Predictors of Clinical Course, Coronary Anatomy and Left Ventricular Function After Recovery From Acute Myocardial Infarction

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SUMMARY Patients who survive an acute myocardial infarction (AMI) have significant coronary disease and are at risk for angina pectoris, recurrent myocardial infarction and sudden death. This study provides data gathered prospectively for 106 patients surviving myocardial infarction who had coronary arteriography, left ventriculography and 24-hour electrocardiographic recordings before hospital discharge and were followed 30 months.

Univariate analysis showed that low ejection fraction, proximal left anterior descending coronary disease and significant disease in all three coronary arteries were associated with a high risk of sudden cardiac death. The ECG location or type of infarction was not helpful in predicting mortality, reinfarction or continuing angina. Multivariate analysis of 30 clinical and laboratory variables identified previous myocardial infarction and an ejection fraction less than 40% as the best predictors of mortality; all 13 patients who died were identified by these two variables. Three-vessel coronary artery disease, proximal left coronary disease and complicated late hospital-phase ventricular arrhythmias did not provide additional information about mortality once the information provided by the first two variables was considered. Multivariate analysis identified hypertension, three-vessel coronary disease, postinfarction angina pectoris and previous AMI as significant predictors of recurrent AMI during the 30 month follow-up.

THE RISK OF DEATH in patients who survive acute myocardial infarction (AMI) is highest during the first 6 months after infarction and is increased in those with evidence of left ventricular (LV) dysfunction, complicated ventricular arrhythmias, and continued cigarette smoking. The electrocardiographic pattern of infarction is not as helpful in predicting prognosis in survivors as previously believed. For example, we and others have shown that patients surviving nontransmural (NTM) infarctions may have a prognosis as poor as those who have survived the early phase of a transmural (TM) infarction. Similarly, risk of sudden death is not limited to those with anterior TM infarction, but also is present in survivors of inferior infarction. Recent studies have demonstrated a high prevalence of multivessel coronary artery disease (CAD) in patients surviving inferior AMI. AMI may thus be a marker of the presence of underlying CAD, but not necessarily an indicator of its severity. Previous studies of patients with angina pectoris have shown that the severity of CAD may be more important in determining prognosis than its clinical manifestations.

This study was undertaken to find whether precise knowledge of coronary anatomy and ventricular function improves the assessment of risk in patients who survive AMI compared with the clinical predictors of high risk. Coronary angiography and left ventriculography were performed in 109 survivors of AMI before hospital discharge; the clinical status of 107 patients was determined at 30 months after discharge.

Methods

Between September 1974 and September 1976, patients admitted to the Coronary Care unit (CCU) of The Johns Hopkins Hospital with the diagnosis of AMI were considered for inclusion in this study. Criteria for diagnosis included a typical history of chest pain within 24 hours of admission to the CCU, serial changes on the ECG and abnormal serum creatine kinase (CK) changes. CK was measured at 4-hour intervals for 16 hours, then daily until it returned to a normal value.

Patients older than 66 years and those with life-threatening disease other than CAD were excluded from the study. Also excluded were patients with cardiogenic shock, ventricular septal defect and papillary muscle rupture during AMI. During the study period, 280 patients were admitted who met the selection criteria; 109 of them (39%) agreed to coronary and LV angiography before hospital discharge. These patients gave informed consent for both angiography and longitudinal follow-up.
Clinical Evaluation

A detailed clinical history was obtained from the patient and the family. Regular physical examinations were performed throughout the hospital stay, and each patient was assigned on clinical criteria to Killip class I-III upon admission to the CCU.*

Electrocardiographic Studies

The appearance of Q waves 0.04 second in duration were considered diagnostic of TM infarction and isolated ST- and T-wave changes of NTM infarction.20, 21 An anterior location of the infarction was designated when these changes were noted in leads I, aVL, and V1 through V3; an inferior location when these changes were noted in leads 2, 3, aVF; and a lateral location when these changes were noted in V4 and V5.

In 87 of the 109 patients, a 24-hour ambulatory ECG recording on magnetic tape was made during routine hospital activities within 48 hours of catheterization. The recordings were on an Avionics model 450 electrocardiorecorder and were played back 60 times real-time on an Avionics model 650 electrocardioscanner. Arrhythmias, detected by trained personnel, were written out at normal paper speed (25 mm/sec), analyzed by a cardiac nurse with review by a cardiologist, and categorized according to the modified criteria of Lown and Wolf.22 Patients with unifocal or no premature ventricular contractions (PVCs) were classified as having uncomplicated ventricular arrhythmias; patients with multifocal or more consecutive, or R-on-T PVCs or ventricular fibrillation were classified as having complicated ventricular arrhythmias. The ambulatory ECG tapes were read independent of LV and coronary angiograms, clinical presentation or subsequent course.

Angiography

After obtaining informed consent, catheterization was performed 8–21 days (12.5 ± 1.6 days, mean ± SEM) after admission to the CCU, and included coronary angiography and left ventriculography in right anterior (RAO) and left anterior oblique (LAO) projections using either the percutaneous femoral (Judkins23) or brachial (Sones24) technique.

Left ventriculograms and coronary angiograms were read independently by at least two authors, and one had no prior knowledge of the patients’ identities. When there was a disagreement between these two readings, a third, blind reading was obtained. Segmental LV wall motion from RAO and LAO left ventriculograms was analyzed. Five of the 109 patients had only RAO ventriculograms. Using the two projections, eight ventricular segments25 were identified and characterized as normal, hypokinetic (decreased but retained wall motion), akinetic (no wall motion) or dyskinetic (paradoxical outward expansion during systole). LV systolic and diastolic volumes were calculated using the area-length method26 and LV ejection fraction (EF) was calculated for each patient.

