Diagnostic Evaluation of Creatine Kinase-2 Mass and Creatine Kinase-3 and -2 Isoform Ratios in Early Diagnosis of Acute Myocardial Infarction

Vipin Bhayana,1 Steve Cohoe,1 Fred Y. Leung,1 George Jablonsky,2 and A. Ralph Henderson1

The diagnostic efficacy of creatine kinase (CK) isoforms (CK-3 and CK-2) was compared with measurement of CK-2 mass concentrations for the early diagnosis of myocardial infarction (MI). Serial serum samples drawn from 76 patients with confirmed MI and 55 non-MI patients were used for determining CK-2 mass concentrations and the MM/M1 (CK-3 isoforms) and MB2/MB1 (CK-2 isoforms) ratios. We compared the diagnostic utility of each by receiver-operating-characteristic (ROC) curve and likelihood ratio analyses. Our results indicate that all three tests were ineffective within the first 4 h after the onset of chest pain. All three were most effective at 4–18 h after onset, but both CK-3 and CK-2 isoform ratios were less effective than CK-2 mass concentrations in the next 6-h period (18–24 h). In the critical time between 3 and 6 h, the diagnostic performance of all three was comparable.

Indexing Terms: receiver-operating characteristic curves 
isoenzymes 
likelihood ratios

Early and accurate diagnosis of acute myocardial infarction (MI) makes it possible to start thrombolytic therapy in the early stages of MI to salvage the myocardium and permits conservation of resources by early triage of patients in costly cardiac care units (1, 2). Within the last few years the use of thrombolytic therapy, such as streptokinase or tissue plasminogen activator, has become routine in an attempt to recanalize the occluded coronary artery and thereby reduce residual myocardial damage. However, maximum benefits are achieved if therapy is started within 4–6 h after the onset of chest pain (3). Thus, a marker is required that can differentiate between MI and non-MI patients within the first 6 h after the onset of infarction.

Creatine kinase (CK; EC 2.7.3.2), the isoenzyme CK-2, lactate dehydrogenase (EC 1.1.1.27), and the lactate dehydrogenase isoenzyme 1/2 ratio are the conventional biochemical markers for acute MI (4–7). These are widely used in conjunction with other nonbiochemical markers to confirm or eliminate a diagnosis of MI. Unfortunately, no conventional indicator has a sufficiently high diagnostic utility during the early stages of MI. The CK-2 activity assay, however, is diagnostically superior to that of the other assays (8).

Several other biochemical markers have been investigated, including CK-2 mass, CK isoforms, myoglobin, troponin T, and cardiac myosin light chains (9–15). Of these, CK-2 mass and CK isoforms have been extensively studied. The assay of CK-2 mass measures the concentration of the isoenzyme molecule instead of the enzymatic activity. Such assays generally involve two specific monoclonal antibodies and measure both enzymatically active and inactive CK-2 molecules. The analytical sensitivity and specificity are excellent, and the turnaround time is short (16, 17). Recently, it was shown that serum CK-2 mass increases earlier and is diagnostically more sensitive than CK-2 activity in the early stages of MI (11, 18, 19). Others have suggested that serial determinations of CK-2 mass are diagnostically more effective (20).

CK isoforms are useful markers for the early diagnosis of MI as well as for assessing coronary reperfusion after thrombolytic therapy (21–26). Puleo et al. (27) reported that isoforms are increased above baseline values as early as 2 h after infarction. The ratio of the tissue isoforms (i.e., the gene product) to the serum isoforms—MM/M1 (CK-3 isoforms ratio) and MB2/MB1 (CK-2 isoforms ratio)—has greater diagnostic sensitivity than do the individual isoforms (25, 26). Routine analysis for serum isoforms was not favored in the past because of technical difficulties and long assay times. Currently, the separation of isoforms by electrophoresis has become easier with automated instrumentation, such as the Rapid Electrophoresis Analyzer/Electronic Data Center—REP™/EDC™ system (Helena Laboratories, Beaumont, TX), and analyses can now be completed within 1 h (28). The analytical sensitivity is also improved to the extent that samples with low CK-2 values (within the reference range) can now be analyzed (27, 28).

