcellular myocardial degeneration.

Statistical methods. The data were arranged into a table with 61 rows (patients) and eight columns (variables). For truly quantitative variables (ejection fraction, wall motion, and percentage of normal cells) the original data were entered into this table. Degree of stenosis was entered with the use of the coding described above (0% to 100% in steps of 10). Degree of fibrosis was coded as follows: 0 for grade I, 1 for grade II, 2 for grade III, and 3 for grade IV. Only ECG changes related to the anterior wall were considered and these were coded as follows: 0 for no changes, 1 for ST segment elevation, and 2 for Q waves. The measurements were first autoscaled and then a principal-component analysis was performed on the full table of data. This multivariate statistical procedure determines the minimum number of independent dimensions that account for a maximum amount of the information present in the table. Projection of the data on the plane formed by the most important dimensions (principal components) provides a visual aid in the interpretation of the table. The Multivariate Data Analysis Program (DATASCOPE)3 was used to carry out the analysis. Relationships between the different variables were also evaluated with the Spearman rank correlation.6 Significance of the correlation coefficients was determined with the Student t test. Differences between related samples (subepicardial and subendocardial) were tested for statistical significance by applying the Wilcoxon test for quantitative variables (percentage normal myocytes) and the sign test for semiquantitative variables (degree of fibrosis). Two-tailed probabilities less than or equal to .05 were considered to indicate significance. Results were represented as median values for quantitative variables and frequency of occurrence of the event for coded data (fibrosis and ECG results). Confidence limits on these estimates were computed from the binomial distribution.

Follow-up. Anderson actuarial survival6 and event-free curves were created with data from the 100% follow-up. The survival curves include the cardiac and the noncardiac operative and late deaths. In the event-free studies data from operative survivors was used and an event was defined as onset of new angina, unannounced myocardial infarction, or sudden death.

Results

Histology. At the light microscopic level, many biopsy samples showed a completely normal myocardial structure (figure 1, A). However, many other specimens showed typical signs of myocardial cell degeneration: the volume fraction of myofibrils was markedly reduced. Such a reduction in contractile material in a cell is a typical characteristic of vacuolization (mottling). This myofibrillar lysis seems to be localized mainly around the nucleus, resulting in a perinuclear halo (figure 1, B to D).

Myocardial fibrosis was often found in these biopsy specimens and was most often associated with degenerative changes in the remaining myocytes (figure 1, D). However, myocardial cell degeneration was not invariably associated with fibrosis (figure 1, B).

In an attempt to quantify these degenerative changes in the myocytes at the light microscopic level, we counted the percentage of those cells sectioned through the nucleus that were normal. This was done in both the subepicardial and the subendocardial samples. The results of this quantitative evaluation are reported in the statistical analysis section.

At the ultrastructural level, normal myocytes showed closely arranged myofibers with rows of mitochondria tightly packed in between (figure 2, A). Degenerated myocardial cells, however, showed severe subcellular defects. The most prominent feature was the loss of sarcomeres and myofibrils. This type of cell degeneration (myofibrillar lysis or vacuolar degeneration6) can be seen in the center of the cell, in the perinuclear zone (figure 2, B and C). The loss of myofibrils, accompanied by the abnormal formation of Z band material, often extends toward the cell periphery. The area around the nucleus becomes completely devoid of contractile material and is filled by large amounts of clumped cytoskeletal filaments, mitochondria, and glycogen. The sarcoplasmic reticulum is practically absent in these severely degenerating cells and only one or two rows of regularly arranged sarcomeres remain along the plasma membrane (figure 2, B and C). The sarcolemma shows numerous regularly spaced microvessicles and T-tubular invaginations are rarely found. The nuclei of these cells are enlarged and
have a tortuous appearance. The mitochondria are dispersed within the cytosol and have an abnormal shape and size. Most mitochondria are small (minimitochondria), but sometimes they are extremely large (giant mitochondria) (figure 3). In many biopsy specimens, myofibrillar lysis was associated with increased amounts of collagen fiber in the interstitial space (fibrosis) (figure 2, C). Coagulation necrosis was seen only focally in the subendocardial samples of two patients with anterior wall hypokinesis but without anterior infarction.

