ROLE OF CPK-MB IN DX OF AMI/Roark, Wagner, Izlar, Roe

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References

Diagnosis of Acute Myocardial Infarction in a Community Hospital

Significance of CPK-MB Determination

STEVEN F. ROARK, GALEN S. WAGNER, M.D., H. L. IZLAR, JR., M.D., AND CHARLES R. ROE, M.D.

SUMMARY Two-daily CPK-MB determinations were performed but not made available to the physicians of 179 consecutive patients with precordial pain admitted to a community hospital to evaluate the diagnostic importance of this isoenzyme. Physician decision was based upon history and once-daily ECG and total enzymes (CPK, SGOT, LDH). Following hospital discharge, each patient's clinical record was reviewed to determine the physician diagnostic decision. The patients were subdivided into three groups. The first group consisted of 46 patients with diagnostic QRS changes and elevated total enzymes. All 46 had physician diagnosis of acute myocardial infarction and CPK-MB was present in 44 (96%). The second group included 55 patients with nondiagnostic QRS but elevated total enzymes. Physician diagnosis was acute myocardial infarction in 28 (51%) but 16 (57%) of these had no CPK-MB. The third group contained 50 patients with nondiagnostic QRS and normal enzyme levels. Six (12%) had physician diagnosis of acute myocardial infarction but none had CPK-MB. Thus, absence of CPK-MB failed to confirm physician diagnosis of acute myocardial infarction when based upon history and total enzymes in the absence of QRS changes in 22 of 34 (65%) patients.

SINCE 1960 there has been a trend toward identification of a special place within the hospital for care of patients with acute myocardial infarction. These coronary care units differ from other areas by the presence of continuous ECG monitoring, maintenance of intravenous lines, maintenance of standby emergency equipment including defibrillators and pacemakers and, most importantly, by the presence of specially trained nurses. The difficulty of diagnosis of acute myocardial infarction from the clinical history was appreciated early. Subsequently, the coronary care unit has been used for management of patients with symptoms suggesting acute coronary insufficiency until either the diagnosis of acute infarction was ruled out or until the patient attained a stable condition after the diagnosis was confirmed. The 12-lead electrocardiogram has proven specific but insensitive, and total serum enzymes sensitive but nonspecific for diagnosis of acute infarction. Thus, when no QRS changes occur and total enzyme levels are elevated, the diagnosis is uncertain. This may result in poor utilization of coronary care beds and potentially erroneous diagnosis and treatment. Therefore, efforts were made to identify organ specific subgroups of the total enzymes (isoenzymes). The specificity and sensitivity of these have been determined within the medical center, but the great majority of patients with symptoms of acute coronary insufficiency are managed in the community hospital. It is the purpose of this study to determine the incidence in which the isoenzymes of creatine phosphokinase provide information capable of altering the diagnosis and thus, potentially, the care of these patients.

Methods

All 179 patients admitted to the Watts Hospital Medical Intensive Care Unit during a six-month period with a presumptive diagnosis of acute coronary insufficiency were included in this study. Twelve-lead ECGs and serum samples were obtained at the time of admission and once daily for at least three days. All serum samples were analyzed for determination of total SGOT (upper limit 40), LDH (upper limit 225) and CPK (upper limit 145).
Reports of ECG interpretations and serum enzyme determinations were returned promptly to the patient record for use by the attending physicians.

In addition, serum was obtained at the time of admission and (unless technical problems prohibited) twice daily (7:00 a.m. and 6:00 p.m.) during the subsequent 48 to 72 hours. Serum samples were analyzed for identification of the isoenzymes of CPK. Results were never disclosed to the attending physicians. Twenty-eight patients were excluded from data analysis because absence of CPK-MB could have been due to delay of more than 24 hours between onset of acute symptoms and initial serum sample.

