Modified Creatine Kinase-MB Plots as a Tool to Detect Perioperative Myocardial Infarction

Evaluation of Sensitivity and Specificity as Compared with Electrocardiographic Changes

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ABSTRACT

Based on electrocardiographic criteria, coronary artery bypass grafting patients were divided into two groups, — one with and one without perioperative myocardial infarction. Serial total-creatine kinase activity did not discriminate between the two groups; however, serial creatine kinase-MB activity showed a consistent difference. Patients with perioperative myocardial infarction showed an increase, whereas patients without perioperative myocardial infarction showed a decrease during the postoperative period. The creatine kinase-MB plots showed a sensitivity of 0.92 and a specificity of 0.98 as compared with the electrocardiograms.

Introduction

The recent decline in mortality from coronary artery bypass grafting is accompanied by a decrease in perioperative myocardial infarction. From 5 to 40 percent in 1975, perioperative infarction is now reported to be less than 10 percent. Although some authors claim that the occurrence of perioperative infarction does not affect prognosis after bypass surgery, others describe reduced late survival and increased morbidity after perioperative infarction.

Diagnosis of perioperative myocardial infarction is difficult owing to nonspecific electrocardiographic changes. Therefore, persistent new Q waves after surgery have generally been taken as the only criterion of perioperative myocardial infarction. To support electrocardiogram diagnosis of perioperative infarction, plasma enzyme activity determinations have been made. Offset of normally used reference values for
enzyme levels is necessary in the post-surgical patient, and this decreases the diagnostic sensitivity of the examination.

**Patients and Operative Procedures**

The *pilot group* comprised 78 patients who were operated upon between March 1980 and February 1981. The characteristics of this pilot group and the operations performed are summarized in table I.

The *study group* consisted of 146 patients who underwent coronary artery bypass grafting with or without associated procedures during the period March to October 1981. Patient assignment to the protocol was prospective and at random. The characteristics of this patient group and the operations performed are summarized in tables II and III. The six extremity leads and lead V5 of the electrocardiogram were monitored during the operation.

Preoperatively and postoperatively on arrival in the Intensive Care Unit, a complete 12 lead electrocardiogram was recorded and repeated during the first three postoperative days and, thereafter, twice weekly until discharge. When indicated, serial electrocardiograms were made. One month postoperatively, a control electrocardiogram was made.

### Table I

<table>
<thead>
<tr>
<th>Patients and Types of Operation Performed in Pilot Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Patients</strong></td>
</tr>
<tr>
<td>78</td>
</tr>
</tbody>
</table>

### Table II

**Preoperative Characteristics of Study Group with Some Indications for Surgery**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Mean Age (Year)</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>146</td>
<td>56.2</td>
<td>129</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operations</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative infarction</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>Left ventricular aneurysm (surgery)</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Left mainstem lesion (&gt;50 percent)</td>
<td>13</td>
<td>9</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>26</td>
<td>18</td>
</tr>
<tr>
<td>Recent preoperative infarction (with unstable angina)</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Evolving infarction</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*Patients can figure in more than one category.*

### Definition of Perioperative Infarction

**Perioperative infarction** is defined as myocardial infarction developing after premedication has been given until 12 hours after the end of the operation.

Perioperative myocardial infarction was diagnosed when the patient was in a stable condition at the time of premedication and then developed electrocardiographic changes within 12 hrs after the operation. Such electrocardiographic

### Table III

**Type of Operations Performed in Patients of Study Group**

<table>
<thead>
<tr>
<th>Total number of operations</th>
<th>146</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean number of distal anastomoses</td>
<td>3.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>First operations</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solitary aortocoronary bypass grafting</td>
<td>118</td>
<td>80</td>
</tr>
<tr>
<td>Aortocoronary bypass grafting + coronary endarterectomy</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Aortocoronary bypass grafting + left ventricle aneurysm resection</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Solitary left ventricle aneurysm resection</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Aortocoronary bypass grafting + carotid endarterectomy</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Angioplasty left main coronary artery</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Second operations</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reoperation aortocoronary bypass grafting</td>
<td>8</td>
<td>6</td>
</tr>
</tbody>
</table>
changes should progress to new Q waves in at least two electrocardiogram leads and persist for at least one month.