Statistical analysis. Table 1 contains the Spearman rank correlation coefficients between the different variables. In observing this correlation matrix, it should be noted that the percentage of normal myocytes in the subepicardium was highly correlated with that of the subendocardium (r = .78). The percentage of normal myocytes in the subendocardium (median 63) was significantly lower (Wilcoxon test, two-tailed p < .001) than that in the subepicardium (median 76). A significant relationship was also found between the subepicardial and subendocardial degrees of fibrosis (r = .34), but no differences in magnitude between the two regions could be demonstrated (sign test, two-tailed p = .076). For the subendocardial region, the percentage of normal myocytes and the degree of fibrosis correlated significantly with each other (r = -.30). No such relationship could be detected for the subepicardial region (r = -.21).

Values available before surgery showed that ejection fraction and anterior wall motion were highly intercorrelated (r = .80). A highly significant correlation was also found between the degree of stenosis and anterior wall motion (r = -.48) and ECG changes correlated well with anterior wall motion (r = -.43), ejection fraction (r = -.40), and degree of stenosis (r = .28).

With regard to the relationship between the morphologic state of the myocardium and the variables available before surgery, the state of the subendocardium...
FIGURE 2. For legend see opposite page.
TABLE 1
Matrix of Spearman rank correlations

<table>
<thead>
<tr>
<th></th>
<th>Subendocard. % myocytes</th>
<th>Subepicard. fibrosis</th>
<th>Subendocard. fibrosis</th>
<th>ECG changes</th>
<th>Degree of stenosis</th>
<th>Ejection fraction</th>
<th>Wall motion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subepicard. % myocytes</td>
<td>0.78(\text{C} )</td>
<td>-0.21</td>
<td>-0.13</td>
<td>-0.30(\text{b} )</td>
<td>-0.23</td>
<td>0.34(\text{C} )</td>
<td>0.48(\text{C} )</td>
</tr>
<tr>
<td>Subendocard. % myocytes</td>
<td>-0.09</td>
<td>-0.30(\text{b} )</td>
<td>-0.38(\text{C} )</td>
<td>-0.44(\text{C} )</td>
<td>-0.30(\text{b} )</td>
<td>-0.34(\text{C} )</td>
<td>0.56(\text{C} )</td>
</tr>
<tr>
<td>Subepicard. fibrosis</td>
<td>0.34(\text{C} )</td>
<td>0.15</td>
<td>0.16</td>
<td>-0.30(\text{b} )</td>
<td>-0.34(\text{C} )</td>
<td>-0.44(\text{C} )</td>
<td>0.56(\text{C} )</td>
</tr>
<tr>
<td>Subendocard. fibrosis</td>
<td>0.50(\text{C} )</td>
<td>0.34(\text{C} )</td>
<td>0.34(\text{C} )</td>
<td>-0.50(\text{C} )</td>
<td>-0.30(\text{b} )</td>
<td>-0.44(\text{C} )</td>
<td>0.43(\text{C} )</td>
</tr>
<tr>
<td>ECG changes</td>
<td></td>
<td>0.28(\text{A} )</td>
<td></td>
<td></td>
<td>-0.25(\text{A} )</td>
<td>-0.25(\text{A} )</td>
<td>0.80(\text{C} )</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ejection fraction</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Significances of correlation coefficients (two-tailed probabilities from Student’s t test): \(A p < .05; B p < .02; C p < .01.\)

Correlated well with all of these variables. Anterior wall motion especially was strongly related to subendocardial damage \((r = .56\) for the percentage of normal cells and \(-.56\) for the degree of fibrosis). The degree of subendocardial fibrosis also correlated highly significantly with ejection fraction \((r = -.50)\) and changes in the ECG \((r = .50)\). The morphologic state of the subepicardium was also related to the preoperative variables. However, the correlation coefficients were always smaller than for the subendocardial region and no significant correlations between subepicardial damage and degree of LAD stenosis could be detected. Subepicardial fibrosis did not correlate with changes on the ECG \((r = .15)\).