Immediately following each patient's hospital discharge, the clinical record was reviewed to determine whether diagnosis of acute myocardial infarction was accepted or rejected by the attending physician. All 12-lead ECGs were reviewed by one of the investigators (G.W.). These were considered diagnostic of acute myocardial infarction only when QRS changes which met criteria for definite infarction (Minnesota Code) were accompanied by evolutionary ST-segment and T wave changes. SGOT and LDH are considered as a unit, SGOT/LDH, because of their broad and relatively similar organ distribution: liver, skeletal muscle, red cell, etc. This unit is termed abnormal only when both exceed normal limits. Thus, when one or both of these are within normal limits, the SGOT/LDH is considered normal. In tables 1, 2 and 4 the term "diagnostic total enzymes" includes all occasions when either CPK or SGOT/LDH exceeds normal limits for the laboratory. Under "nondiagnostic total enzymes" are included all instances in which CPK remains within normal limits and SGOT/LDH fulfills the above definition of normal. CPK isoenzymes were considered diagnostic of acute myocardial infarction when CPK-MB was detected in a single serum sample.

Sensitivity of a diagnostic parameter is calculated by consideration of only those patients in whom diagnosis of acute myocardial infarction is confirmed without reference to that parameter. Thus, ECG sensitivity is defined as the percentage of those patients with diagnostic SGOT/LDH, CPK and CPK-MB in whom QRS changes are also observed. Specificity of a diagnostic parameter is calculated by consideration of only those patients in whom diagnosis of acute myocardial infarction is excluded without reference to that parameter. Thus, ECG specificity is defined as the percentage of those patients with nondiagnostic SGOT/LDH, CPK and CPK-MB in whom QRS changes are also absent.

### Results

The 151 patients admitted to the study during a six-month period can be divided into three groups based on their ECG and total enzyme findings (table 1). Those with both a diagnostic QRS change and elevated enzyme levels constituted 46 of the 151 patients, or 30.5%. Within this group the attending physician diagnosed all 46 as having had acute myocardial infarction. The second group comprising those with elevated enzymes but nondiagnostic ECG changes accounted for 55 patients or 36.4% of the total population. The attending physician diagnosed acute myocardial infarction in 28 (51%) of these. The third group contained 50 patients or 33.1% of the total, with normal enzymes and nondiagnostic ECG changes. Six of the patients (8.3%) were thought to have had acute myocardial infarction by their attending physician on the basis of a suggestive clinical history.

Table 2 presents the sensitivity and specificity of the ECG, total enzymes and isoenzymes. The ECG is a specific (100%) but relatively insensitive (78%) indicator of infarction. Total enzymes, SGOT/LDH and CPK are sensitive (98% and

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**Table 1. Diagnostic Subgrouping and Physician Decision in Consecutive Patients Admitted to the Community Hospital CCU for Suspected Acute MI**

<table>
<thead>
<tr>
<th>Patients in Study</th>
<th>Diagnostic QRS and total enzymes</th>
<th>Nondiagnostic QRS and diagnostic total enzymes</th>
<th>Nondiagnostic QRS and total enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>151</td>
<td>46</td>
<td>55</td>
<td>50</td>
</tr>
<tr>
<td>MD dx MI</td>
<td>46</td>
<td>MD excl MI</td>
<td>MD excl MI</td>
</tr>
<tr>
<td>MD excl MI</td>
<td>0</td>
<td>MD dx MI</td>
<td>MD dx MI</td>
</tr>
<tr>
<td>28</td>
<td>27</td>
<td>6</td>
<td>44</td>
</tr>
</tbody>
</table>

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**Table 2. Comparative Sensitivities and Specificities of Diagnostic Parameters**

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>% Sensitivity</th>
<th>% Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG</td>
<td>78% (43 of 55)</td>
<td>100% (50 of 50)</td>
</tr>
<tr>
<td>SGOT/LDH</td>
<td>98% (43 of 44)</td>
<td>89% (50 of 56)</td>
</tr>
<tr>
<td>Total CPK</td>
<td>100% (43 of 43)</td>
<td>65% (50 of 77)</td>
</tr>
<tr>
<td>CPK-MB</td>
<td>96% (43 of 45)</td>
<td>100% (50 of 50)</td>
</tr>
</tbody>
</table>

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**Table 3. Sensitivity and Specificity of CPK-MB in Groups Where MI Diagnosed or Excluded by ECG and Total Enzymes**

<table>
<thead>
<tr>
<th></th>
<th>Diagnostic QRS and total enzymes</th>
<th>Nondiagnostic QRS and total enzymes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPK-MB present</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>CPK-MB absent</td>
<td>2</td>
<td>50</td>
</tr>
</tbody>
</table>
TABLE 4. Patients with Confirmed Diagnosis of Acute MI but Absence of CPK-MB

