Perioperative Myocardial Infarction After Coronary Artery Bypass Surgery
Clinical Significance and Approach to Risk Stratification

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The clinical significance of perioperative myocardial infarction (MI) after coronary artery bypass surgery is not known. Therefore, strategies for the risk stratification of these patients do not exist. This study was undertaken to define the effect of perioperative MI on prognosis after discharge from the hospital and to develop an approach to the risk stratification of these patients. Fifty-nine patients with and 115 patients without perioperative MI were observed for 30 months for the development of cardiac events (death, nonfatal MI, and admission to hospital for unstable angina or congestive heart failure). Patients with perioperative MI were significantly more likely than patients without to have a cardiac event (31% versus 12%, p < 0.01) and multiple events (19% versus 1%, p < 0.001). Cox regression analysis identified two independent predictors of cardiac events other than perioperative MI (relative risk, 2.7): inadequate revascularization (relative risk, 3.5) and depressed (<40%) postoperative ejection fraction (EF) (relative risk, 2.1). Event-free survival rate of patients with perioperative MI varied markedly depending on the number of other negative prognostic variables present. Patients with perioperative MI who were adequately revascularized and had a postoperative EF greater than 40% had an event-free survival rate similar to patients without a perioperative MI (92% versus 87%, p = NS). Patients with perioperative MI who were inadequately revascularized and had depressed postoperative EF had an event-free survival rate of 13% (p < 0.001 versus all other subsets). Event-free survival rate was intermediate (68%) in patients with perioperative MI and with only one of the other two variables (p < 0.001 versus other subsets). In conclusion, perioperative MI adversely affects prognosis. Patients can be stratified into low, high, and intermediate risk subsets based on a simple assessment of the adequacy of revascularization and a determination of residual left ventricular function. (Circulation 1990;82:903–912)

The clinical significance of perioperative myocardial infarctions (MI) occurring after coronary artery bypass surgery (CABG) has puzzled clinicians for many years as evidenced by the number of reports addressing the question.1–18 After numerous studies, there is still no consensus. Studies have been evenly divided between those showing a negative effect on long-term prognosis1,2,6–8,12,14,16,18 and those showing no effect.3–5,9,10,13,17 It is generally agreed that perioperative MI increases in-hospital mortality.12,13,18 However, for those patients who survive to hospital discharge, it is not clear that a perioperative MI has the same adverse consequences as nonoperative MI.18

Most distressing for the clinician is the near-complete lack of data from the “modern era” of cardiac surgery. With the exception of one small study,16 all studies were performed with methods of myocardial preservation that are now outmoded.1–10,12–14,17,18 Hypothermic potassium crystalloid cardioplegia has dramatically changed the practice of surgery,19,20 the incidence of perioperative MI,21 and almost certainly the pathophysiology of perioperative MI. Consequently, the sequelae and clinical significance of perioperative MI may have changed as well.

Given the confusion surrounding the significance of perioperative MI and the paucity of studies from the modern era, it is not surprising that strategies for the risk stratification of these patients have not been
developed. If perioperative myocardial infarctions have a significant impact on postdischarge prognosis, then the same kind of approaches that have been so successfully used in the risk stratification of patients with nonoperative MI might also be applied to the 13,000 patients annually who can be estimated to have a perioperative MI.

There are unique problems of the perioperative period that make this difficult. For example, treadmill performance, so commonly used to evaluate patients with nonoperative MI, is affected by many intercurrent problems unrelated to prognosis (deconditioning, postoperative anemia, incisional pain in the leg, atrial arrhythmias, and so on).

Residual left ventricular function is one critically important determinant of prognosis in patients with nonoperative MI that could be evaluated easily in the perioperative period. If an analysis of predischarge ventricular function improved risk stratification of patients, it would be extremely helpful.

The purposes of this study were 1) to determine the clinical significance of perioperative MI in patients operated on with modern methods of myocardial preservation and 2) to develop an approach to risk stratification of patients after CABG surgery by defining the important predictors of postdischarge prognosis from a number of preoperative, operative, and postoperative variables including residual left ventricular function.

Methods

Patient Population

The study group was selected from a population of male patients who underwent CABG surgery at the West Roxbury Veterans Administration Hospital (the primary cardiac surgery referral center for Veterans Hospitals in the New England states) between July 1981 and June 1985. Patients with previous CABG, concomitant valve replacement, significant valvular heart disease but no valve replacement (that is, greater than 2+ regurgitation or a peak-to-peak aortic valve gradient greater than 20 mm Hg), congenital heart disease, or mechanical complications of acute MI were excluded.