Principal-component analysis on the complete 61 \times 8\ table of data revealed two dominant factors. The physiologic meaning of a factor can be found by looking at the table of individual factor loadings (table 2). Variables with a large coefficient are highly correlated with the corresponding factor. The first component accounted for 47% of the total variance and was related to all eight variables. Anterior wall motion and ejection fraction had the largest coefficients. Hence, this major component was interpreted as a measure for the extent of obstructive coronary heart disease, as is reflected by the functional state of the myocardium. The second factor accounted for an additional 16% of the variance and was attributed to histologic changes that did not affect myocardial function. The plane formed by these two factors (first factorial plane) explained 63% of the information contained in the original data matrix. In observing table 2 it should also be noted that degree of stenosis, subepicardial fibrosis, and ECG changes had the greatest residuals. This was probably caused by the rather crude coding system applied to these variables. Figure 4 shows the projection of the variables and individual patients on the first factorial plane. Variables distributed along the horizontal axis (first principal component) belong to two negatively correlated sets. On the left side the pathologic variables are situated (fibrosis, stenosis, and ECG changes) and on the right the variables related to viability of the myocardium are found (wall motion, ejection fraction, and presence of normal myocytes).

Projection of the individual patients points on the first factorial plane revealed the existence of three clusters (figure 4, groups I, II, and III). The first principal component (figure 4, horizontal axis) discriminates between group I and the two others, indicating that the difference will be found mainly in the functional state of the myocardium. This can be verified with the data in tables 3A and 3B, which contain a detailed description of the individual variables for the three groups. Group I included 59% of the patients who could be identified as “patients with viable myocardium.” Patients in this group had moderate-to-severe LAD ste-

FIGURE 2. Electron micrographs of subendocardial biopsy specimens. A, Electron micrograph (\(\times 3000\)) from a subendocardial biopsy sample of a normokinetic anterior wall in a patient with a 70% LAD stenosis. Subcellular details in this longitudinal section show normally arranged myofilaments with their \(Z\) bands in register. Sarcolemma, mitochondria, and T-tubuli have a normal appearance. In between the two myocytes, a capillary vessel, filled with erythrocytes, can be seen. B, Electron micrograph (\(\times 2800\)) from a subendocardial biopsy sample of a hypokinetic anterior wall in a patient with a 90% LAD stenosis but without an anterior wall infarction. This longitudinal section shows several severely degenerated myocytes. Only at the cell periphery is there a small rim of sarcomeres left. The center of the cells is filled with cytoskeletal filaments, mitochondria, and glycogen. There is no additional fibrosis. C, Electron micrograph (\(\times 4500\)) of a subendocardial biopsy sample from the hypokinetic anterior wall in a patient with complete LAD occlusion and anterior wall infarction. Several myocardial cells are sectioned longitudinally through the nucleus. There is considerable myofibrillar lysis in the perinuclear area, and only a small number of rows of myofilaments are left at the cell periphery. In between the myocytes increased amounts of collagen can be observed, indicating interstitial fibrosis.

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FIGURE 3. Electron micrographs of myocardial cells (×13,500) illustrating the changes in shape and size of the mitochondria. A, Normal appearance of mitochondria in a structurally normal myocardial cell. The mitochondria have a regular shape and size, a dark matrix, and normal membranes and cristae. B, Mitochondria in a degenerated chronically ischemic myocardial cell. These mitochondria have a normal structure but they are irregularly shaped and small (minimitochondria). C, Mitochondria in a severely degenerated chronically ischemic myocardial cell. These mitochondria are extremely large (giant mitochondria) and the cristae exhibit a typical concentric appearance.
TABLE 2

<table>
<thead>
<tr>
<th></th>
<th>First factor</th>
<th>Second factor</th>
<th>Residual</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Subepicard. % myocytes</td>
<td>1.84</td>
<td>1.65</td>
<td>1.38</td>
<td>2.83</td>
</tr>
<tr>
<td>Subendocard. % myocytes</td>
<td>2.10</td>
<td>1.51</td>
<td>1.13</td>
<td>2.83</td>
</tr>
<tr>
<td>Subepicard. fibrosis</td>
<td>-1.21</td>
<td>1.53</td>
<td>2.05</td>
<td>2.83</td>
</tr>
<tr>
<td>Subendocard. fibrosis</td>
<td>-1.91</td>
<td>1.43</td>
<td>1.52</td>
<td>2.83</td>
</tr>
<tr>
<td>ECG changes</td>
<td>-1.87</td>
<td>0.28</td>
<td>2.10</td>
<td>2.83</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>-1.62</td>
<td>-0.42</td>
<td>2.28</td>
<td>2.83</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>2.21</td>
<td>-0.73</td>
<td>1.61</td>
<td>2.83</td>
</tr>
<tr>
<td>Wall motion</td>
<td>2.49</td>
<td>-0.08</td>
<td>1.34</td>
<td>2.83</td>
</tr>
</tbody>
</table>

noses (80%) but normal ejection fraction (72%) and normal anterior wall motion (44%). ECG abnormalities were rarely found in these patients and were restricted to ST segment elevations (11% of instances). Biopsy samples showed almost no fibrosis (3% of instances) and a high percentage of normal myocytes (81.5% in the subepicardial and 77% in the subendocardial region).