<table>
<thead>
<tr>
<th>Patient</th>
<th>Interval from onset of symptoms until serum sampled (hr)</th>
<th>Initial CPK</th>
<th>Peak CPK</th>
<th>Longest sampling interval within initial 48 hr (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RIT</td>
<td>2.0</td>
<td>125</td>
<td>594</td>
<td>15</td>
</tr>
<tr>
<td>CC</td>
<td>7.5</td>
<td>211</td>
<td>472</td>
<td>18</td>
</tr>
</tbody>
</table>

100%, respectively) but relatively nonspecific (89% and 65%, respectively) parameters. However, CPK-MB is both sensitive (present in 96% of patients with diagnostic ECG, SGOT/LDH and CPK) and specific (absent in 100% of patients with nondiagnostic ECG, SGOT/LDH and CPK).

The patients in the two groups in which ECG and total enzymes were most indicative of either exclusion (46) or confirmation (50) of acute myocardial infarction are presented in table 3. They are subgrouped into those with and without presence of CPK-MB. Thus, diagnosis of infarction on the basis of compatible history alone in six patients (table 1) was not supported by the isoenzyme. However, two of the 46 patients with QRS and total enzyme changes (CPK, SGOT and LDH were elevated in all) had persistent absence of CPK-MB. These are further described in table 4. It is not likely that CPK-MB had disappeared prior to serum sampling since both patients had initial serum determination within eight hours following onset of acute symptoms and had initial total CPK less than a subsequent peak. There was some irregularity in serum sampling within the 48 hours following onset of acute symptoms with longest intervals of 15 and 18 hours. Also, peak total CPK was relatively low (472 and 594). These were two of a group of 11 patients with peak CPK < 600, whereas all 46 patients with peak > 600 had CPK-MB present.

The group where CPK-MB had the greatest potential for aiding the physician in reaching a diagnosis contained the 55 patients in whom the ECG was nondiagnostic but the total enzymes were abnormally elevated. As shown in table 1, 28 of these were diagnosed as having had acute myocardial infarction. Table 5 presents comparative instances of CPK-MB appearance in those in whom the attending physician excluded or diagnosed acute infarction. CPKMB absence concurred in all 27 instances when infarction had been excluded. However, CPK-MB presence confirmed the physician's positive diagnosis in only 12 of 28 instances (43%).

Table 6 presents the enzyme and isoenzyme finding in all patients in whom there were no diagnostic QRS changes. All combinations of total enzyme abnormality are found within the 93 patients with no CPK-MB. However, all three are abnormal in only 10 patients. Thus, CPK-MB was never seen when any of the three total enzymes remained normal (83 patients). The attending physician diagnosed acute infarction in 34 patients when QRS changes were not evident. This can be considered a confirmed diagnosis in the 12 in whom all total enzymes were abnormal and CPK-MB was present; and as an unconfirmed diagnosis in 17 instances where absence of CPK-MB is accompanied by normal CPK or SGOT/LDH values. The true diagnosis cannot be determined in the remaining five patients in whom all total enzymes are abnormal but CPK-MB was never detected.

Discussion

A laboratory method for identification of the MM, BB and MB isoenzymes of creatine phosphokinase was described by Dawson et al. in 1965 and modified by Roe et al. in 1972. In 1973, Wagner et al. and Konttinen and Somer documented the importance of CPK-MB detection in the diagnosis of acute myocardial infarction in man. Thus, physicians charged with the diagnosis and management of patients with acute myocardial infarction have been presented with an alternative to the dependence upon total enzyme levels in patients without definite QRS changes on electrocardiogram. The argument for addition or substitution of any new diagnostic test would be convincing only if its sensitivity and specificity were confirmed by prospective analysis and if the incidence of its capability of altering the physician's diagnosis were documented.

The myocardium contains principally CPK-MM. The hybrid or MB form has been found to account for at least 10% of total myocardial CPK content. Isoenzyme analysis of homogenates from human tissues has confirmed the absence of the MB isoenzyme from all noncardiac sources with the exception of skeletal muscle. Other studies have failed to identify any significant skeletal muscle CPK-MB.