All patients who met criteria for the development of a perioperative MI (new Q waves on postoperative electrocardiogram [ECG] greater than or equal to 0.03 seconds in duration in two or more adjacent leads) and survived to hospital discharge were followed up. In addition, all patients with no exclusion criteria, operated on during 1982 who did not develop pathological Q waves on ECG and who survived to hospital discharge were also followed up. These patients were believed to be representative of those operated on during the 4-year period because during this time there was no change in patient profile (age, percent presenting with unstable angina, preoperative ejection fraction, preoperative left ventricular end-diastolic pressure, number of vessels diseased, and presence of left main coronary artery stenosis), in senior operating room personnel, and in operative techniques (including methods of myocardial preservation, average number of grafts placed per patient, and aortic cross-clamp time) (Table 1). In addition, operative mortality and rate of perioperative MI in 1982 were similar to rates for the other years of the study (Table 1).

Preoperative Variables

The preoperative variables provided information on the patients regarding the extent of coronary artery disease, the severity of left ventricular dysfunction, and their clinical sequelae.

Historical data. Hospital records were reviewed for the patients’ ages and for a history of congestive heart failure (either pulmonary congestion on chest radiography or at least two of the following physical examination findings: S3, rales, or peripheral edema). Previous MI was determined from review of the preoperative ECGs (pathological Q waves in at least two adjacent leads). Unstable angina as the primary indication for surgery was defined as typical chest pain, occurring at rest with a minimum duration of 30 minutes and accompanied by ST segment depression of 1 mm or more or T wave inversion in at least two adjacent ECG leads. In addition, the patient must have been admitted to an intensive care unit and have undergone CABG during the same admission.

Cardiac catheterization. All patients underwent left heart catheterization and coronary arteriography 3 months or less before surgery. Left ventricular end-diastolic pressure was determined before injection of contrast material.

The number of diseased vessels (from one to three) defined as the presence of a 70% or greater luminal narrowing was determined for each patient. The coronary circulation was divided into three

<table>
<thead>
<tr>
<th>TABLE 1. Preoperative and Operative Variables of Control Patients and Patients Undergoing CABG</th>
<th>1982 (n=115)</th>
<th>1981–1985 (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59±7</td>
<td>59±8</td>
</tr>
<tr>
<td>Patients with unstable angina (%)</td>
<td>17</td>
<td>21</td>
</tr>
<tr>
<td>Patients with left main disease (%)</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Ejection fraction by contrast ventriculogram (%)</td>
<td>61±14</td>
<td>59±13</td>
</tr>
<tr>
<td>Vessels diseased (n)</td>
<td>2.8±0.5</td>
<td>2.7±0.5</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>15±5</td>
<td>16±6</td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td>53±18</td>
<td>56±22</td>
</tr>
<tr>
<td>Bypass grafts placed (n)</td>
<td>2.7±0.7</td>
<td>2.9±0.8</td>
</tr>
<tr>
<td>Operative mortality (%)</td>
<td>4.2</td>
<td>4.0</td>
</tr>
<tr>
<td>Patients with perioperative MI (%)</td>
<td>10.8</td>
<td>10.2</td>
</tr>
</tbody>
</table>

Values are mean±SD where appropriate.
CABG, coronary artery bypass graft; LVEDP, left ventricular end-diastolic pressure; MI, myocardial infarction.
regions as previously described\textsuperscript{32}: anterior (supplied by the left anterior descending coronary artery), lateral (supplied by the left circumflex coronary artery), and inferior (supplied by the right coronary artery in right dominant systems or by the left circumflex artery in left dominant systems). Left main coronary artery stenosis (\geq 50\% stenosis) was considered equivalent to two vessels diseased in a right dominant system or to three vessels in a left dominant system. Presence of a left main coronary artery stenosis was also noted separately from the category of number of diseased vessels.