Groups II and III comprised patients with impaired ventricular function. The second principal component (figure 4, vertical axis), which defined pure histologic changes, discriminated between these two groups. Group II included 23% of the subjects and comprised those patients with impaired ventricular function but without scar tissue. Patients in this group had severe LAD stenoses (100%) and a severely reduced wall motion (18.5%), but their global ejection fractions were only moderately reduced (57.5%). This group showed a low incidence of ECG abnormalities (36% of instances) and a low incidence of fibrosis in the subepicardium (7% of instances) and the subendocardium (21% of instances). However, a considerable percentage of cells were degenerated in these patients; only 34.5% of cells in the subepicardium and 20.5% of those in the subendocardium were normal.

The third group comprised 18% of the patients who could be characterized as "patients with compromised ventricle and scar tissue." In this group LAD stenosis was also severe (100%), wall motion was considerably decreased (12%), and global ejection fraction was very low (31%). There was also a high incidence of ECG abnormalities (73% of instances) and a high incidence of fibrosis (45% of instances for subepicardium and 91% of instances for subendocardium). The remaining myocytes showed a moderate incidence of myofibrillar lysis: 71% of the subepicardial and 45% of the subendocardial cells were normal.

Follow-up. An Anderson actuarial survival and event-free study was made of the three groups (figure 5). The cumulative actuarial survival at 24 months was...
94.4 ± 3.8% for group I patients, 92.8 ± 6.8% for group II patients, and 72.7 ± 13.4% for group III patients. Cardiac survival at this time was 97.1 ± 2.8% for those in group I, 100 ± 0% for those in group II, and 88.8 ± 10.4% for those in group III. The actuarial event-free curve of the survivors showed that 85.8 ± 5.8% of patients in group I were event free after 24 months; in groups II and III 77.4 ± 11.4% and 88.8 ± 10.4% of patients, respectively, were event free at 24 months.

**Discussion**

Nosology, the classification and identification of types and subtypes of disease, is of some importance to clinical practice. The existence of a satisfactory system of classification provides the physician with a tool

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**Table 3A**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 36)</th>
<th>Group II (n = 14)</th>
<th>Group III (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subepicard. myocytes</td>
<td>81.5 (71-90)</td>
<td>34.5 (14-50)</td>
<td>71.0 (50-87)</td>
</tr>
<tr>
<td>Subendocard. myocytes</td>
<td>77.0 (66-84)</td>
<td>20.5 (12-31)</td>
<td>45.0 (24-75)</td>
</tr>
<tr>
<td>Degree of stenosis</td>
<td>80.0 (70-90)</td>
<td>100.0 (80-100)</td>
<td>100.0 (90-100)</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>72.0 (64-77)</td>
<td>57.5 (36-64)</td>
<td>31.0 (21-62)</td>
</tr>
<tr>
<td>Wall motion</td>
<td>44.0 (41-48)</td>
<td>18.5 (10-30)</td>
<td>12.0 (7-21)</td>
</tr>
</tbody>
</table>