Appearance and attainment of peak levels and disappearance of the CPK-MB have been found to conform with those parameters of the total CPK. However, Wagner et al. have documented the disappearance of CPK-MB at a time when total CPK levels persisted above the normal range. That study, in which serum sampling was performed every four hours, documented persistence of CPK-MB for as brief a period as 24 hours. It is quite probable that frequent sampling of larger patient groups might document an even shorter time of persistence of CPK-MB in some instances. Thus, one may interpret the absence of CPK-MB as evidence for exclusion of the diagnosis of acute myocardial infarction only when the initial sample has been obtained within 24 hours of the onset of acute symptoms and when twice-daily sampling is subsequently maintained. Twenty-eight patients were excluded from data analysis in this study.

TABLE 6. The Relative Usefulness of Total Values of CPK and SGOT/LDH When ECG Changes Are Nondiagnostic

<table>
<thead>
<tr>
<th>Total CPK diagnostic</th>
<th>MD dx MI</th>
<th>MD excl MI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MB present</td>
<td>MB absent</td>
</tr>
<tr>
<td>Total CPK nondiagnostic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGOT/LDH diagnostic</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>SGOT/LDH nondiagnostic</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

TABLE 5. Physician Decision and CPK-MB Results in 70 Patients with Nondiagnostic QRS but Diagnostic Total Enzymes

<table>
<thead>
<tr>
<th>CPK-MB</th>
<th>MD diagnosed acute MI</th>
<th>MD excluded acute MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>present</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>absent</td>
<td>16</td>
<td>27</td>
</tr>
</tbody>
</table>
because more than 24 hours had elapsed between onset of acute symptoms and initial serum sample.

CPK-MB has been documented in a previous report to be 99% specific for diagnosis of acute myocardial infarction. In the present series there were no patients in whom myocardial infarction was excluded by the absence of CPK-MB, QRS changes and persistence of total enzymes within normal limits, but in whom CPK-MB was identified (100% specificity). However, studies from this Center and elsewhere have documented the presence of CPK-MB in the absence of acute myocardial infarction. Tonkin et al identified four patients in whom CPK-MB was present and persisted for more than 24 hours following minor iatrogenic cardiac trauma: intra-cardiac puncture, external cardiac massage, and epicardial pacemaker electrode implantation. These patients subsequently died and none had evidence of acute myocardial infarction at postmortem examination. However, all had anatomic documentation of cardiac trauma. Brownlow and Elevitch detected CPK-MB in six patients with myositis. Autopsy data from one of these patients are available and focal areas of myocarditis are documented. Somer et al have documented the presence of CPK-MB in 29 patients with Duchenne's form of muscular dystrophy. Cardiac involvement in this disease is well known and, again, could possibly be the source of the CPK-MB. Roe et al identified CPK-MB in five patients with Reye's syndrome. Three patients had no evidence of cardiomyopathy on postmortem examination. One patient had CPK-MB present on muscle biopsy. Thus, it is certain that CPK-MB is not specific for myocardial infarction and is seen following other forms of myocardial damage. In view of its appearance in myopathic conditions, it is not yet known whether appearance of CPK-MB in human serum is a specific indicator of some form of myocardial damage.

CPK-MB has been documented in a previous report to be 100% sensitive for the diagnosis of acute myocardial infarction. However, the current series has identified two patients in whom QRS changes were present and total enzyme levels were transiently elevated but CPK-MB was never detected (sensitivity of 96%). Less than 24 hours elapsed between onset of symptoms and initial serum sample in both patients. Konttinen and Somer identified one patient with ECG evidence of transmural myocardial infarction but no CPK-MB detected during the 48 hours following onset of symptoms. As was documented in the current study, peak total CPK in that patient was quite low. These studies are not sufficient to determine whether the laboratory tests indeed lacked sensitivity or whether the transient nature of appearance time requires shorter sampling intervals.

It is not yet known whether cardiac muscle damage can occur without release of detectable levels of CPK-MB into the serum. It is apparent, however, that sampling at least every 12 hours will be necessary if all patients with acute infarction are to be identified.