Each patient was considered to have three major coronary arteries: left anterior descending (LAD), left circumflex and right. Coronary artery narrowings were considered hemodynamically significant if the narrowing was greater than 50% of the vessel diameter in any projection. The location of each narrowing was classified according to a 15-segment model.26 Only the most severe narrowing of the coronary artery segments was recorded, and each patient was classified as having one-, two- or three-vessel CAD. Significant narrowings in diagonal branches of the LAD were recorded as distal LAD. Narrowing of the left main coronary artery (LMCA) was considered to represent disease in both the LAD and left circumflex artery. All patients with LMCA narrowings also had narrowings in the LAD proximal to the first septal branch.

Correlating the location of coronary lesions with regional LV wall motion requires an assumption of which coronary artery perfuses a given LV segment.26 We have assumed that the anterior LV wall and the ventricular septum are perfused by the LAD. The lateral wall is considered the territory of the circumflex artery and the proximal inferior and diaphragmatic walls of the right coronary artery. The distal inferior wall was felt to be supplied by the right coronary artery when the circumflex artery system was small, but in most patients was recorded as being supplied by the circumflex artery.

Complications

Five complications resulted from cardiac catheterization in our patients. Two patients had a femoral artery thrombosis, which was treated surgically; these patients have had no subsequent symptoms. A 52-year-old man with inferior MI had an anterior transmural AMI at the time of catheterization, possibly caused by catheter-induced embolus. He has had angina pectoris (AP) and congestive heart failure since, but has returned to work. Because this particular complication significantly altered his coronary anatomy, he has been excluded from follow-up analysis. Another 52-year-old man, who had rest angina after AMI, developed ischemic signs and symptoms in both lower extremities and right hemiparesis 2 hours after catheterization, probably caused by arterial emboli. An organized thrombus was removed from the femoral arteries and no symptoms of lower-extremity ischemia are present, but the right hemiparesis persists. A 52-year-old woman had transient aphasia and right arm weakness 24 hours after catheterization and has since remained asymptomatic.

Follow-up

The clinical status of all patients was evaluated at 3, 6, 12, 18, 24 and 30 months after catheterization. Clinical status, physical examination, resting ECG, chest x-ray and 24-hour ECGs were obtained at each visit. In addition, each patient was followed by his private physician, who had access to all study results.
and who regulated therapy. No attempt was made to standardize medical therapy. In the present study, AP after AMI was diagnosed by the patient's description of his symptoms. Follow-up is complete on 107 of the 109 patients who had angiography. Follow-up information on the 171 patients who refused angiography is not available. Because one patient was excluded from follow-up because of AMI at the time of angiography (noted above), subsequent analyses include 106 patients. For the purposes of statistical analysis only the 30-month results are presented.

### Statistical Methods

Contingency table analysis using chi-square tests of significance was used to test individually the effect of a large number of variables one at a time against the dichotomous outcomes of death, recurrent AMI or angina pectoris, three-vessel CAD, proximal LAD or LMCA disease, and LVEF of less than 40% (tables 1–7). Multivariate stepwise discriminant function analysis, based on the uniform 30 month follow-up data, was then applied in order to consider simul-

#### Table 1. Number of Diseased Vessels Compared with Outcome Variables

<table>
<thead>
<tr>
<th>Number of involved vessels</th>
<th>Total</th>
<th>Dead*</th>
<th>New MI*</th>
<th>AP</th>
<th>CABG</th>
<th>Proximal LCA ≥ 50%</th>
<th>EF &lt; 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>1/28 (4%)</td>
<td>2/28 (7%)</td>
<td>10 (36%)</td>
<td>0</td>
<td>7 (25%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>1/18 (6%)</td>
<td>4/18 (22%)</td>
<td>15 (68%)</td>
<td>4 (18%)</td>
<td>9 (41%)</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>3</td>
<td>56</td>
<td>11/41 (27%)</td>
<td>6/41 (15%)</td>
<td>43 (77%)</td>
<td>15 (27%)</td>
<td>44 (79%)</td>
<td>21 (38%)</td>
</tr>
</tbody>
</table>

*p < 0.025† NS  p < 0.025  p < 0.025  p < 0.001  p < 0.05

*Excluding 19 patients who had CABG surgery.
†Number of vessels with 50% or greater obstruction (see text).
‡p values for columns above the solid line (contingency table analysis, 2 × 3 matrix)

Abbreviations: AP = angina pectoris; CABG = coronary artery bypass graft surgery; EF = ejection fraction; LCA = left coronary artery stenosis, including 12 patients who had left main coronary artery stenosis ≥ 50% and 48 with left anterior descending stenosis ≥ 50%.

#### Table 2. Proximal Left Coronary Artery Disease Compared with Outcome Variables

<table>
<thead>
<tr>
<th>Proximal LCA§</th>
<th>Total</th>
<th>Dead*</th>
<th>New MI*</th>
<th>AP</th>
<th>Extent CAD‡</th>
<th>EF &lt; 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>60</td>
<td>11/41 (27%)</td>
<td>4/41 (10%)</td>
<td>46 (77%)</td>
<td>44 (73%)</td>
<td>7 (12%)</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>2/46 (4%)</td>
<td>8/46 (17%)</td>
<td>22 (48%)</td>
<td>12 (26%)</td>
<td>21 (46%)</td>
</tr>
</tbody>
</table>

*p < 0.01† NS  p < 0.05  p < 0.001  p < 0.005

*Excluding 19 patients who had coronary artery bypass grafting.
†p values for columns above the solid line.
‡Extent of coronary artery disease—number of vessels with 50% stenosis.
§Includes 12 patients with left main coronary artery and 48 with proximal left anterior descending coronary artery stenosis.