Radionuclide ventriculography. First-pass radionuclide ventriculography was performed during the week before surgery. Details of the technique have been described previously.\textsuperscript{33} Briefly, a bolus of 15 mCi technetium-99m pertechnetate was injected into a large-bore intravenous catheter placed in an antecubital vein. A multicrystal scintillation camera in the 30° left anterior oblique position with a 20° caudal tilt was interfaced with a computer that acquired data at 40 frames/sec. The left ventricular region of interest was defined manually, and a time-activity curve was generated for the left ventricle with use of a computer algorithm. Ejection fraction was determined by averaging the counts of five to eight consecutive beats. Ejection fraction determined by this technique is highly reproducible\textsuperscript{33} and correlates closely with ejection fraction by contrast cineangiography.\textsuperscript{34}

Operative Variables

All patients underwent CABG at a systemic temperature of 25°C. The left ventricle was vented through the right superior pulmonary vein. Distal bypass graft anastomoses were performed during one period of aortic cross-clamping. Myocardial preservation was achieved with cold (4°C) potassium crystalloid cardioplegia administered through the aortic root and through the free ends of the grafts immediately after the distal anastomoses were completed. Topical hypothermia was produced with iced saline slush. The proximal anastomoses were performed with an aortic side-biting clamp while the patient was being rewarmed. In all patients, segments of reversed saphenous vein were used exclusively. The pericardium was left open after surgery.

Data on the duration of aortic cross clamping and the adequacy of revascularization were obtained from review of the operative reports. Revascularization was judged to be adequate if every region (defined above) with a diseased native coronary artery received a bypass graft, even if a diseased branch of the grafted vessel was not bypassed.\textsuperscript{32}

Postoperative Variables

Perioperative myocardial infarction. ECGs were obtained daily for the first five postoperative days and then at least every other day for the remainder of the hospitalization. All ECGs from the hospitalization were reviewed for the development of new Q waves by two physicians unaware of the clinical follow-up. Only pathological Q waves that persisted to hospital discharge were considered diagnostic of perioperative MI. Disagreements were settled by consensus.

In the patients with perioperative MI, location of the infarction was classified as anterior (Q waves in leads V\textsubscript{1} to V\textsubscript{6}, I and aVL) or inferior (leads II, III, or aVF).

Radionuclide ventriculography. First-pass radionuclide ventriculography identical in technique to that of the preoperative study was repeated 7 to 14 days after surgery, during the ambulatory phase of the patient's postoperative recovery and before discharge from the hospital.

Follow-up Data

Follow-up data were obtained from hospital and outpatient charts. For those patients whose Veterans Administration charts did not contain follow-up for 30 months, primary physicians were contacted. If neither of these sources provided complete follow-up (9% of cases), the patient was interviewed by telephone. If the patient denied having been admitted to hospital for any reason after CABG surgery, no further attempt was made to acquire records. If the patient had been admitted for any reason, then hospital charts from all admissions were obtained and reviewed. Four end points were considered by an observer unaware of all other clinical data: 1) cardiac death, 2) nonfatal MI, 3) admission to hospital for treatment of congestive heart failure, and 4) admission to hospital for unstable angina. All events were recorded with the interval from surgery to the occurrence of the event. Deaths were interpreted as cardiac or noncardiac related after review of hospital charts (for all inpatient deaths) or after discussions with family members who were with the patient at the time of death (for outpatient-witnessed deaths). Outpatient-unwitnessed deaths were considered cardiac related if they were sudden, unexpected deaths or if they occurred within 24 hours of the onset of new cardiac symptoms (after discussion with family members). Patients who died from noncardiac causes were considered event free until the day of death and were analyzed as patients without events.

MI was defined as any admission to the hospital during which a rise in CK-MB was documented. Admission for treatment of congestive heart failure required that the admission specifically address congestive heart failure as an active diagnosis and documentation either by pulmonary vascular congestion on the radiogram or at least two of the following physical examination findings: S\textsubscript{3}, rales, or peripheral edema. Unstable angina was defined as typical chest pain occurring at rest with a minimum duration of 30 minutes and accompanied by ST segment depression of 1 mm or more or T wave inversion in at least two adjacent ECG leads.

Because chest pain histories are often difficult to interpret, and nonspecific ST segment and T wave abnormalities are often seen in the first few months after CABG surgery, a minimum duration of hospi-
talization of 5 days was required for the diagnosis of unstable angina. This was done to limit further the number of episodes of nonanginal chest pain that would be given a diagnosis of unstable angina if shorter hospitalizations were allowed.