In addition, perioperative myocardial infarction was identified in those cases where there was a substantial increase of already existing (pathological) Q-waves, increase or decrease of R-wave voltage in the right precordial leads, or ST-elevation associated with reciprocal ST-depression and followed by the development of symmetrically inverted T-waves.

Electrocardiographic changes compatible with pericarditis, postoperative axis deviation with or without complete or incomplete bundle branch block, or intraventricular conduction defects were not considered indicative of myocardial infarction if they occurred without other changes.28

EQUIVOCAL CRITERIA FOR PERIOPERATIVE INFARCTION

Ventricular fibrillation, occurring in the intensive care unit, sustained ventricular tachycardia, and episodes of accelerated ventricular rhythm were considered highly suspicious for myocardial infarction.

Haemodynamic abnormalities were also used to indicate the possibility of perioperative myocardial infarction. Postoperative need for intraaortic balloon pumping to come off bypass in the presence of a preoperative adequate left ventricular function (ejection fraction >35 percent) was considered an indicator for myocardial infarction. If preoperative left ventricular function was normal, the prolonged need of inotropic agents such as dopamine or dobutamine in the presence of a low cardiac index was a possible sign. Frequent ventricular ectopy in the presence of high-normal serum potassium levels and responding to xylocaine was also considered suggestive of myocardial infarction.

Supraventricular tachycardias and temporary or permanent postoperative arterioventricular (AV)-conduction disturbances were not considered indicative of perioperative myocardial infarction. The postoperative use of nitrpide, nitroglycerine, or the need of a temporary pacemaker were not considered as clinical indicators for perioperative myocardial infarction. Patients who fulfilled none of the previously mentioned criteria were considered free of perioperative myocardial infarction. If one equivocal criterion was fulfilled, myocardial infarction was considered equivocal. When a definite electrocardiographic criterion for perioperative myocardial infarction was met, perioperative myocardial infarction was considered established.

BIOCHEMICAL METHODS

Venous blood samples were drawn in a heparin-containing vacuum blood collecting system. The tubes were centrifuged within 30 min, and the plasma stored at −20°C until analysis.

Glutamate oxalacetate transaminase, α-hydroxybutyric acid dehydrogenase, and lactate dehydrogenase were measured 24 hrs after arrival in the intensive care unit. Creatine kinase and creatine kinase-MB activities were measured with n-acetylcysteine activation* at 25°C. Separation of the creatine kinase-isoenzymes was performed with ion-exchange chromatography.†

The activity of creatine kinase-MB was corrected for postoperative haemodilution. For this purpose, all creatine kinase-MB values, expressed in U per L in the pilot group were recalculated to the preoperative hematocrit of the individual patient.

In the study group, all creatine kinase-MB values were recalculated to a

* Kit no. 126537, Boehringer Mannheim, G.F.R.
† Kit no. 189219 from Boehringer Mannheim.
haemoglobin value of 7.5 mmol per L (103 patients had a mean haemoglobin of 7.5 ± 0.18 at 24 hrs postoperatively) to facilitate laboratory and computer handling of the results.

Results

Pilot Study

All patients in the pilot group survived. The patients were divided into two groups, either with arguments indicative for myocardial infarction according to the criteria (group A, 16 patients) or without arguments suggestive of perioperative myocardial infarction (group B, 56 patients). In six patients, equivocal criteria were met.

Creatine kinase-MB and creatine kinase levels obtained were displayed in curves and examined. In all patients, enzyme levels at the end of bypass and at arrival in the intensive care unit were elevated above reference values. The increase in total creatine kinase did not correlate with the clinical status of the patient, nor did any of the other enzymes measured at 24 hrs after arrival in the intensive care unit. The medians of total creatine kinase, glutamate oxalacetate transaminase, α-hydroxybutyric acid dehydrogenase, and lactate dehydrogenase observed at 24 hrs with the 90 percent confidence intervals are shown in table IV. The overlapping intervals show that these enzyme measurements will not allow differentiation between patients with and without perioperative myocardial infarction.