The purpose of this study was to compare the diagnostic utility of two markers for MI—CK-2 mass and the CK isoforms—by means of receiver-operating-characteristic (ROC) curve and likelihood ratio analyses.

Materials and Methods

Study population. The study population comprised 131 patients admitted to the Coronary Care Unit of University Hospital with chest pain. A diagnosis of MI was later either confirmed or excluded by one of us (GJ) using established criteria: history of chest pain compatible with prolonged myocardial ischemia, appropriate electrocardiographic evolution of transmural (Q-wave)
infarction or ischemic ST-T changes compatible with subendocardial (non-Q-wave) injury, 2-D echo, and radionuclide (scintigraphy) evidence of left ventricular dysfunction. Of the 76 MI patients, 61 were men (ages 33–91 years, median 65 years) and 15 were women (ages 53–83 years, median 67 years); 19 received thrombolytic therapy with streptokinase, 21 received thrombolytic therapy with tissue plasminogen activator, and treatment was contraindicated in 36. Specimens were collected from patients until thrombolytic therapy was commenced. MI was excluded in 55 other patients, of whom 34 were men (ages 42–84 years, median 64 years) and 21 were women (ages 32–82 years, median 66 years). The characteristics of the patient population were tabulated (Table 1) and the time distribution of samples used for the analyses is shown in Figure 1.

**Blood collection.** Blood samples were drawn on admission and at 2–6-h intervals thereafter, up to 48 h. Sampling time was related to the time of onset of symptoms. Samples for isoform analyses were treated with EGTA and 2-mercaptoethanol to give final concentrations of 5 mmol/L each and then stored at −20 °C. CK-2 mass and CK isoform analyses were performed without delay after the samples were thawed.

**CK and CK isoenzyme assays.** Total CK was determined with a Cobas Fara™ (Roche Diagnostic Systems Inc., Montclair, NJ) centrifugal analyzer as described elsewhere (9); the upper reference limit is 140 and 174 U/L for women and men, respectively. CK isoenzymes were determined by electrophoresis with agarose gels on the Helena REP/EDC system. CK-2 mass concentrations were determined with the Magic Lite™ II analyzer (CIBA Corning Diagnostic Co., Medfield, MA), which uses a double-antibody chemiluminescent assay; the locally determined upper reference limit is 10 μg/L, the analytical sensitivity is 0.65 μg/L, and total assay time is 1 h.

**CK isoforms.** CK-3 and CK-2 isoforms were separated by electrophoresis (1400 V for 16 min) on agarose gel with the automated REP/EDC system and 1-μL samples. The gel was cooled during electrophoresis by a Peltier cooling device in the automated system. After electrophoresis, the gel was treated with the CK substrate reagent at 45 °C and then dried for 5 min at 54 °C. Isoforms were detected by fluorescence densitometry. CK-3 separated into three isoforms (MM₃, MM₂, and MM₁) and CK-2 into two (MB₂ and MB₁). The EDC system was programmed to print out the relative percentage of each peak and the MM₃/MM₁ and MB₂/MB₁ ratios.

### Table 1. Population Studied

<table>
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<th>Patients treated with thrombolytic therapy</th>
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<tr>
<td>Anterior</td>
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<tr>
<td>Subendocardial</td>
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<tr>
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<td>Posterior</td>
<td>2</td>
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<tr>
<td>No site given</td>
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*Non-MI: 55 (M = 34, F = 21); MI 76 (M = 61, F = 15).*

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**Fig. 1.** The number and time distribution of MI patients used
A, CK-2 mass assay; B, CK-3 isofom ratio; and C, CK-2 isofom ratio

**Time, h**

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Within- and between-run precisions (CVs) were <10% for CK-3 and CK-2 isoforms. The minimum CK-2 activity for isoform analyses was 4 ± 1 U/L (mean ± SD). Several samples, in particular from the non-MI population, had undetectable MB₂ and MB₁ activities. The MB₂/MB₁ ratio for these samples was arbitrarily given a value of 0.80, which is the mean value (SD = 0.37) obtained from our nondiseased population. Samples containing >60 U/L of CK-2 were diluted with saline or heat-inactivated sera before isoform analyses. We observed an extra band anodal to MM₁ (MM₁₄) in a few samples. This is probably the cleavage product of MM₁, so for simplicity we included the area under this extra peak with the area for MM₁.