Statistical Analysis

Follow-up duration and time to event (continuous variables) were expressed as mean±SD. The following continuous variables were reclassified as ordinal variables before data analysis. Left ventricular end-diastolic pressure was grouped as normal (<12 mm Hg), moderately elevated (13–18 mm Hg), or markedly elevated (>18 mm Hg). Duration of aortic cross-clamping was arbitrarily classified as 60 minutes or less, or greater than 60 minutes. Ejection fraction determined by radionuclide ventriculography was classified as normal (>50%), moderately depressed (40–50%), or severely depressed (<40%) based on previously determined normal values from our laboratory and previously used definitions of depressed left ventricular function for risk stratification.29,30

Continuous variables were compared by use of the unpaired two-sample t test. Nominal and ordinal data were compared by use of the χ² or Fisher’s exact test. Differences were considered significant when p was less than 0.01 after Bonferroni’s correction for multiple comparisons.

To compare the prognostic power of the different variables, a Cox proportional-hazards survival analysis was performed with BMDP P2L. Variables were entered or removed according to a stepwise selection process from the regression equation on the basis of a computed significance probability (maximized partial likelihood ratio). This process identified variables correlated with time to event. Only one event (the first) was considered for each patient. The relative risk for each independent variable was expressed as the exponent of the coefficient of the variable in the hazard equation and was directly proportional to the risk contributed by that variable to the model. The p values reported for the predictors correspond to the importance of the variable in predicting an increased hazard for a cardiac event after accounting for all other significant predictors.

Kaplan-Meier survival curves were calculated with BMDP 1L. Both Mantel-Cox and Breslow tests were used to determine the statistical significance of differences in cumulative event rates.

Results

Patient Follow-up

During the 4 years of the study, 62 patients (10.6% of patients undergoing CABG) developed new pathological Q waves on postoperative ECGs. Fifty-nine survived to hospital discharge and were followed up. None were lost to follow-up. During 1982, 115 study-eligible patients without new pathological Q waves on ECG survived to hospital discharge and were followed up. One was lost to follow-up. Two died of noncardiac causes. The mean duration of follow-up (excluding patients who died) was 29.4±2.5 months (range, 23–30 months). Ninety-one percent of patients were followed up for 30 months.

Effect of Perioperative Myocardial Infarction on Event-Free Survival

Cardiac events during the 30-month follow-up period were significantly more frequent in the group who developed a perioperative MI: 31% of patients with perioperative MI had an event versus 12% of the 115 patients without a perioperative MI (p<0.01) (Table 2). Patients with perioperative MI were also more likely to have two or more events: 19% of patients with versus 1% of those without (p<0.001). When the data were analyzed without the less-definite end point of unstable angina, cardiac events remained significantly more common in the group with perioperative MI (25%) compared with events in the group without (7%, p<0.01). For individual end points, trends were toward higher cardiac event rates in the group with perioperative MI but only congestive heart failure reached statistical significance (22% versus 1%, p<0.001). Seventy-seven per-

Table 2. Cardiac Events According to Presence or Absence of a Perioperative Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Perioperative</th>
<th>No perioperative</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>59</td>
<td>115</td>
<td>–</td>
</tr>
<tr>
<td>Cardiac event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>10 (17)</td>
<td>7 (6)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (8)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>13 (22)</td>
<td>1 (1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>5 (8)</td>
<td>5 (4)</td>
<td></td>
</tr>
<tr>
<td>Any cardiac event</td>
<td>18 (31)</td>
<td>14 (12)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Death, MI, CHF</td>
<td>15 (25)</td>
<td>8 (7)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multiple events</td>
<td>11 (19)</td>
<td>1 (1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
MI, myocardial infarction; CHF, congestive heart failure.
cent of patients with congestive heart failure had other cardiac events as well.

Figure 1 is the survival analysis for patients with compared with those without perioperative MI. Eighty-seven percent of patients without a perioperative MI survived event free to 30 months compared with 69% of patients with a perioperative MI ($p<0.009$). In those patients with cardiac events, the first event occurred within the first three months of surgery in 25% of patients and within the first 12 months in 63% of patients.

Univariate and Multivariate Analyses

As in most previously reported series, patients in this series who suffered perioperative MI differed from those who did not in certain preoperative characteristics that might negatively affect postdischarge prognosis (a greater percentage with elevated left ventricular end-diastolic pressure and more advanced age). Thus, survival analysis alone was inadequate to determine whether perioperative MI was an independent predictor of postdischarge cardiac events. To determine this and to detect other independent prognostic variables so that a risk stratification approach could be developed, univariate and multivariate analyses were performed.