Abbreviations: LCA = left coronary artery; MI = myocardial infarction; AP = angina pectoris; CAD = coronary artery disease; EF = ejection fraction.

#### Table 3. Left Ventricular Ejection Fraction Compared with Outcome Variables

<table>
<thead>
<tr>
<th>Ejection fraction</th>
<th>Total</th>
<th>Dead*</th>
<th>New MI*</th>
<th>AP</th>
<th>3-vessel‡ CAD</th>
<th>Proximal‡ LCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30%</td>
<td>8</td>
<td>6/7 (86%)</td>
<td>1/7 (14%)</td>
<td>3 (38%)</td>
<td>6 (75%)</td>
<td>7 (88%)</td>
</tr>
<tr>
<td>30–39%</td>
<td>21</td>
<td>3/17 (18%)</td>
<td>1/17 (6%)</td>
<td>16 (76%)</td>
<td>15 (71%)</td>
<td>17 (81%)</td>
</tr>
<tr>
<td>40–49%</td>
<td>26</td>
<td>2/18 (11%)</td>
<td>3/18 (17%)</td>
<td>17 (65%)</td>
<td>17 (65%)</td>
<td>16 (62%)</td>
</tr>
<tr>
<td>≥50%</td>
<td>51</td>
<td>2/45 (4%)</td>
<td>7/51 (14%)</td>
<td>32 (63%)</td>
<td>18 (35%)</td>
<td>20 (39%)</td>
</tr>
</tbody>
</table>

*p < 0.005†  p < 0.01

*Excluding 19 patients who had coronary artery bypass grafting.
†p values for columns above the solid line (contingency table analysis, 2 × 4 matrix).
‡Stenosis ≥ 50%.

Abbreviations: MI = myocardial infarction; AP = angina pectoris; CAD = coronary artery disease; LCA = left coronary artery.
Variables considered included all of those appearing in tables 1–7 as well as obesity, cigarette smoking, admission systolic and diastolic blood pressures, 3-month blood pressure, duration of AP premyocardial infarction, cholesterol, triglycerides, atrioventricular block, LV hypertrophy on ECG, peripheral vascular disease, peak CK, collaterals and number of “risk segments.” This approach has been applied successfully to similar data in previous work. The independent variables were separately examined for their ability to discriminate patients into proper dichotomous classifications of death, angina, three-vessel CAD and proximal left coronary disease. This technique, in addition to ranking the independent variables in order of their contribution to the discrimination, also allows for statistical significance testing of that contribution of each step. Therefore, we could assess whether a variable makes a significant contribution over and above the other variables studied. The p values presented in the technique refer to the statistical tests of significance of additional information provided by the variable being tested to the information provided by the variables already being used.

Table 4. Myocardial Infarct Location and Type Compared with Clinical Outcome Variables

<table>
<thead>
<tr>
<th>Location</th>
<th>Total</th>
<th>Dead*</th>
<th>New MI*</th>
<th>AP</th>
<th>CABG</th>
<th>Peak CK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>TM</td>
<td>29</td>
<td>7/25 (28%)</td>
<td>3/25 (12%)</td>
<td>15 (52%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td></td>
<td>NTM</td>
<td>21</td>
<td>1/16 (6%)</td>
<td>2/16 (13%)</td>
<td>16 (76%)</td>
<td>5 (24%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>TM</td>
<td>35</td>
<td>3/30 (10%)</td>
<td>5/30 (17%)</td>
<td>21 (60%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td></td>
<td>NTM</td>
<td>8</td>
<td>1/6 (17%)</td>
<td>1/6 (17%)</td>
<td>5 (63%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Lateral</td>
<td>NTM</td>
<td>13</td>
<td>1/10 (10%)</td>
<td>1/10 (10%)</td>
<td>11 (85%)</td>
<td>3 (25%)</td>
</tr>
</tbody>
</table>

*Excluding 19 patients who had CABG surgery.

Table 5. Myocardial Infarct Location and Type Compared with Angiographic Findings

<table>
<thead>
<tr>
<th>Location</th>
<th>Total</th>
<th>Extent CAD†</th>
<th>Proximal†</th>
<th>EF &lt; 40%</th>
<th>Anterior akinetic</th>
<th>Inferior akinetic</th>
<th>Lateral akinetic</th>
<th>Number akinetic segments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>TM</td>
<td>29</td>
<td>14 (48%)</td>
<td>12 (41%)</td>
<td>18 (62%)</td>
<td>18 (62%)</td>
<td>25 (86%)</td>
<td>6 (21%)</td>
</tr>
<tr>
<td></td>
<td>NTM</td>
<td>21</td>
<td>13 (62%)</td>
<td>4 (19%)</td>
<td>15 (71%)</td>
<td>4 (19%)</td>
<td>12 (57%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Inferior</td>
<td>TM</td>
<td>35</td>
<td>20 (57%)</td>
<td>6 (17%)</td>
<td>18 (50%)</td>
<td>4 (11%)</td>
<td>10 (29%)</td>
<td>30 (86%)</td>
</tr>
<tr>
<td></td>
<td>NTM</td>
<td>8</td>
<td>4 (50%)</td>
<td>2 (25%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Lateral</td>
<td>NTM</td>
<td>13</td>
<td>5 (38%)</td>
<td>4 (31%)</td>
<td>7 (54%)</td>
<td>3 (23%)</td>
<td>6 (46%)</td>
<td>5 (38%)</td>
</tr>
</tbody>
</table>

*p values for columns above the solid line (contingency table analysis, 2 × 5 matrix).
†Stenosis ≥ 50%.