Median creatine kinase-MB values at arrival in the intensive care unit were elevated (10.2 U per L). Subsequent creatine kinase-MB plots of the two groups showed a distinctly different course (figures 1 A and B). The medians and the 90 percent intervals are presented. Although the course of the median for both groups of patients differed, an overlap for the measured creatine kinase-MB values is present.

From the results of the serial measurements of total creatine kinase and creatine kinase-MB in the pilot group, it was concluded that total creatine kinase-plots did not differentiate between patients without clinical evidence of perioperative infarction and patients with

\[
\begin{array}{c|c|c|c|c|c|c}
\text{No Infarction} & \text{Infarction} \\
\text{CK (U/L)} & 101 & 224 & 584 & 156 & 493 & 1615 \\
\text{GOT (U/L)} & 20 & 18 & 49 & 26 & 49 & 174 \\
\text{HBDH (U/L)} & 147 & 179 & 385 & 185 & 335 & 750 \\
\text{LDH (U/L)} & 208 & 310 & 467 & 201 & 442 & 1078 \\
\end{array}
\]

CK: creatine kinase
GOT: glutamate oxalacetate transaminase
HBDH: α-hydroxybutyric acid dehydrogenase
LDH: lactate dehydrogenase

![Figure 1](image)
electrocardiographic signs consistent with perioperative infarction.

However, when the individual patients' creatine kinase-MB plots were considered, there was a consistent postoperative increase starting three hrs after arrival in the intensive care unit for those patients with definite perioperative myocardial infarction, whereas patients without perioperative infarction did not show an increase in their postoperative creatine kinase-MB values. This difference in the course of the postoperative creatine kinase-MB values was independent of the value measured. Even in patients operated upon during an evolving infarction, it was possible to differentiate between those patients in whom the procedure arrested tissue loss and those patients who continued to lose cardiac tissue.

Based on these initial results, a postoperative serial creatine kinase-MB measurement protocol was designed with a minimum of sample points to be applied to the prospective study group.

Sample points were at 2, 4, 8, 12, and 24 hrs after arrival in the intensive care unit. For practical reasons, arrival at the intensive care unit was chosen as the reference time, since the pilot group showed no differences during the operation period and the initial postoperative hours. To improve the comparability of the individual patient plots, the creatine kinase-MB was modified. This modification was done by dividing each for haemodilution corrected creatine kinase-MB value by the intensive care unit +2 hrs value. This brings the +2 hrs point to unity and gives relative values of the other time points. The unification of the creatine kinase-MB at +2 hrs with subsequent relatification of the later time points eliminates the individual variation of the measured creatine kinase-MB and makes the patient his own control. These plots were graphically presented by computer (figure 2) to the clinicians. Criteria for perioperative infarction based on creatine kinase-MB plots from the pilot group were: two or more points of the plot elevated by more than 10 percent above unity (intensive care unit +2 hrs point) as indicated by the dotted line, and absolute maximum value of creatine kinase-MB more than 10 U per L.

**Study Group**

All 146 patients in the study group completed their enzyme curves. Eleven patients (7.5 percent) exhibited persistent new Q waves as a result of perioperative infarction, and all had creatine kinase-MB plots typical for myocardial infarction. Thirteen other patients exhibited no new Q-waves on the electrocardiogram but complied with ST-T wave and QRS criteria for perioperative myo-
cardiac infarction. Of these patients, 11 had creatine kinase-MB plots indicative of infarction whereas two had negative creatine kinase-MB plots. One hundred and eleven patients had neither clinical nor enzymatic signs of perioperative infarction. Another two patients had increasing creatine kinase-MB plots without any clinical sign of myocardial infarction. In nine patients, clinical signs of myocardial infarction were equivocal. Six of them had positive creatine kinase-MB plots and three had negative plots. For the evaluation of sensitivity and specificity, these nine patients were disregarded.

Thus for final evaluation, there were 137 patients who showed either definite perioperative myocardial infarction according to electrocardiogram criteria or no signs of perioperative myocardial infarction at all. From these results, a sensitivity can be calculated for detection of perioperative myocardial infarction by creatine kinase-MB plot of 0.92 and specificity of 0.98. The population contains 18 percent patients with perioperative myocardial infarction and the index of merit amounts to 0.90 (figure 3).