Considering all preoperative, operative, and postoperative variables, significant univariate predictors of a cardiac event during follow-up were 1) inadequate revascularization, 2) perioperative MI, and 3) depressed postoperative ejection fraction (<40%) as determined by radionuclide ventriculography. No other preoperative, operative, or postoperative variable was predictive of a subsequent cardiac event (Table 3).

With stepwise Cox regression, all three variables (perioperative MI, inadequate revascularization, and depressed postoperative ejection fraction) remained as independent predictors of cardiac events (all $p<0.01$). Adequacy of revascularization had the greatest prognostic value. Relative risk (or the independent risk of a cardiac event associated with this variable) was 3.6 with a 95% confidence interval of 1.4–8.9. Relative risk for perioperative MI was 2.7 (95% confidence interval, 1.1–6.4) and for depressed postoperative ejection fraction relative risk was 2.1 (95% confidence interval, 1.2–3.8). These three variables remained as independent predictors of subsequent cardiac events when unstable angina was not included as an end point.

Survival Analysis of Subgroups

Figure 2 compares the event-free survival rate in patients who had perioperative MI stratified by the number of additional negative prognostic variables present (inadequate revascularization and depressed ejection fraction). A 30-month event-free survival rate in patients who were adequately revascularized and had had preserved left ventricular function was 92%, not significantly different from patients who did not have perioperative MI (87%). Half of the patients with perioperative MI were in this low-risk group. However, patients with perioperative MI who had one additional negative variable (either inadequate revascularization or depressed ejection fraction) had an event-free survival rate of 68% ($p<0.001$). The event-free survival rate was only 13% in patients with perioperative MI and both variables ($p<0.001$ versus all other groups). This extremely poor event-free survival did not appear to be due solely to severe left ventricular dysfunction because ejection fraction was depressed but only moderately so in this high-risk group (34±5%).

Discussion

Clinical Significance of Perioperative Myocardial Infarction

Perioperative MIs occur in more than 6% of the over 200,000 patients who undergo CABG surgery annually. Despite this relatively high frequency, their clinical significance is not clear. Studies are approximately evenly divided into those showing an impact on morbidity and mortality,1,2,6–8,12,14,16,18 and those showing no impact.3–5,9,10,13,17
TABLE 3. Variables According to the Presence or Absence of a Cardiac Event

<table>
<thead>
<tr>
<th>Event (n=32)</th>
<th>No event (n=142)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preoperative variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.1±7.2</td>
<td>59.3±6.7</td>
</tr>
<tr>
<td>History of CHF</td>
<td>5 (16)</td>
<td>9 (6)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>7 (22)</td>
<td>24 (17)</td>
</tr>
<tr>
<td>MI on ECG</td>
<td>16 (52)</td>
<td>47 (34)</td>
</tr>
<tr>
<td>Catheterization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;13</td>
<td>9 (30)</td>
<td>67 (52)</td>
</tr>
<tr>
<td>13–18</td>
<td>13 (43)</td>
<td>43 (33)</td>
</tr>
<tr>
<td>&gt;18</td>
<td>8 (27)</td>
<td>20 (15)</td>
</tr>
<tr>
<td>Vessels diseased (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One</td>
<td>2 (6)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Two</td>
<td>4 (13)</td>
<td>27 (19)</td>
</tr>
<tr>
<td>Three</td>
<td>26 (81)</td>
<td>111 (78)</td>
</tr>
<tr>
<td>Left main coronary stenosis</td>
<td>7 (22)</td>
<td>30 (21)</td>
</tr>
<tr>
<td>Radionuclide ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>9 (31)</td>
<td>31 (25)</td>
</tr>
<tr>
<td>41–49</td>
<td>11 (38)</td>
<td>48 (39)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>9 (31)</td>
<td>44 (36)</td>
</tr>
<tr>
<td><strong>Intraoperative variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aortic cross-clamp time (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60</td>
<td>27 (84)</td>
<td>109 (79)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>5 (16)</td>
<td>29 (21)</td>
</tr>
<tr>
<td>Grafts per patient (n)</td>
<td>2.9±0.8</td>
<td>2.7±0.7</td>
</tr>
<tr>
<td>Inadequate revascularization</td>
<td>19 (59)</td>
<td>48 (34)</td>
</tr>
<tr>
<td><strong>Postoperative variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative MI</td>
<td>18 (56)</td>
<td>41 (29)</td>
</tr>
<tr>
<td>Radionuclide ejection fraction (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>13 (47)</td>
<td>18 (16)</td>
</tr>
<tr>
<td>41–49</td>
<td>11 (39)</td>
<td>37 (34)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>4 (14)</td>
<td>55 (50)</td>
</tr>
<tr>
<td>*Location of Perioperative MI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior</td>
<td>12 (67)</td>
<td>24 (59)</td>
</tr>
<tr>
<td>Inferior</td>
<td>6 (33)</td>
<td>17 (41)</td>
</tr>
</tbody>
</table>