**Table 3B**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group I (n = 36)</th>
<th>Group II (n = 14)</th>
<th>Group III (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subepicard. fibrosis</td>
<td>3 (0-15)</td>
<td>7 (0-34)</td>
<td>45 (17-77)</td>
</tr>
<tr>
<td>Stinson Grade II</td>
<td>3 (0-15)</td>
<td>7 (0-34)</td>
<td>27 (6-61)</td>
</tr>
<tr>
<td>Grade III</td>
<td>0 (0-10)</td>
<td>0 (0-23)</td>
<td>18 (2-52)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0 (0-10)</td>
<td>0 (0-23)</td>
<td>0 (0-28)</td>
</tr>
<tr>
<td>Subendocard. fibrosis</td>
<td>3 (0-15)</td>
<td>21 (5-51)</td>
<td>91 (59-100)</td>
</tr>
<tr>
<td>Stinson Grade II</td>
<td>3 (0-15)</td>
<td>21 (5-51)</td>
<td>36 (11-69)</td>
</tr>
<tr>
<td>Grade III</td>
<td>0 (0-10)</td>
<td>0 (0-23)</td>
<td>36 (11-69)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>0 (0-10)</td>
<td>0 (0-23)</td>
<td>18 (2-52)</td>
</tr>
<tr>
<td>ECG changes</td>
<td>11 (3-26)</td>
<td>36 (13-65)</td>
<td>73 (39-94)</td>
</tr>
<tr>
<td>ST segment</td>
<td>11 (3-26)</td>
<td>0 (0-23)</td>
<td>9 (0-41)</td>
</tr>
<tr>
<td>Q wave</td>
<td>0 (0-10)</td>
<td>36 (13-65)</td>
<td>64 (31-89)</td>
</tr>
</tbody>
</table>
to allocate a particular patient without ambiguity to a
certain diagnostic category. Consequently, the pa-
tient’s prognosis is estimated more accurately and the
most appropriate therapy can be determined. Traditionally,
systems of classification were achieved in an
informal manner, based on rather arbitrary human
judgment and with the use of a single criterion. Formal
definitions of classifications are provided by multi-
variate statistical methods. These techniques use sev-
eral variables simultaneously and the final result is
obtained by an elaborate series of computations. This
latter approach is particularly appealing, since a priori
weight is not assigned to any special variable and the
data are allowed to speak for themselves. At present
there are a number of computerized methods for nu-
merical classification available; principal-component
analysis and cluster analysis are two of these for which
widespread applications have been found. Two ele-
ments are inherent to all types of pathophysiologic
classification: the grouping of features (symptoms,
variables) into syndromes, and the clustering of pa-

tients into diagnostic categories.\textsuperscript{10} Principal-component
analysis addresses this duality of classification; it
not only provides components with a certain patho-
physiologic meaning in terms of syndromes, but it
simultaneously uses the same components to classify
patients. The method of principal components has al-
ready been used by Noda\textsuperscript{11} to evaluate histopathologic
data from endomyocardial biopsies in patients with
idiopathic cardiomyopathy. Correspondence analysis,
another kind of principal-component analysis, has
been used to identify profiles of patients with acute
myocardial infarction complicated by pump failure.\textsuperscript{12}

In our study, principal-component analysis clearly
divides the patient population into three groups accord-
ing to the histologic and functional characteristics of
the left ventricular segment studied (anterior wall). In
the first group of patients moderate-to-severe stenosis
of the coronary vessel (in this study the LAD) appar-
ently did not affect regional contractile function of its
perfusion area. Global ejection fraction was normal.
With the exception of ST changes in a small percent-
age of instances, ECG abnormalities related to the
LAD area were not found. Because myocardial his-
tology was normal in the LAD segment of these pa-
tients, they can be considered optimal candidates for
myocardial revascularization, as was proved by the
excellent clinical outcome observed in the follow-up
study.

Our second group of patients was characterized by
severe coronary arterial stenosis combined with im-
paired regional function. Global ejection fraction was
only slightly reduced (57.5%), indicating that most of
the other segments were unaffected by the disease in
terms of local function. Of special interest is the fact
that the majority of patients in this group showed no
ECG signs of transmural infarction related to the an-
terior wall. Q waves related to this area were found in
only 36% of instances. As could be expected with this
low incidence of anterior infarction, the incidence of
myocardial fibrosis was relatively low in this group. In
a comparable class of patients, Stinson and Bil-
lingham\textsuperscript{1} also described such a lack of fibrosis. They
found moderate-to-severe fibrosis in only 25% of seg-
ments with reduced contractile movement. Ideker,
Baltaxe, Bodenheimer, and their colleagues\textsuperscript{13-15} also
reported dyskinesis in segments containing 0% to 5%
fibrosis. Ideker et al.\textsuperscript{15} stated that the fact that asynergy
is associated with myocardial fibrosis does not neces-
sarily mean that fibrosis invariably causes asynergy.
Asynergy and fibrosis may have a common cause:
chronic ischemia.