Data analysis. The analyzed samples were separated into six groups: 0–4, 3–6, 4–8, 8–12, 12–18, and 18–24 h after time of onset of chest pain. Diagnostic sensitivity, specificity, positive and negative likelihood ratios, and decision thresholds were calculated by a MUMPS program as described elsewhere (3, 29, 30). The program provides ROC curves along with the area under each curve and its 95% confidence interval. The 95% confidence intervals (31) for the likelihood ratios were calculated by using a confidence interval program (32).

Results

Analytical aspects. Cleavage of the C-terminal lysine residue of both the CK-3 and CK-2 isoenzymes continues after blood collection. To halt this conversion we initially used 50 mmol/L EGTA and 5 mmol/L 2-mercaptoethanol (final concentrations), as recommended by Puleo et al. (22). However, we found an almost complete loss of CK activity under these conditions. Therefore, we optimized our storage conditions and found that using final concentrations of 5 mmol/L for both EGTA and 2-mercaptoethanol resulted in little or no loss of activity (data not shown). In addition, we immediately stored the treated serum specimens at -20°C to further suppress the conversion process. The specimens were thawed at room temperature for 15 min before electrophoresis. We found that specimens collected and stored under these conditions were stable for at least 2 weeks.

Puleo et al. (28) reported that the isoform assay of the REP/EDC system, performed at 30°C, can detect 1.2 U/L of either CK-2 isoform. Accordingly, we determined the minimum activity of CK-2 that can easily be separated electrophoretically into two distinct peaks and that is still detectable by the densitometer. Figure 2 (A, B, and C) shows the serial dilution of a specimen (CK-2 activity 8 U/L) with saline solution. The isoforms can be quantitated up to a CK-2 activity of 4 U/L, although the peaks are harder to distinguish from assay noise at this activity than at 8 U/L (Figure 2, A and B). The isoforms cannot be accurately quantitated by further dilution of this specimen to 2 U/L (Figure 2C). The densitometric scans of the undiluted serum specimens are shown in Figure 2, D, E, and F; at 15 U/L CK-2 isoforms are easily quantifiable but not at 1 or 3 U/L. In general, we had difficulty in determining the CK-2 isoform ratio for specimens with CK-2 activity of <5 U/L; CK-2 activity >5 U/L was easily quantifiable. There is some discrepancy between our data on minimum detection limit of

![Figure 2](image-url). Densitometric tracings of CK-2 isoforms analysis by the REP/EDC electrophoretic system

A, a serum sample with total CK-2 activity of 8 U/L; B, CK-2 activity of 4 U/L after dilution with saline solution; C, CK-2 activity of 2 U/L after dilution with saline solution; D, a serum sample with CK-2 activity of 15 U/L; E, a serum sample with CK-2 activity of 1 U/L; and F, a serum sample with CK-2 activity of 3 U/L.

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CK-2 isoforms and the data of Puleo et al. (28); however, the discrepancy could partially be due to the different methods used for the CK-2 activity determination in the two laboratories.

**Diagnostic evaluation by ROC curves.** The ROC curves for the results of the CK-2 mass assay, for the CK-3 isoform ratio, and for the CK-2 isoform ratio are shown in Figure 3. Diagnostic efficacies increase with time, as shown by the increase in the areas under the curve. ROC curves of all three tests for the critical time 3–6 h after the onset of chest pain are shown in Figure 4. Table 2 shows the estimates of the area under each ROC curve together with their 95% confidence intervals and standard errors.

**Likelihood ratios.** We calculated the likelihood ratios,
the 95% confidence intervals, and the standard errors for a positive test result at a sensitivity of 95% at each time interval (Table 3). We also calculated the likelihood ratios, the 95% confidence intervals, and the standard errors for a negative test result at a specificity of 95% at each time interval (Table 4).

**Decision thresholds.** The decision thresholds for 95% sensitivity and specificity were determined for each test at each time interval (Figure 5).