Values in parentheses are percentages.
*Applies to Perioperative MI patients only.
CHF, congestive heart failure; MI, myocardial infarction; ECG, electrocardiogram; LVEDP, left ventricular end-diastolic pressure.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Event-free survival curves in patients with perioperative myocardial infarction stratified by the number of additional negative prognostic variables present (inadequate revascularization and depressed [<40%] postoperative ejection fraction). There were 26 patients in the 0 additional variables group, 18 patients in the one additional variable group, and eight patients in the two additional variables group. Curves are significantly different from one another (p<0.01). Number of and time of occurrence of cardiac events are below the graph.
There are many possible reasons for these disparate results, including the use of suboptimal diagnostic criteria for perioperative MI in some studies\textsuperscript{5,10} and inadequate numbers of patients in others.\textsuperscript{3,4,7,9,16} However, the major methodological problem with most of the studies is the statistical analyses used. Most of the studies have simply used survival analyses to determine the clinical significance of perioperative MI.\textsuperscript{1-10,13,14,16-18} This approach does not control for the differences in baseline (preoperative) patient characteristics that may affect the survival rate in those who do and those who do not develop a perioperative MI. Patients who develop perioperative MI have been reported to have more extensive coronary artery disease,\textsuperscript{3,16} worse angina,\textsuperscript{2} more extensive surgical procedures,\textsuperscript{2,16} longer bypass times,\textsuperscript{2,13,18,36} or ischemic (cross-clamp) times,\textsuperscript{13,16} fewer coronary artery collaterals,\textsuperscript{12} greater incidence of previous MI,\textsuperscript{8} and worse left ventricular function as evidenced by cardiomegaly on the chest radiogram.\textsuperscript{18} Our patients with perioperative MI also differed from those without in two important preoperative characteristics: They were older and had a higher left ventricular end-diastolic pressure. Results of studies that do not control for covariates such as these are difficult to interpret.

Three prior studies have had sufficient numbers of patients, used adequate diagnostic criteria for perioperative MI, and examined for\textsuperscript{13,18} and, in one case,\textsuperscript{12} controlled for covariates. One showed no effect on in-hospital mortality or late mortality,\textsuperscript{12} and one showed an effect on in-hospital mortality only.\textsuperscript{18} Not surprisingly, some investigators have concluded that perioperative MI does not have the same adverse impact on survival as does nonoperative MI.\textsuperscript{2,5,37}

Theories have been advanced to explain this, but the most plausible one is that the patients with perioperative MI who are adequately revascularized have less residual ischemic myocardium compared with the patient with nonoperative MI.\textsuperscript{38,39} This certainly appeared to be the case at one time. Before the advent of hypothermic potassium cardioplegia as the technique of myocardial preservation, most perioperative MIs were probably due to poor intraoperative myocardial preservation because pathologically most of the infarctions were of the contraction band type (indicative of intraoperative ischemia followed by reperfusion). In the series of Bulkley and Hutchins,\textsuperscript{40} 82% of transmural infarctions were of this type. Furthermore, 68% were in areas supplied by patent grafts. This latter finding was supported by postoperative catheterization studies that have reported that 50–80% of infarctions were in areas supplied by patent grafts.\textsuperscript{17,36,39}

A reduction in this type of infarction almost certainly accounted for the marked reduction in overall rate of perioperative MI after the introduction of cold potassium cardioplegia. The perioperative MI rate abruptly dropped by half at a time when there were no other major changes in operative technique.\textsuperscript{21} Furthermore, the single most important predictor of whether a patient would have a perioperative MI was the method of myocardial preservation.\textsuperscript{21}

Presently, perioperative MIs appear more likely to be associated with a stenosis or occlusion of the bypass graft, especially at its anastomosis with the native coronary artery. In one series, only 25% of patients had patent grafts supplying the area of infarction.\textsuperscript{41} Thus, the resemblance, both pathologic and pathophysiologic, to nonoperative MI is much greater than that for the perioperative MI before cold cardioplegia. Not only is there an infarct, but with the compromised graft, there is residual ischemia as well.