Abbreviations: TM = transmural; NTM = nontransmural; MI = myocardial infarction; AP = angina pectoris; CABG = coronary artery bypass graft; CK = creatine kinase.

Results

The mean age of 106 patients was 48.6 ± 9.9 years (± sd) (range 27–66 years). Seventy-eight were men and 28 were women. Thirteen of 87 patients treated medically died 3 weeks to 30 months after AMI; six died within 3 months, two within 6 months, another two within 12 months and three others 12–30 months after AMI. Eleven of these 13 patients died within 1 hour of the onset of any symptoms and are considered sudden deaths. The other two patients died within 24 hours of onset of a new myocardial infarction. Reinfarction during the follow-up period occurred in 12 of 87 medically treated patients. AP was noted in 68 of the 106 patients during the follow-up period.

Coronary Artery Bypass Graft Surgery and Clinical Outcome

Coronary artery bypass graft (CABG) surgery was performed in 19 of the 106 patients (18%), the indication being unstable or intolerable AP in 17 and high-grade narrowing of the LMCA in two. The effect of
CABG surgery on mortality in patients with CAD is controversial; additionally, CABG surgery was not applied in a controlled, randomized fashion in the present study. Therefore, we excluded the 19 surgical patients from subsequent analyses of mortality (table 1–7), so that there were 13 deaths among 87 medically treated patients (16%).

Five of the 19 patients who had CABG surgery died either intra- or perioperatively. The EFs of those who died after CABG surgery were 28%, 37%, 38%, 45% and 60%. Two of the five had LMCA narrowings of greater than 70% and two others had surgery within 3 weeks of AMI because of continuing AP at rest. Fourteen surgical patients have survived; 10 have had no AP and four have stable exertional angina.

There is question about whether exclusion of CABG patients skews the analysis of those features associated with mortality. All of the CABG patients who died had three-vessel CAD and proximal LAD disease, and three of the five had an EF of less than 40%. Four of the five had a history of MI; two were Killip class III and two others were Killip II on admission to the CCU. If this information is applied to tables 1–7, the features that most accurately predicted mortality among medically treated patients also were most useful in surgical patients. Finally, multivariate analysis was applied to the combined medical and surgical group: prior infarction and LVEF less than 40% were the significant predictors of mortality. This result is similar to that obtained when considering medical patients only.

**Relation of Angiography to Outcome Variables**

Twelve of the 106 patients had LMCA narrowings of 50% or more. Of these patients, five have been treated medically and only one of the five has died. The four medical survivors have 50% stenosis of the LMCA, and only one has AP. Seven patients had CABG, the indication being AP in five and high-grade
Table 7. Clinical Features and Outcome Variables

<table>
<thead>
<tr>
<th>History of hypertension</th>
<th>Total</th>
<th>Dead*</th>
<th>New MI*</th>
<th>AP</th>
<th>CABG</th>
<th>Extent CAD</th>
<th>Proximal LAD</th>
<th>EF &lt; 40%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>53</td>
<td>10/44 (23%)</td>
<td>12/44 (27%)</td>
<td>39 (74%)</td>
<td>9 (17%)</td>
<td>37 (70%)</td>
<td>6 (11%)</td>
<td>31 (58%)</td>
</tr>
<tr>
<td>No</td>
<td>53</td>
<td>3/43 (7%)</td>
<td>0/43</td>
<td>29 (55%)</td>
<td>10 (19%)</td>
<td>19 (36%)</td>
<td>22 (42%)</td>
<td>29 (55%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>*p &lt; 0.1</td>
<td></td>
<td>*p &lt; 0.001</td>
<td></td>
<td>p = 0.07</td>
<td></td>
<td>p &lt; 0.005</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (years)</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>25</td>
<td>4/25 (16%)</td>
<td>3/25 (12%)</td>
<td>12 (48%)</td>
<td>1 (4%)</td>
<td>5 (20%)</td>
<td>13 (52%)</td>
<td>9 (36%)</td>
</tr>
<tr>
<td>40–49</td>
<td>23</td>
<td>1/18 (6%)</td>
<td>3/18 (17%)</td>
<td>14 (61%)</td>
<td>4 (17%)</td>
<td>11 (48%)</td>
<td>6 (26%)</td>
<td>15 (65%)</td>
</tr>
<tr>
<td>≥ 50</td>
<td>58</td>
<td>8/44 (18%)</td>
<td>6/44 (14%)</td>
<td>42 (72%)</td>
<td>14 (24%)</td>
<td>41 (69%)</td>
<td>9 (16%)</td>
<td>36 (62%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>*p &lt; 0.025†</td>
<td>*p &lt; 0.001</td>
<td>*p &lt; 0.01</td>
<td></td>
<td>p &lt; 0.025</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excluding 19 patients who had CABG surgery.
†p values for columns above the solid line (contingency table analysis).
‡For more than one month prior to hospital admission.

Abbreviations: MI = myocardial infarction; AP = angina pectoris; CABG = coronary artery bypass graft; CAD = coronary artery disease; LAD = left anterior descending coronary artery; LMCA = left main coronary artery; EF = ejection fraction.

LMCA narrowing in two who were asymptomatic. Two of the surgically treated patients died perioperatively; both of them had postmyocardial infarction AP. Eight of the 12 with LMCA stenosis had either inferior or lateral infarction; two had anterior TM and two anterior NTM infarction. Thus, the ECG pattern of infarction was not predictive of LMCA stenosis. However, some clinical features were more frequently observed among patients with than those without LMCA stenosis. Eight of the 12 (67%) had a prior infarction, compared with 20 of the 94 (21%) patients without LMCA stenosis (p < 0.05). Seven of the 12 (58%) were in Killip class II or III compared with 38 of the 94 (40%) of those without LMCA stenosis (NS). Four of those with LMCA stenosis had LVEF less than 40%, and all 12 had three-vessel CAD.

