Diagnosis of Perioperative Myocardial Infarction by Considering Relationship of Postoperative Electrocardiogram Changes and Enzyme Increases after Coronary Bypass Operation

Andrea Griesmacher, Michael Grimm, Wolfgang Schrelner, and Mathias M. Müller

We report the results of enzyme determinations in sera from 88 patients, 65 of whom showed inconspicuous convalescence, 14 who had myocardial infarction within 24 h (MI 1) after bypass surgery, and nine with myocardial infarction between 24 and 48 h postoperatively (MI 2). We wanted to determine whether the consequent measurement of activities of total creatine kinase (CK), CK isoenzyme MB (CK-MB), lactate dehydrogenase, α-hydroxybutyrate dehydrogenase, and aspartate aminotransferase, conducted as a part of routine laboratory diagnostics, provided meaningful information for diagnosing infarcts besides that obtained from the electrocardiogram. The postoperative mean values of the enzyme activities in blood were significantly different among the three groups; however, only a combined evaluation of CK and CK-MB by means of a discriminant analysis allowed the prediction of MI (sensitivity: MI 1 = 98.5%, MI 2 = 95.4%; specificity: MI 1 = 71.4%, MI 2 = 81.8%). CK >600 U/L or CK-MB >45 U/L supports the diagnosis of acute MI.

Additional Keyphrases: creatine kinase • isoenzymes • lactate dehydrogenase • α-hydroxybutyrate dehydrogenase • aspartate aminotransferase • discriminant analysis

Perioperative myocardial infarction (MI) still is one of the most severe complications in patients undergoing aorto-coronary bypass operations (1). Early diagnosis of infarction is an important condition for optimal postoperative patient management and strongly influences the success rate of the surgical interventions (1). In routine postoperative care the electrocardiogram (ECG) still offers the most effective method for detection of MI; however, its usefulness in the postoperative setting is limited (2, 3). On the other hand, the clinical relevance of infarct-associated increases of enzyme activities in plasma is strongly diminished in cardiac surgery: The increase of enzyme activities in blood, induced by the general operative trauma, is judged to be a common event (4), which, therefore, masks the diagnostic effectiveness of these otherwise sensitive markers (5–9). Consequently, increased enzyme values are routinely accepted after cardiac operations, resulting in widespread neglect of high enzyme values in routine postoperative care.

Because recognition of a distinct enzyme increase attributable to early postoperative MI is severely hampered by the unspecific postoperative enzyme increase, we compared the enzyme activities measured in control patients up to the second postoperative day with those in patients who had MI on the first or the second postoperative day. To do this, we collected blood samples from all subjects exactly 24 and 48 h postoperatively. Because the various cardiac-related enzymes peak at different times after MI, the relationship between this event and the expected peak values of enzymes will not be the same for different times of blood sampling. We compared the state of enzyme activities noted at the standardized time of blood collection with patient status grouped by ECG classification. Our objective was to investigate whether collection of blood samples at fixed times postoperatively could provide a suitable guideline for improved diagnosis of perioperative MI.

Materials and Methods

Patients

We studied a total of 88 consecutive patients from the 2nd Department of Surgery, University of Vienna, who were undergoing aorto-coronary bypass operations (three or four grafts). None of them had preoperatively shown signs of acute MI, either by ECG or blood enzyme activities.

During the operation, protection of the heart involved systemic cooling to 27°C, topical cooling, and arresting the heart with ice-cold St. Thomas's cardioplegic solution, applied in repetitive doses into the aortic root.

We recorded a 12-lead ECG one day preoperatively and 1, 6, 12, and 24 h postoperatively. On the second through the tenth postoperative day, another 12-lead ECG was recorded daily at 0800 hours. According to Séguin et al. (10), a new persistent Q-wave, loss of R-waves, or ST-T changes were considered positive signs of MI. In contrast, the patients who had absolutely no changes in their ECGs and vector cardiograms (measured preoperatively and on the 10th postoperative day) were considered as having no evidence of acute MI; these were entered in the control group.

On this basis, we divided the patients into three groups: controls (n = 65) and two MI groups: MI 1 (n = 14), patients with MI within 24 h postoperatively; and MI 2 (n = 9), patients with MI between 24 and 48 h postoperatively. For statistical analysis, enzyme values for the control patients were those taken on the postoperative days that corresponded to the MI group investigated. For a further description of the groups, see Table 1.