Because the pathophysiology of perioperative MI has changed so dramatically with the use of cold cardioplegia, the clinical significance has probably changed as well. Therefore, we reexamined this question in a group of patients operated on with modern methods of myocardial preservation. Furthermore, we wished to focus on the postdischarge period because the greatest confusion has been over the clinical significance of perioperative MI in this period as opposed to the in-hospital phase.

We found that patients with perioperative MI were far more likely to suffer an adverse event (31% of patients) within the first 2.5 years after surgery than were those without a perioperative MI (12%). Furthermore, multiple events were far more common in patients with perioperative MI.

Perioperative MI remained an important predictor of cardiac events even after controlling for baseline differences in historical variables, preoperative left ventricular function, extent of coronary artery disease, the extent of the surgical procedure, the adequacy of the revascularization procedure, and even postoperative left ventricular function.

In summary, perioperative MI is an important clinical event that adversely affects prognosis. We suspect that the striking difference in findings between our study and many of those before that have not found perioperative MI to be important is because of the marked change in the pathophysiology of perioperative MI after the introduction of hypothermic potassium cardioplegia.

Risk Stratification

With such a high rate of cardiac events in patients with perioperative MI, a risk stratification approach would be clinically helpful. Presently, there are no such approaches\textsuperscript{52} because the important clinical variables predictive of postdischarge prognosis are not known. Because 25% of the events that occurred in the 2.5-year period of the follow-up occurred in the first 3 months after surgery, any approach must be applicable to the early postdischarge period. As noted, many of the usual tests used in the nonoperative MI patient are not applicable to the early postoperative period. The problems with early postoperative exercise testing have been mentioned. The prognostic significance of ventricular arrhythmias on
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predischarge 24-hour monitoring, another important
gistic variable for patients with nonoperative MI, has not been evaluated adequately. In one
preliminary report, which examined all patients undergoing CABG surgery and not just those with
perioperative MI, complex ventricular ectopy was of no help in risk stratifying patients.45

We assessed a number of readily available clinical
variables for their prognostic significance and found
only adequacy of revascularization to be an import-
tant independent clinical predictor of an adverse
outcome. This is not surprising, but data supporting
the contention have been nonexistent, and methods
of defining “inadequate revascularization” have not
been delineated clearly. We used a simple method
that we32 and others44 had used successfully before.

As defined here, inadequate revascularization would
predict in most cases a high likelihood of residual
ischemia in the distribution of a major coronary
artery. The most common reason for failure to revas-
cularize adequately was that the recipient vessel was
decom at surgery to be too diseased to be grafted.

In addition to the clinical variables evaluated, we
evaluated one test that has been used successfully in
the risk stratification of patients with nonoperative
MI—an evaluation of residual left ventricular
function.23–26,29,31 Prognosis in nonoperative MI is
critically related to residual left ventricular function,
and a noninvasive determination of ejection fraction
is one of the few tests that is feasible in the early
postoperative period. Our data showed that predis-
charge ejection fraction provided important pro-
gnostic information over and above that which was readily
available on all patients. With these two variables
(adequacy of revascularization and predischarge
ejection fraction), groups of patients with perioperative
MI with a low risk of a clinical event (neither variable
present, 8%), a high risk (both present, 87%), and inter-
mediate risk (only one of the two present, 32%) could be identified. Thus, patients
with a perioperative MI who are adequately revascu-
larized and have preserved postoperative ejection
fraction have an event-free survival rate (92%) that is
equivalent to that of patients without a perioperative
MI (87%).