The influence of the extent of CAD on outcome is shown in table 1. Fifty-six of 106 patients had three-vessel CAD and only 28 had one-vessel CAD. The mortality after AMI was much higher in patients with three-vessel than in those with less extensive CAD. Patients with three-vessel CAD were more likely to have a low EF or disease in the left coronary artery proximal to the first septal perforator (including both LMCA and proximal LAD). Although the mortality was greatest in the patients with multivessel disease, the 28 patients with one-vessel disease, one died, two have had new infarction and 10 have had AP after recovery from infarction.

The effect of proximal left CAD on outcome is shown in table 2. Proximal LAD narrowings without LMCA narrowings were observed in 48 patients; 10 died (21%). Only two patients died without a demonstrable narrowing of the LAD proximal to the first septal perforator branch. Proximal LAD disease also was often accompanied by a low EF, postinfarction AP and multivessel CAD (table 2).

A low EF was a significant predictor of increased mortality (table 3). Six of seven patients with EF less than 30% died, while only four of 77 with EF of 40% or greater died. A low EF did not have a significant association with AP or reinfarction during follow-up. However, patients with a low EF were more likely to have extensive CAD. Patients with EF less than 40% had an average of 2.7 ± 1.1 akinetic or dyskinetic LV segments, and those with EF of 40% or higher had an average of 1.6 ± 1.3 akinetic or dyskinetic segments (not significantly different). Low EF was more common in patients with clinical evidence of LV dysfunction, such as advanced Killip class during AMI and cardiomegaly, as well as in patients with previous infarction or anterior TM MI (vide infra).

LV Risk Segments

Contracting, presumably viable, myocardial segments perfused by a narrowed coronary artery might be considered at risk for subsequent ischemia and are referred to as risk segments. None of the 22 patients without an LV segment at risk for further ischemia have died or had reinfarction. Three of 22 with no risk segments have had postinfarction AP (14%), compared with a 75% incidence of AP among those with risk segments (p < 0.01). Four of these 22 patients without risk segments have narrowings of the proximal LAD (with no motion of anteroseptal LV
segments), and five of the 22 have EF less than 40%. Thus, the good prognosis of this group of 22 patients without risk segments is not related to absence of other angiographic predictors of risk.

Collateral Circulation

Angiographically demonstrable collaterals were observed in 65 of the 106 patients. Of the 87 followed medically, nine of 50 (18%) with collaterals died and three of 37 (8%) without collaterals died (NS). As previously suggested by Connolly,28 there was an association of collaterals with AP during the follow-up. In our study, 34 of the 65 (52%) with collaterals had AP and only 14 of 41 (34%) without collaterals had AP (p < 0.1). This likely is because of the common association of collaterals and multivessel CAD: 43 of 56 (77%) with three-vessel, 12 of 22 (55%) with two-vessel and 10 of 28 (36%) with one-vessel CAD had collaterals (p < 0.005). Clinically apparent ischemic heart disease before AMI was the only clinical predictor of a developed collateral circulation. Thus, 34 of 48 (71%) patients with and 31 of 58 (53%) without a history of AP before AMI had coronary collaterals. Similary, 22 of 38 (79%) with and 43 of 78 (55%) without a history of AMI had collaterals (p < 0.05). NTM infarction was not associated with collaterals more often than TM infarction; 21 of 42 (50%) patients with NTM infarction had collaterals and 44 of 64 (69%) with TM infarction had collaterals. The incidence of collaterals was similar in patients with or without a history of hypertension, diabetes mellitus, cigarette smoking or obesity.

Electrocardiographic Location of the Acute Infarction

AMI location by ECG had no significant influence on mortality after discharge (table 4). Three of 32 (9%) medically treated patients with NTM infarction died, compared with 10 of 55 (18%) with TM infarction who died (NS). Reinfarction and AP were observed with equal frequency in those with TM and NTM infarction. The peak CK level was highest in patients with anterior TM infarction and lowest in those with NTM infarction.

Coronary angiography showed an equal frequency of three-vessel CAD between those with TM and NTM infarction and between those with anterior and inferior infarction (table 5). Proximal left coronary narrowing (LMCA and proximal LAD lesions) was seen slightly but insignificantly more often in those with anterior infarction. As noted previously, only two patients with LMCA stenosis had anterior TM infarction and two others had anterior NTM infarction.

Those with anterior TM infarction did have significantly lower EFs than others (table 5). Anterior akinesis was seen more often in patients with anterior infarction. The high incidence of akinesis in patients with anterior TM infarction was not surprising, but in addition, 12 (57%) of those with anterior NTM infarction had akinesis anteriorly; eight of these 12 patients had akinesis in the mid-anterior wall and four had apical akinesis.29 Inferior akinesis was most frequently associated with inferior TM infarction.

Clinical Features

Previous AMI was the clinical feature that correlated best with late mortality (table 6). Twenty-eight of the 106 patients had at least one previous AMI. Six of these 28 subsequently had CABG surgery. Of the remaining 22 patients with previous AMI, nine died, giving patients with previous AMI twice the mortality rate of patients without previous AMI (p < 0.001). All four patients who died and had no history of AMI had proximal LAD disease and three of these four had EF of less than 30%. Although patients with previous AMI had a higher incidence of three-vessel CAD, they did not have an appreciably higher incidence of postinfarction AP (table 6). Low EF was more common among patients with previous AMI.