Specimen Collection

Blood samples were collected from all patients under standardized conditions in the evening before operation, and exactly 24 and 48 h postoperatively. Beginning on the third through the tenth postoperative day, blood was collected at about 0800 each day. Lithium heparin anticoagulant was added to all samples. All assays were performed immediately after centrifuging at 1500 × g for 10 min.

Analyses

Activities of creatine kinase (CK; EC 2.7.3.2), isoenzyme
Table 1. Description of Patients

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>MI 1</th>
<th>MI 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>65(0)*</td>
<td>14(2)</td>
<td>9(1)</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>37–77</td>
<td>40–76</td>
<td>39–75</td>
</tr>
<tr>
<td>Mean</td>
<td>57.9</td>
<td>60.2</td>
<td>56.3</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>6/70</td>
<td>4/10</td>
<td>1/6</td>
</tr>
<tr>
<td>Total operation time, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>170–480</td>
<td>170–430</td>
<td>165–451</td>
</tr>
<tr>
<td>Mean</td>
<td>272.3</td>
<td>270.3</td>
<td>276.4</td>
</tr>
<tr>
<td>Extracorporeal circulation time, s</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>61–240</td>
<td>67–208</td>
<td>63–256</td>
</tr>
<tr>
<td>Mean</td>
<td>116.9</td>
<td>120.4</td>
<td>123.7</td>
</tr>
</tbody>
</table>

* Numbers in parentheses refer to no. of deaths within 30 days after surgical intervention.

CK-MB, lactate dehydrogenase (LDH; EC 1.1.1.27), α-hydroxybutyrate dehydrogenase (HBDH; no EC no. assigned), a combination of LDH-1 and LDH-2, and aspartate aminotransferase (ASAT; EC 2.6.1.1) were determined in the plasma samples spectrophotometrically with commercial test kits (all from Boehringer, Mannheim, F.R.G.) and a Hitachi 737 at 25 °C. All tests were optimized standard methods of the Deutschen Gesellschaft für Klinische Chemie (11).

To determine CK-MB activity, we used polyclonal antibodies to inhibit the CK-M subunits (12). To measure HBDH activity, a combination of LDH-1 and LDH-2, we used α-oxobutyrate as the enzyme substrate (9, 11). LDH-1 and LDH-2 are relatively more active with α-oxobutyrate as substrate than with pyruvate.

The following upper limit for enzyme values in non-MI were (U/L) as follows: CK 70, CK-MB 10, LDH 240, HBDH 140, and ASAT 22. The day-to-day CVs for the assays of CK, CK-MB, LDH, HBDH, and ASAT were 1.83%, 4.5%, 2.0%, 1.44%, and 2.11%, respectively. To correct for hemodilution due to postoperative infusion therapy, we referred the decrease of hematocrit (HCT) to the preoperative hematocrit (13) by using the following formula:

Correction factor = \( \frac{100 - \text{present HCT}}{100 - \text{initial HCT}} \)

Statistics

Preprocessing of data and explorative analysis. Before making further statistical analyses, we verified the gaussian distribution of the results. We then used unpaired Student's t-test, considering as statistically significant differences (P < 0.05) between the control group and MI groups.

For prognostic factors, we determined the differences between post- and preoperative values of each enzyme (normalizing for each individual)—CK, CK-MB, LDH, HBDH, and ASAT—in each patient during the first two postoperative days, then subjected these values to discriminant analysis. According to the literature (14) and the frequency of perioperative MI observed in our hospital, we set the a priori probabilities (affecting estimates of sensitivity and specificity) to 20% for MI groups and to 80% for control groups before analysis. We validated results by a jackknife procedure, using SAS (15) in conjunction with BMDP (16). The jackknife procedure allows one to compute the distance from each individual result to the mean for each group and to the posterior probabilities after the final step of discriminant analysis, so that one can compare the results for an individual with the collective results for all other patients, to verify the membership of that individual in this group.

Predictive analysis. Discriminant analysis can be used as a statistical tool to quantitatively relate the incidence of a certain disorder (e.g., MI) to several prognostic factors (e.g., enzyme values). Given a sample of patients for which each of the prognostic factors as well as the outcome is known, one estimates the so-called discriminant functions so as to optimally predict the (known) outcome in each case. For the particular sample investigated, the discriminant function is associated with certain values of sensitivity and specificity. Applying the same discriminant functions to predict the outcome for future patients (i.e., for whom the outcome is unknown) generally will lessen sensitivity and specificity, because the discriminant function obtained from a finite set of patients can never be fully optimal for another group of patients. It is therefore important to estimate this loss in prediction accuracy.