This study was designed to use a proven sensitive and specific index of acute myocardial infarction, CPK-MB, to document the performance of the practicing physician who had access only to history, ECG, and total enzymes. The diagnosis or exclusion of infarction presented little challenge in the 64% of patients in whom new QRS changes were seen on electrocardiogram or in whom total enzyme values were within normal limits. However, QRS changes were absent in the presence of abnormality of at least one of the total enzymes in 36% of patients. The absence of CPK-MB in all of those patients within this subgroup in whom any of the total enzymes remained within normal limits is quite interesting. One may conclude that the diagnosis of acute myocardial infarction can be safely excluded when, in the absence of new QRS changes, SGOT/LDH or CPK remain within normal limits. The physicians observed in this study did not follow this concept and consequently their diagnosis of acute infarction in 31% of this subgroup could not be confirmed.

The only subgroup in which ECG and total enzyme data provided no insight into the correct diagnosis included those patients in whom no QRS changes were seen but SGOT, LDH and CPK were all abnormal. These comprised 15% of the total population. Myocardial origin of the enzymes was confirmed by identification of CPK-MB in 55% of these, but its absence in the remaining 45% fails to allow a diagnostic conclusion. The CPK-MB could be truly negative with origin of total enzymes from a noncardiac source, or it could be falsely negative because of a lack of either sensitivity of the laboratory determination or of sufficiently frequent serum sampling, as discussed above.

This study has investigated the usefulness of the CPK-MB isoenzyme in patients admitted to a community hospital. The ultimate value of this clinical tool depends upon the incidence in which it enables the physician to make a definitive diagnosis when he otherwise would have relied upon speculation. Table 7 presents an attempt to evaluate this incidence. The group of patients in which the physician's speculative diagnosis would be changed by use of the CPK-MB comprises 11% of the population. In all of these, the physician diagnosed acute infarction despite nondiagnostic ECG and persistence of at least one of the total enzymes within normal limits. There were no patients in whom the physician diagnosed acute myocardial infarction but no CPK-MB was identified. Thus, in all instances in which the physician was in doubt concerning the true diagnosis, he opted for the conservative approach: diagnosis of acute infarction. Thus, adverse effects of this "error" in clinical judgment would be confined to patient morbidity associated with delayed return to previous lifestyle. This does not imply that exclusion of diagnosis of infarction should dictate exclusion of coronary care, but rather that development of an optimal therapeutic program requires differentiation between coronary insufficiency with and without infarction.

The CPK-MB confirmed a speculative diagnosis or exclusion of acute infarction in 26% of the population. Thus, the test provided information which was clinically useful in a total of 37% of patients.

The CPK-MB served to corroborate a definite diagnosis or exclusion of infarction in 59% of patients. The isoenzyme failed to clarify a speculative diagnosis in an additional 3% of patients and confused the diagnosis previously thought to be definitive in 1%. This group contained those two patients in whom the electrocardiogram and total enzymes were in-

<table>
<thead>
<tr>
<th>Table 7.</th>
<th>Evaluation of Effect upon Accuracy of Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changed speculative diagnosis</td>
<td>Confirmed speculative diagnosis</td>
</tr>
<tr>
<td>17 (11%)</td>
<td>39 (26%)</td>
</tr>
</tbody>
</table>

This table summarizes the results of the diagnosis process. It shows the number and percentage of patients in each category.
dicative of infarction but no CPK-MB was detected. Therefore, CPK-MB can be said to have had no influence upon the diagnosis of 62% of patients and to have provided incorrect information in 1%.

Use of CPK-MB, then, can be presumed to have altered diagnostic capability in this group of patients by increasing the number of definitive diagnoses from 62% to 96%. It has provided evidence for alteration of the clinical diagnoses in 11% of patients.

Acknowledgment

The authors wish to acknowledge the participation of Mrs. Barbara Hatley in collecting and compiling the patient data. They would also like to thank Mrs. Betty Riggsbee and her staff of nurses on the Watts Hospital Medical Intensive Care Unit, and Donald F. Calbreath, Ph.D., and his staff at the Hospital Clinical Laboratory, for their kind cooperation; Mrs. Elise Roseborough and Mrs. Virginia Utley for preparing the manuscript.

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Diagnosis of acute myocardial infarction in a community hospital: significance of CPK-MB determination.
S F Roark, G S Wagner, H L Izlar, Jr and C R Roe

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