Advanced Killip class, an indicator of increased late mortality, also was associated with proximal LAD disease and low EF (table 6). Killip class II or III was observed in 19 of 29 patients with anterior TM infarction, 15 of 35 with inferior TM infarction and 11 of the remaining 42 patients with NTM infarction (p < 0.05). None of the patients with NTM infarction were in Killip class III. The incidence of clinical LV failure in the CCU was slightly higher in patients with previous AMI; 14 of 28 of those with previous AMI were in Killip class II or III while 31 of 78 without previous AMI were in Killip II or III.

Cardiomegaly correlated well with low EF (table 6). Additionally, 17 of 24 (70%) patients with cardiomegaly were in Killip class II or III, while only 24 of 82 (33%) without cardiomegaly were in Killip II or III (p < 0.005). Mortality was twice as high in patients who had cardiomegaly (NS) (table 6). Cardiomegaly was not helpful in predicting postinfarction AP or in detecting three-vessel CAD or proximal LAD or LMCA disease.

Ventricular Arrhythmias

Ventricular tachycardia (VT) during the first 72 hours after AMI occurred in 22 patients and ventricular fibrillation (VF) in seven. Four patients had accelerated idioventricular rhythm and are not included in the group with VT. The occurrence of early VT or VF did not predict late mortality (table 6). Additionally, these early arrhythmias had no positive correlation with recurrent infarction, postinfarction AP, multivessel CAD, proximal left coronary artery disease or poor LV function. Complex late hospital-phase ventricular arrhythmias were observed in 45% of patients, compared with a 30% incidence in those without VT or VF in the first 72 hours after AMI.

Patients with complicated ventricular arrhythmias in the late hospital phase of AMI had twice the mortality rate and twice the incidence of low EF, although neither was statistically significant (table 6). There was a significant increase in the incidence of three-vessel CAD and proximal LAD disease in those with complicated arrhythmias.

There was no association of late ventricular arrhythmias with a particular AMI location (anterior vs inferior) or type (TM vs NTM). Patients with a history of MI had a 79% (19 of 24) incidence of com-
plex late-hospital-phase arrhythmias, compared with a 14% (12 of 63) incidence in those who had their first infarction \( (p < 0.005) \). Patients with complex late arrhythmias also often had a history of hypertension \( (12 \text{ of } 43 \text{ vs nine of } 42, p < 0.01) \) and were older than 50 years \( (22 \text{ of } 45 \text{ vs eight of } 40, p < 0.01) \).

Fourteen patients had VT when monitored 10–14 days after AMI and three have died (21%). However, three of 33 (9%) with no arrhythmia and two of 19 (11%) with infrequent, uniform PVCs (Lown class I) died in the follow-up period. Thus, 24-hour monitoring 10–14 days after AMI identified a group at high risk, but this high-risk group did not include all patients who died.

**Other Risk Factors**

The influence of other clinical features on clinical outcome and angiographic findings is summarized in table 7. Patients with a history of hypertension had a high rate of reinfarction and more extensive CAD. Their mortality was triple that of patients without hypertension \( (\text{NS}) \). Complex ventricular arrhythmias in the late hospital phase of infarction also were more common in the hypertensive group. Systolic (\( \geq \) 150 mm Hg) or diastolic (\( \geq \) 90 mm Hg) hypertension at the time of CCU admission or 3 months after infarction was less effective than a history of hypertension in predicting clinical outcome.

Hypertension at the time of AMI was more common in those with than those without a history of hypertension. Only 22 of 53 patients with hypertension by history had a systolic blood pressure \( \geq \) 150 mm Hg, and 30 had a diastolic blood pressure \( \geq \) 90 mm Hg upon hospital admission. However, of 53 patients without a history of hypertension, only six had an elevated systolic and 10 an elevated diastolic blood pressure on admission \( (p < 0.005) \). Three months after AMI, 55% of those without a history of hypertension and 65% who had hypertension on admission (blood pressure \( \geq \) 150/90 mm Hg) had persistent hypertension.

Unlike previous reports involving larger populations with no limitation of age,\(^2,4\) there was no significant relationship between age and mortality or reinfarction, probably because this study excluded those older than 66 years or with noncardiac disease. Older patients had a higher incidence of multivessel CAD and somewhat more AP than younger patients. Those younger than 40 years old had a 52% chance of having one-vessel CAD. Low EF and proximal LAD disease were more frequent, but not significantly so, in older patients.

Risk factors for CAD, including cigarette smoking (greater than 10 pack-years), diabetes, obesity and hyperlipidemia, had no significant effect on mortality after AMI. This may confirm earlier reports about the lack of additional prognostic value of these factors once CAD has manifested itself clinically.\(^8\)

AP for more than 1 month before AMI was noted in 48 patients (table 7). This was associated with a higher mortality, rate of reinfarction, and incidence of AP after AMI as well as with more extensive CAD. Postinfarction AP was noted in 99% of those with AP before AMI and developed in 30% of those who had not had AP before AMI \( (p < 0.01, \text{table 7}) \).

**Multivariate Analysis**

All variables that correlated with mortality after infarction that were significant \( (p < 0.1) \) were included in stepwise, discriminant-function analysis of death among 87 medically treated patients, and the result is presented as a classification matrix in table 8. A history of infarction and an EF of less than 40% were independent predictors of mortality. Using these two variables, 51 of 74 (69%) living patients were correctly identified as being alive, and all 13 dead patients were so identified. Age, history of hypertension, AMI location and type, Killip class, three-vessel CAD, proximal LAD disease or LMCA disease, postinfarction angina or recurrent infarction did not provide a significant additional contribution to prediction or mortality. Analysis of mortality for the combined group of both medical and surgical patients produced a similar result: previous AMI and low EF were significant predictors of mortality.