The most important finding in this group of patients
was that hypokinetic segments not previously infarcted
showed severe myofibrillar lysis. In these patients only
34.5\% of the myocytes in the subepicardium were
normal and only 20.5\% of those in the subendocar-
dium were normal. The histologic lesions found in our
biopsy material from poorly contracting segments
were very similar to the morphologic changes de-
scribed by Geer et al.\textsuperscript{16} in a postmortem study of 13
patients who had fatal chronic ischemic heart disease
but had not had infarction. In this study, however, a
much higher incidence of coagulation necrosis and
fibrosis was found, but it must be taken into account
that all of the patients of Geer et al. died from heart
disease, suggesting a more advanced stage of chronic
ischemic myocardial damage. The results of our study
and those of previous studies provide no evidence with
regard to the reversibility, or the lack thereof, of myo-

fibrillar lysis.\textsuperscript{16-19} In a recent study we demonstrated
that in patients with patent grafts to the previously
uninfarcted anterior wall, reduced anterior wall motion
became normal.\textsuperscript{20} Postoperative function studies indi-
cate an improvement in left ventricular function after
coronary artery bypass grafting.\textsuperscript{21-26} This suggests
some late reversibility of structural damage: the mas-
sive loss of contractile material excludes the possibility
of an immediate recovery of function, as can be seen
after short periods of acute ischemia. Indeed, recovery
of function means regeneration of contractile material
and this process will require time. This is in agreement
with the results of Mintz et al.,\textsuperscript{25} who described an
early (7 days after surgery) decrease in left ventricular
function followed by a late recovery (30 days to 1 year). In patients with ECG evidence of anterior infarction we found a higher incidence of myocardial fibrosis in combination with myofibrillar lysis in the remaining myocytes that apparently survived infarction. This is in agreement with the results of others.3, 17, 27-30 Functional recovery in these segments after revascularization seems to be unpredictable,20-22 and the results probably will depend on the extent of the fibrous component.20 Patients of this group did well after surgery in terms of survival (100% cardiac survival after 2 years), but only 77.4% of them are event free at this time.

The third group of patients was made up of those with compromised ventricles. Their disease was characterized by severe coronary arterial stenosis, severely impaired regional wall motion, and severely reduced global ejection fraction (31%). In contrast to the other two groups, a very high incidence of transmural anterior wall infarctions was found in group III (64%). This high incidence of infarction and the reduction in global ejection fraction suggest that the disease is more pronounced in this group in terms of the severity of coronary pathology and number of vessels involved. In this group of patients we also found a high incidence of fibrosis (mainly subendocardially: 91% of instances) and demonstrated that the remaining myocardium was not normal (there was a considerable amount of myofibrillar lysis). Patients in this group did not do as well after surgery: total survival was only 72.7% and cardiac survival 88.8% at 2 years. Although 88.8% of the survivors were event free after this interval, the question arises as to whether surgical treatment would be superior to medical treatment when long-term survival is considered in this class of patients.

A possible limitation of this study is related to the small amount of myocardium examined histologically (two transmural biopsy specimens, weight ± 15 mg/biopsy). Sampling error can be counteracted by the removal of multiple samples from the same area and by the use of a large patient population. For reasons of safety we limited the number of biopsies to two samples per patient. The transmural biopsy technique used in this study was first reported by Stinson and Billingham3 in patients with coronary heart disease. We have used this technique in previous studies31, 32 and we believe that the sampling error is small and the technique is safe because it is performed under direct vision. A further limitation is that only one particular area of the left ventricle was examined histologically. However, all the other nonhistologic variables, including global ejection fraction, were significantly related to the histology of the segment studied. Furthermore, our definition of the compromised ventricle is not based on a single variable (global ejection fraction ± 30%), but on a combination of all eight variables.

In summary, this study shows that the morphologic picture of a certain myocardial zone can be predicted from preoperative and angiographic parameters. Reduced contractile function is invariably related to myocardial cell degeneration and ECG signs of infarction suggest additional fibrosis. The degree of coronary stenosis also correlates with histology: critical stenosis is associated with significant subendocardial degeneration. With principle-component analysis it was possible to identify profiles of patients with coronary artery disease and to classify them into subtypes of the disease. Patient prognosis in terms of postoperative outcome seems to be related to this classification.

References
5. Lewi PJ: Multivariate data analysis program. Beerse, 1979, Jansen Pharmaceutica N V. (Licensed material, program property of IBM, 5787-FAE[6].)
Multivariate analysis of angiographic, histologic, and electrocardiographic data in patients with coronary heart disease.

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