The goal of any risk stratification procedure
 bey ond simple prognostication) is to identify high-
and low-risk groups so that therapeutic interventions
can be aimed at the former and the latter can be spared the expense and risk of the intervention. In
patients after CABG surgery, further invasive
options are obviously very limited. Those patients
who were not able to be revascularized usually had
diffusely diseased coronary arteries and are unlikely
to be candidates for percutaneous transluminal cor-

The risk group was not so severely depressed (34±5%)
that they could not tolerate such medications.

Limitations of the Study

One potential limitation of this study is the string-
ent diagnostic criterion for perioperative MI—new
pathological Q waves in at least two adjacent ECG
leads. Certainly, the “no MI” control group may have
contained some patients with non-Q wave perioper-
ative MI.32 However, if less stringent criteria had
been used (cardiac enzymes or less-specific ECG
abnormalities), large numbers of patients with no
infarction would have been included in the perioper-
ative MI group. This, we specifically wished to avoid.

As the study was designed, there was some risk of not
detecting an important effect of perioperative MI
because of the inclusion of some patients with non-Q
wave MI in the control group (whose prognosis may
have been falsely worsened). However, because an
effect of Q wave perioperative MI was found, we can
be certain that it is real.

Second, it should be reiterated that unlike most
previous studies of perioperative MI, this was a study
of patients who survived to hospital discharge. Thus,
some of the preoperative variables that have previ-
uously been shown to affect survival may not have
been predictive in this study. This may be particularly
true of variables such as preoperative unstable
angina. That is, while unstable angina certainly
increases operative mortality, if the patient survives
surgery and the early perioperative period, a history
of unstable angina may have little impact on late

Third, there is a potential concern that our results
may not be applicable to patients who have received
internal mammary artery grafts. We, like other cen-
ters at the time,46 performed far too few internal
mammary artery grafts to be able to determine how
this variable interacted with the other variables in
our model. With the numerous studies showing an
improved prognosis in patients with internal mam-
mary artery grafts,47–49 use of the internal mammary
artery graft has increased, although many surgeons
continue to use saphenous vein grafts exclusively in
most of their nonelective cases. It is conceivable that
in future series of patients in which most will have
one or more internal mammary artery grafts, inade-
quately revascularized and depressed left ventricu-
lar function might not be important prognostic vari-
ables. This seems unlikely, however, especially in
light of findings from one series of patients that
demonstrated that both of these variables were pre-
dictive of future cardiac events independent of
whether or not an internal mammary artery graft was
placed.44

Fourth, we did not assess graft patency postoper-
avely with coronary angiography. Thus, some
patients in the “completely revascularized” group
can be expected to have been incompletely revascular-
ized because of early graft closures. It is imprac-
tical to perform routine postoperative angiography in
a study of this size that was designed to assess prognosis rather than the results of a therapeutic intervention. The approach we used could have falsely worsened the prognosis of the “completely revascularized” control group by including in that group some patients with early graft occlusions. Thus, one can expect that if adequacy of revascularization was assessed with a more sensitive technique, its prognostic power should be at least as great as we found it to be.

Last, it is critical to be able to generalize the results of this study to all patients undergoing CABG. This must be done cautiously because the preoperative data on our patients indicate that they may have had more severe coronary disease than previously reported series. Seventy-eight percent of all patients with 34-48\%12,18), had three-vessel coronary artery disease (compared with 10–11\%12,13). This may explain our higher perioperative MI rate (10.6\%) compared with the 6.4\% rate of the Coronary Artery Surgery Study (CASS),28 performed in patients with much less severe angina, less extensive coronary disease, and better preoperative ventricular function. Thus overall event rates may have been higher in our patients.

It is evident from Table 2 that a larger sample size might have allowed us to detect other univariate predictors of cardiac events. Although true, to our knowledge, this series is the second largest of patients with Q wave perioperative MI reported to date12 and the largest of patients operated on with modern methods of preservation. Furthermore, the sample size does not diminish the significance of the prognostic variables identified. Assessment of the performance of the risk stratification approach in other patient populations should answer these concerns.

Conclusions

In summary, perioperative MI is an important clinical event that has negative prognostic implications. Risk stratification of patients into high, low, and intermediate risk groups can be accomplished by a combination of a readily available clinical variable (adequacy of revascularization) and a simple predischarge test (determination of ejection fraction). Such an approach is important because a large percentage of events tend to occur early after discharge. Last, because ejection fraction even in the highest risk group is not severely depressed, secondary prevention trials with medical therapy may be feasible.

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