Application of this multivariate technique to recurrent AMI during the 30 month follow-up showed that a history of hypertension \( (p < 0.001) \), three-vessel CAD \( (p < 0.01) \), postinfarction AP \( (p < 0.05) \) and prior AMI \( (p < 0.05) \) were independent predictors of reinfarction. Using these four variables, all 12 patients who had recurrent infarction were correctly identified and 59 of 75 (70%) of those who did not have recurrent infarction were properly classified.

Multivariate analysis of postinfarction AP in all 106 patients showed that proximal LAD disease \( (p < 0.01) \) and the presence of LV risk segments \( (p < 0.05) \) independently predicted this outcome. These two variables correctly classified 63% of patients with and 66% of patients without angina.

**Table 8. Prediction of Mortality by Stepwise Discriminant Function Analysis—87 Medical Patients**

<table>
<thead>
<tr>
<th>Step</th>
<th>Alive ((n = 74))</th>
<th>Dead ((n = 13))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correctly predicted alive</td>
<td>Correctly predicted dead</td>
</tr>
<tr>
<td>Previous AMI</td>
<td>61 ((82%))</td>
<td>9 ((69%))</td>
</tr>
<tr>
<td>EF (&lt; 40%)</td>
<td>51 ((69%))</td>
<td>13 ((100%))</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(p)</th>
<th>Incorrectly predicted alive</th>
<th>Incorrectly predicted dead</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>23</td>
</tr>
</tbody>
</table>

Degrees of freedom 2, 84; \(F\) statistic = 15.509.
Abbreviations: AMI = acute myocardial infarction; EF = ejection fraction.
Prediction of low EF using discriminant-function analysis showed that cardiomegaly ($p < 0.001$) and proximal LAD disease ($p < 0.01$) were significant predictors. Together, they properly classified 92% of patients with EF less than 40% and 56% of those with EF of at least 40%. Proximal left coronary disease including LMCA and proximal LAD disease were significantly identified by Killip class II or III on CCU admission ($p < 0.01$) and complex late-hospital-phase PVCs ($p < 0.05$). Prediction of three-vessel CAD was best accomplished using late-hospital-phase complicated ventricular arrhythmias ($p < 0.001$), postinfarction AP ($p < 0.001$) and a history of hypertension ($p < 0.05$).

Discussion

This is the first prospective study of patients surviving both TM and NTM infarction which included angiography, and thus, a knowledge of coronary anatomy before hospital discharge. Patients who die in the hospitalization period are included in these analyses, in contrast to previous studies in which angiography was performed 6 weeks or longer after AMI. A similar prospective study is currently in progress at the University of Alabama with patients who had coronary angiography 6 weeks after AMI. Madigan et al. reported an additional 50 patients with NTM infarction who had coronary angiography within 4 weeks of AMI. These prospective studies also differ from others in that the indication for angiography was assessment of prognosis as part of the research protocol; other reports of patients culled from catheterization laboratory files presumably had coronary angiography for specific clinical indications rather than assessment of prognosis.

Univariate chi-square analyses of our results (tables 1-7) provide useful descriptive information. For example, among survivors of AMI we found that the incidence of multivessel CAD, proximal left coronary disease (LMCA and proximal LAD disease) is high (tables 1 and 2), and is not appreciably lower in patients having NT or inferior AMI than in those having anterior or TM infarction (table 5). AMI thus appears to be a marker of advanced CAD and its ECG manifestation is not a reliable indicator of the extent of disease or prognosis.

Other clinical features of AMI have considerable prognostic value, however. Using multivariate analysis, a history of AMI was the most powerful predictor of mortality and survival. This variable correctly classified 82% of survivors and 70% of those who died. The addition of a single angiographic finding, an EF of less than 40%, allowed proper identification of all 13 patients who died. Thirty-six patients were included in a high-risk group using history of infarction and EF of less than 40%. This high-risk group thus had a mortality of 36% (13 of 36) during the 2½-year follow-up. Possibly of equal importance is that a group of patients with very low risk of dying was identified using these two variables; none of 51 patients in the low-risk group died (table 8).

A potential error of stepwise discriminant function analysis is the exclusion as insignificant of a variable that offers unique information. In the present study, for example, three-vessel CAD and proximal left coronary disease were not identified as contributing uniquely to estimates of mortality. The stepwise method, instead, having chosen previous AMI and EF less than 40%, found that knowledge of coronary anatomy added no further or unique information.

Another clinical feature found not to provide additional independent predictive information by multivariate analysis was late-hospital-phase complicated ventricular arrhythmias. Schulze et al. using stepwise discriminant function analysis, identified previous AMI to be the most important factor that separates those with from those without late-hospital-phase complicated ventricular arrhythmias. They additionally showed that complicated arrhythmias are more common in patients with extensive LV injury, a result consistent with our own conclusions and with those of Califf et al. Thus, once the history of infarction and a reduced EF are taken into account, serious arrhythmias add no predictive information. The recent studies of Davis et al. and Ruberman et al. have identified complicated PVCs in the recovery phase of AMI as providing important predictive information of survival independent of heart failure and history of MI. Additionally, both of these studies established that uniform PVCs, even if frequent, did not provide such independent predictive information. The complicated arrhythmias probably occurred in patients with extensive myocardial damage.

In contrast to the risk of sudden death, prediction of recurrent MI was significantly improved when multivessel disease was considered in multivariate analysis. Hypertension, however, was the most powerful predictor of recurrent MI, suggesting that hypertension works independently of coronary anatomy in producing further ischemic injury. It may be that hypertensive patients, with an increased risk of repetitive ischemic damage, will have worse prognosis beyond the 2½-year follow-up period of this study; this was true in the long-term study of Norris et al.