In figure 4 it is shown that especially at eight and 12 hours after arrival in the intensive care unit, the distributions of normalized creatine kinase-MB values of the groups with and without perioperative myocardial infarction showed no overlap. The two populations were easy to differentiate. The method proved easy to implement in the intensive care routine, and results were available within 36 hours after the end of the operation. It is estimated that use of this method will approximately double the now accepted incidence of perioperative myocardial infarction. Although based on different criteria, this has also been suggested by several other authors.\(^1,6,22,24,30,31\)

**Discussion**

As our goal was to develop a fast and reliable method for the detection of infarction directly caused by the operation and to compare this method with electrocardiographic criteria as a standard, a strict definition of perioperative myocardial infarction...
infarction was needed. Recent preoperative myocardial infarction is considered as a separate entity because of the increased operative risk in these patients. At the moment of premedication, the procedure has begun, and it was taken as the beginning of the perioperative period. The end of this period at 12 hours after arrival in the intensive care unit was arbitrarily chosen. Myocardial infarction occurring after this time is generally easy to recognise electrocardiographically and enzymatically.\(^3\,27\,29\)

Patients with proven myocardial infarction do not always develop new Q-waves. Nontransmural infarction, in which necrosis can be quite extensive, may only be characterized by ST-T changes with or without loss of R-wave voltage or sometimes small Q-waves. Furthermore, particularly with inferior wall infarction, new Q-waves may disappear. All these cases of myocardial infarction are missed in the postoperative setting if only new Q-waves are accepted as proof of myocardial infarction. Evolutionary ST-T wave changes were used by the current authors in the postoperative surgical intensive care unit to come to the diagnosis of perioperative myocardial infarction as well.\(^2\,6\,37\)

Serial change as seen in nontransmural infarction can be recognised and differentiated from pericarditis.\(^18\,33\) Postoperative patients with small perioperative infarctions may have other manifestations, such as arrhythmias or severe depression of myocardial contractility, which can exist without electrocardiographic changes compatible with infarction. In the absence of a low serum potassium concentration, serious ventricular arrhythmias suggest the presence of myocardial infarction.\(^6\,8\,10\) To avoid this problem in the analysis of sensitivity and specificity of the enzyme method as compared to the electrocardiogram, these symptoms were summarized as being equivocal and patients with only equivocal symptoms for the evaluation of the specificity and selectivity of the creatine kinase-MB plots were excluded. It is clear that especially in those patients, the enzyme method will be of great value.

Total creatine kinase and creatine kinase-MB are the most reliable enzymes for diagnosis of myocardial necrosis since they are present in high concentration in the myocardium.\(^17\) As shown by others,\(^14\,15\,16\,19\) results of the present authors confirm that during open heart surgery, and especially after coming off bypass, high levels of creatine kinase and creatine kinase-MB may be present. However, the predictive value of intraoperative creatine kinase-MB rise could not be confirmed, as suggested in the literature.\(^36\) In the present pilot study, it was found that the absolute values of serum total creatine kinase and creatine kinase-MB at one to three hrs postoperatively have no relation with the presence or absence of clinical signs of perioperative myocardial infarction. Also, the postoperative course of the total creatine kinase-plot was not related to the occurrence of perioperative myocardial infarction.

Serial postoperative creatine kinase-MB determinations in patients without clinical signs of myocardial infarction showed a consistent decline of enzyme activity following the operation. In cases where there were electrocardiographic and clinical signs of myocardial infarction during or directly after the operation a consistent increase in serum creatine kinase-MB activity was demonstrated during the first 12 hours postoperatively. Absolute values of creatine kinase-MB during the first 12 postoperative hours showed a considerable overlap in patients with and without perioperative infarction. This overlap is absent in the normalized creatine kinase-MB curves (figure 4). By normalizing the initial creatine kinase-MB value to unity, the patient serves as his own control irrespective of the initial value (figure 2).
Patients with only equivocal signs of perioperative myocardial infarction showed positive normalized creatine kinase-MB plots in six out of nine cases. Based on the results in patients with definite proof of the presence or absence of perioperative myocardial infarction, it seems possible that these six patients did, in fact, sustain small perioperative myocardial infarctions.

References

23. MCINTOSH, H. D., and GARCIA, J. A.: The first