The best approach for this would be to repeat the study with a different set of patients, which is usually not available. Another method of assessment is offered by the jackknife procedure. One patient at a time is removed from the sample, the discriminant functions are recalculated from the remaining patients, and the patient taken out is classified according to the recalculated discriminant functions. This process is repeated for every patient in the group, and the classification quality (sensitivity and specificity) is estimated. These "jackknifed" values are a better estimate of the performance of the classification for future patients than those provided by the "primary" discriminant analysis. Furthermore, the jackknife procedure is especially reliable if the patients are selected to be highly representative for the disease investigated.

Results

Postoperative Ranges of Enzyme Activities

For each day after cardiac surgery we calculated the median and the 5th and 95th percentiles of the enzyme values. Figure 1 shows the results for the MI 1 group vs the control group. Figure 2 displays the enzyme results for the MI 2 group vs the control group. In both, the overlapping area (5th percentile of the MI group and >95th percentile of the control group) characterizes an enzyme range shared by infarct and control patients, the "suspect" range.

In the control group the 95th percentiles as well as the medians of CK, CK-MB, LDH, and ASAT show a distinct increase on the first postoperative day, which decreases within 24 h to a plateau of still above-normal values. This is explainable on the one hand by the half-lives of the enzymes and on the other hand by early mobilization of the patients. Remarkably, in some cases enzymes do not even exceed the normal range. In contrast, the 5th percentile for patients with MI always shows increased enzyme activities within 24 h after the ischemic event.

For MI patients all enzymes showed statistically significant differences (P < 0.05) between preoperative values the first 24 h after MI. If MI took place within the first 24 h postoperatively, the CK, CK-MB, LDH, and ASAT activities showed significant increases for the following two days; HBDH activity was noticeably higher on the second and third day after the ischemic event. If infarction took place...
between 24 and 48 h postoperatively (Figure 2), CK and CK-MB, LDH, HBDH, and ASAT activities were all significantly increased for the following two days. As presented in Figures 1 and 2, peak values of CK and CK-MB activity immediately after infarction were in the same range for both MI groups, indicating that these enzymes were less affected by the general trauma of the unspecified myocardial damage of the operation. In contrast, LDH, HBDH, and ASAT typically show a decrease in activity after surgical intervention; therefore, a perioperatively later event (MI 2) of ischemic damage (Figure 2) does not induce prolonged enzyme decrease. In all cases, no uniform trends are exhibited by the LDH/HBDH ratio or by any other combination of parameters (data not shown).

**Predictive Analysis**

Results of the stepwise discriminant analysis of CK, CK-MB, LDH, HBDH, and ASAT activities (Table 2) showed that the combination of CK and CK-MB was the only suitable parameter for group classification in the first two days after myocardial infarction. In other words, the only useful diagnostic tool proved to be a combination of CK and CK-MB values. The values for LDH, HBDH, and ASAT and the CK/CK-MB and LDH/HBDH ratios did not meet the criteria for inclusion as predictive variables. Although the values for these analytes and ratios varied significantly for the control patients, their diagnostic potency is rather low.

Our findings were validated and corrected by use of a jackknife procedure, which led to a decrease of the sensitivity for the MI 2 group (95.4%) and of the specificity of the MI 1 group (71.4%). In practice the results of the discriminant analysis can be applied as follows. From the constants given and the enzyme values (CK, CK-MB) for a particular patient, discriminant functions can be obtained and evaluated for each group. Different coefficients apply to the first postoperative day and the second postoperative day. The measured values of CK and CK-MB are inserted into the following formulas, fitted for the first (a) or second (b) postoperative day:

(a) \( FCON1 = (CK \times 0.00182) + (CK-MB \times 0.01289) - 0.70207 \)

(b) \( FCON2 = (CK \times 0.00161) + (CK-MB \times 0.01252) - 0.65851 \)
Table 2. Classification Matrix (Jackknifed Classification) for CK and CK-MB Combined Values

<table>
<thead>
<tr>
<th>Group</th>
<th>% correctly classified</th>
<th>No. classified into group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>1st postoperative day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>98.5 (98.5)*</td>
<td>64 (64)</td>
</tr>
<tr>
<td>MI 1</td>
<td>85.7 (71.4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Total</td>
<td>96.2 (93.7)</td>
<td>66 (68)</td>
</tr>
<tr>
<td>2nd postoperative day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100 (95.4)</td>
<td>65 (62)</td>
</tr>
<tr>
<td>MI 2</td>
<td>81.8 (61.8)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>94.4 (91.7)</td>
<td>67 (64)</td>
</tr>
</tbody>
</table>

* Values in parentheses indicate results for jackknifed classification.