Patient selection is a potential problem with the present study. Patients admitted to The Johns Hopkins Hospital CCU may not be representative of those with AMI admitted to community hospitals. Additionally, those who chose to have coronary angiography in a research setting may not be typical of all patients. This introduces potential patient selection error, yet our results are strikingly similar to those previously reported. Norris et al., the Coronary Drug Project, and Davis et al. identified previous AMI as a major indicator of poor prognosis in large clinical series. The other clinical variables identified as significant predictors of mortality by those studies were related to LV dysfunction. Knowledge of LVEF, a more specific measure of LV function than Killip
class, heart size or late-hospital-phase arrhythmias, resulted in a much shorter list of variables providing independent predictive information in the present study. The 2½-year mortality of 17% in this group of 106 intensively studied patients after MI was not greatly different from the 22% 3-year mortality reported by Norris et al. for patients under age 60 years.44 or the 13% 3-year mortality reported by the Coronary Drug Project for male survivors of AMI under age 65 years.3 This suggests that selection bias as a result of either the university hospital population or acceptance of catheterization is not a significant factor.

Surgical treatment of 18% of patients in this study may affect the validity of mortality data (table 1-7). When the combined medical and surgical groups were considered, prior AMI and low EF remained the only significant predictors of mortality using multivariate analysis. On the other hand, survivors of CABG surgery, most of whom had three-vessel CAD and proximal LAD disease, could have died without surgery, thus excluding these variables as important in assessing prognosis. The present study, of course, is not a controlled trial of therapy and the effect of surgical and new medical therapies on survival is unknown.

With this reservation in mind, our results do not suggest a need for routine cardiac catheterization after myocardial infarction. Identification of the patient at high risk of dying within 2½ years after AMI can be accomplished using history, physical examination and noninvasive assessment of LV function.45 Further study will be required to determine whether asymptomatic and relatively low-risk patients with a combination of well-preserved ventricular contracture but severe coronary obstructive disease have improved long-term survival with CABG surgery.46 At present, consideration of coronary artery surgery after recovery from infarction should be based on usual indications for surgery, usually disabling AP.

References
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Effects of Methylprednisolone on $P_{50}$, 2,3 Diphosphoglycerate and Arteriovenous Oxygen Difference in Acute Myocardial Infarction

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SUMMARY In a double-blind randomized study, 30 mg/kg of methylprednisolone sodium succinate (MPN) or 15 mg/kg of mannitol placebo (PL) were infused in 28 patients after acute myocardial infarction. Measurements were obtained immediately before and for 24 hours after the initial infarction. The partial pressure of oxygen at 50% saturation of hemoglobin ($P_{50}$) did not change significantly in vitro or in vivo after MPN, whereas 2,3 diphosphoglycerate (2,3 DPG) increased from 13.2 to 14.2 μmol/g Hb ($p < 0.05$) in the group receiving PL. The arteriovenous oxygen difference (Ca-vO$_2$) remained constant after MPN or PL. The cardiac index (CI) increased after MPN ($p < 0.02$) associated with an increase in the oxygen consumption index (CI X A-V O$_2$) from 146 to 170 ml/min/m$^2$ ($p < 0.05$). These data show that MPN increases CI after acute myocardial infarction, but has no specific effects on $P_{50}$, 2,3 DPG or Ca-vO$_2$.

ACUTE MYOCARDIAL INFARCTION is characterized by a reduction in the left ventricular myocardial mass and is often associated with a reduction in blood flow.¹ ² Reduction in tissue perfusion may result in inadequate tissue oxygenation unless compensatory changes occur in the other determinants of oxygen supply: pulmonary gas exchange, the oxygen-carrying capacity of the blood and the shape and position of the oxyhemoglobin dissociation curve (ODC).³⁻⁴ A decrease in the affinity of hemoglobin (Hb) for oxygen enhances oxygenation of the tissues without increasing myocardial work and has been observed during angina pectoris, acute myocardial infarction, low-output cardiac failure and cardiogenic shock.⁵⁻⁹,¹¹⁻¹⁹ Pharmacologic manipulation of the ODC, favoring unloading of oxygen by Hb at the cellular level, is a logical approach to therapy in patients with compromised cardiac performance.⁹,¹¹⁻¹⁵,¹⁹,²¹ The partial pressure of oxygen at 50% saturation of Hb ($P_{50}$) represents the position of the ODC and may be influenced by temperature, pH, P$_{CO_2}$, carboxyhemoglobin (HbCO) and 2,3 diphosphoglycerate (2,3 DPG).¹³,¹⁰,²²⁻²⁶ In vitro studies have shown that increases in $P_{50}$, related to increases in 2,3 DPG, may be achieved by incubating red blood cells with MPN,¹⁸,²⁷⁻²⁹ McCaughan and Bryan-Brown et al.¹¹,²¹,³⁰ reported an increase in $P_{50}$ after MPN in patients with bacterial shock or after massive transfusions of stored blood. The increase in $P_{50}$ was not, however, consistently associated with an increase in 2,3 DPG.

In the present double-blind randomized study, MPN or mannitol placebo (PL) was administered to patients within 12 hours after the onset of acute myocardial infarction to evaluate the influence of MPN on $P_{50}$, 2,3 DPG and the arteriovenous oxygen content difference (Ca-vO$_2$).

Materials and Methods

Thirty patients admitted to our coronary care unit within 12 hours after the onset of acute myocardial infarction were studied during a 12-month period. Acute
Predictors of clinical course, coronary anatomy and left ventricular function after recovery from acute myocardial infarction.
G J Taylor, J O Humphries, E D Mellits, B Pitt, R A Schulze, L S Griffith and S C Achuff

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