**Discussion**

The assay of CK isoforms on the Helena REP system, although mostly automated, has certain drawbacks: the quantification of isoforms with low CK activity requires manual override of the otherwise automatic scanning parameters, which is technically demanding on the operator; analytical sensitivity is insufficient, as is evident from Figure 2; and special care is required for the appropriate collection and storage of samples. The concentration of stabilizers and the storage conditions we used were essentially similar to those recently reported by Davies et al. (39). Moreover, electrophoretic migration of the isoforms on the agarose gel can often vary from one run to another, thus requiring resetting the "scan-begin" and "scan-end" parameters and resulting in longer assay times.

By contrast, mass assays for CK-2 are now well established and routinely used in many laboratories. For example, in a recent College of American Pathologists quantitative CK-2 isoenzyme survey (Electrophoresis/Chromatography Survey set EC-C, specimen EC-21, September, 1991), >70% of the participants used such assays. Both manual and automated methods are available and most involve a sandwich-type system with two monoclonal antibodies. Turnaround times are often short, making these assays excellent for stat determinations (16, 17).

Puleo et al. (27) used fixed decision thresholds to evaluate the diagnostic utility of the CK-2 isoforms compared with CK-2 activity by determining their sensitivity at specified times after the onset of MI. For their samples collected at 0–2, 2–4, 4–6, and 6–8 h after MI, the CK-2 isoforms had sensitivities of 12.5%, 59%, 92%, and 100%, whereas the comparable sensitivities for CK-2 activity were 0%, 23%, 50%, and 71%, respectively. However, the data were not examined by ROC curve analysis and the decision thresholds chosen may not have been optimal. The aggregate sensitivity of the CK-2 isoform assay reported by Puleo et al. within the first 4 h of MI was 46.7% (14 of 30). Such a sensitivity indicates a test with no clinical utility.

In addition, no information was provided by Puleo et al. (27) on the confidence intervals of the sensitivity estimates. We calculate, by using binomial distributions (34), that Puleo's reported sensitivities for 0–2, 2–4, and 4–6 h have 95% confidence intervals as follows: 0–52%, 36–79%, and 75–99% for the CK-2 isoforms and 0–37%, 8–45%, and 30–70% for CK-2 activity, respectively. Thus, the two techniques give values for sensitivity that are actually more comparable than is indicated by the

| Table 3. Diagnostic Specificities and Likelihood Ratios at a Constant High Sensitivity (95%) at Various Times after the Onset of Suspected MI |
|---------------------------------|------|-----------|-----------|
| Time, h | Specificity, % | Mean SE | 95% confidence interval |
| CK-2 mass |
| 0–4 | 21.8 | 1.2 | 0.082 | 1.0–1.4 |
| 3–6 | 50.9 | 2.0 | 0.142 | 1.5–2.6 |
| 4–8 | 92.7 | 13.3 | 0.483 | 5.2–34.3 |
| 8–12 | 100 | 0 | 0 | 0–0 |
| 12–18 | 100 | 0 | 0 | 0–0 |
| 18–24 | 100 | 0 | 0 | 0–0 |
| CK-3 isoform ratio |
| 0–4 | 40.0 | 1.6 | 0.117 | 1.3–2.0 |
| 3–6 | 60.0 | 2.4 | 0.171 | 1.7–3.4 |
| 4–8 | 74.5 | 3.8 | 0.234 | 2.4–6.0 |
| 8–12 | 74.5 | 3.8 | 0.235 | 2.4–6.0 |
| 12–18 | 87.3 | 7.4 | 0.356 | 3.7–14.8 |
| 18–24 | 27.3 | 1.4 | 0.089 | 1.1–1.6 |
| CK-2 isoform ratio |
| 0–4 | 10.2 | 1.1 | 0.084 | 0.9–1.2 |
| 3–6 | 14.3 | 1.1 | 0.075 | 0.9–1.2 |
| 4–8 | 93.9 | 15.6 | 0.561 | 5.2–46.8 |
| 8–12 | 100 | 0 | 0 | 0–0 |
| 12–18 | 95.9 | 23.0 | 0.694 | 5.9–88.8 |
| 18–24 | 18.3 | 1.2 | 0.071 | 1.0–1.3 |

* = denotes a very large number.
reported figures. Moreover, Puleo et al. compared the CK-2 isoforms with measurements of CK-2 activity, but it is now recognized that measurements of CK-2 mass are superior to measurements of CK-2 activity. For example, Mair et al. (18) presented evidence that CK-2 mass assays are often abnormal when CK-2 activities are still within the reference interval. Although Mair et al. performed ROC curve analysis of their data, they did not provide an estimate of the area under the ROC curve, so that the significance of their data is not entirely clear. Likewise, Wu et al. (23) used ROC curve analysis in their comparison of the CK-2 isoforms and CK-2 activity measurements for 3–9 and 10–18 h after MI. They did not, however, provide areas under the ROC curve, so it is difficult to fully assess the significance of their findings.