If FMI1 or FMI2 is greater than FCON1 or FCON2, the patient is predicted to have an MI.

Discussion

This study was undertaken to assess the validity of monitoring enzymes in blood after cardiac surgery, to obtain better discrimination between the general operative trauma and the perioperative and postoperative ischemic myocardial damage. Independently, each is known to induce significant increases of enzyme activities in blood.

At first glance, most of the investigated enzymes seemed suitable for prediction of MI. However, a significant difference in mean values between the control group and clinically assessed MI groups is insufficient for a sensitive and specific discrimination between MI groups and the control group for individual patients and are no substitute for the ECG. Although some infarct-associated enzymes, e.g., CK-MB, ASAT, or the LDH1/LDH2 ratio, have been considered to be reliable indicators of MI, recent reports have emphasized false-positive and false-negative results (10, 14, 17–21). This could be explained by the fact that many investigators only examine the mean concentrations of enzymes in plasma separately. Reviewing our results in this way, we found significant differences in all mean enzyme values.
investigated in both MI groups at least one day after the ischemic event. For detection of an MI 24 h postoperatively (MI 1), the so-called suspect range for CK-MB (e.g.) on the 2nd postoperative day included only 7% of the MI patients and 2.7% of the control patients. For total CK, the suspect range was applicable to 28.6% of the MI patients and 6.9% of the control patients. For all other enzymes, more than 25% of both groups (MI and the control group) are in this overlapping enzyme range, which makes it difficult to differentiate the groups. Applying a stepwise discriminant analysis, we determined for the combination of all enzymes results a diagnostic potency order, with CK being most potent, followed by CK-MB. Correction of the results for CK and CK-MB by the jackknife procedure yields a sensitivity of 98.5%, a specificity of 71.4%, and a positive predictive value of 90.9% for MI. These unusual findings about the total CK activity may be explained by the relatively high activities of isoenzymes other than CK-MB in the human heart (22).

In contrast, HBDH activity is a result not only of myocardial damage but also of hemolysis. Examination of patients who had an MI between 24 and 48 h postoperatively shows no overlapping CK-MB or ASAT values between groups on the 2nd postoperative day. The suspect range for CK on this day contained values measured in 2.46% of the MI patients and 3% of control patients. This increased discrimination between both groups is explainable by the continuous decrease of enzyme activity in plasma after surgical intervention involving the thoracic muscles.

In contrast to the satisfying results obtained with the LDH1/LDH2 ratio (14), we did not find the LDH/HBDH ratio to be good enough for diagnostic relevance after aorto-coronary bypass operation. Perhaps the variable degree of hemolysis, due to extracorporeal circulation, or the variable extent of injury of muscular tissue impairs the predictive value of this ratio, because the other LDH isoenzymes (LDH3, LDH4, LDH5) also transfer D-oxobutyrate, although in physiologically irrelevant amounts (9).

By our investigations, a CK value >600 U/L, CK-MB >45 U/L, and ASAT >65 U/L indicate a pathological deviation from normal reconvalescence after an aorto-coronary bypass operation. We stress that the upper limit of the CK-MB activity is in accordance with the results of Graeber et al. (19), whereas we could not find a good correlation between acute MI and LDH, HBDH, or the LDH/HBDH ratio.

In conclusion: For the daily clinical routine, the diagnosis of the perioperative and postoperative MI still will remain a sophisticated challenge, owing to the complex, patient-associated situation. The therapeutic strategy often depends strongly on the individual predominance of factors, such as the extent of operation, the clinical condition of the patient, the state of postoperative mobilization, and the significance of the occurrence of diagnostic markers. We emphasize that data on sensitivity and specificity, even when corrected by a jackknife procedure, are reliable only for patients who underwent comparable operative and perioperative treatment, because only in this case can the sample study be considered representative. Given the acceptance of the common ECG criteria, the objective of the present study was to prove that the monitoring of distinct enzyme activities in plasma may be useful. Our suggestion to apply a mathematical formula may generate severe critical discussion but, in our opinion, each approach to improve diagnostic capacity is worthwhile.

References