The area under the ROC curve is an important measurement because it provides, in a single numerical value, the overall utility of the test (35). Its calculation also provides an estimate of the standard error of the ROC curve and thus an estimate of the confidence interval of the tested system (36). Consequently, we have fully documented our comparison of the CK-3 and CK-2 isoform ratios with the CK-2 mass assay to establish its statistical significance.

The ROC curves for the performance of the three tests are shown in Figures 3 and 4, and the data from these curves is summarized in Table 2. During the 0–4 h interval, the area under the ROC curve suggests that the CK-3 isoform ratio is the best assay of the three, followed by the CK-2 isoform ratio and the CK-2 mass assay. However, when the 95% confidence intervals are considered, it is clear that all three assay results overlap considerably. Therefore, we can tentatively conclude that all three assays are equivalent at 0–4 h. In the diagnostic and therapeutically important 3–6 h interval, the CK-2 mass assay has the highest area under the ROC curve, followed by the CK-2 isoform ratio and the CK-3 isoform ratio, but all areas are numerically very similar and, of course, the 95% confidence intervals closely overlap, suggesting that all these assay results are equivalent. Similar conclusions can be drawn from the results for 4–8, 8–12, and 12–18 h. Thereafter, the CK-2 mass assay is clearly better, whereas the results from the isoform ratios are less good, but comparable.

It is also useful to obtain the likelihood ratio (37–39) of a positive test result, because it is decision-threshold dependent; it is defined as the slope (or tangent or differential) of the ROC curve at a designated point [e.g., likelihood ratio (LR) = true positive rate (TPR)/false positive rate (FPR)]. Each point on the ROC curve is defined by its TPR and FPR coordinates, but each such point also has an associated decision threshold value (39). The likelihood ratio is also defined as the ratio of the posttest odds to the pretest odds of the presence of the target disease (38) or, alternatively, because it is the slope of the ROC curve, as the ratio of the probability of a given test result when the disease is present to the probability of the same test result when the disease is absent. Because the likelihood ratio can be calculated for many different values of the decision threshold, it can actually provide more information about the test than can the area under the ROC curve, which is an aggregate measure of overall test accuracy. For the early diagnosis of MI, the 95% confidence intervals (37) of the likelihood ratios for the three tests all overlap for the 0–4 h interval (Table 3).

Fig. 5. Decision thresholds for the CK-2 mass assay (A) and the CK-3 (B) and CK-2 (C) isoform ratios

Filled circle, Decision thresholds for 95% sensitivity; Open circle, decision thresholds for 95% specificity
that the results of all three tests at the decision thresholds used are diagnostically equivalent.

Another property of the likelihood ratio, implied by one of the definitions given above, is that it is a simple and very useful expression of Bayes's theorem. The likelihood ratio is the multiplier that is applied to the pretest odds of disease to produce the posttest odds for the presence of the target disease. (The relationship between odds and probability, which does not concern us here, is examined in considerable detail elsewhere (40).) From the definition of Bayes's theorem mentioned above, it can be appreciated that a good test is one possessing a large, i.e., $>>1$, value for the likelihood ratio of a positive test result. During the 0–4 h period, as noted earlier, all tests have very similar values for the likelihood ratio (and the 95% confidence intervals overlap); during the 4–8 h period, only two tests are comparable and, therefore, more diagnostically useful and the CK-3 isoform ratio is clearly not as good, although there is a marginal overlap of the 95% confidence intervals. In the 3–6 h period, CK-2 mass and CK-3 isoform assays are superior to the CK-2 isoform assay. Thereafter, the CK-2 mass assay (and for one time period only, the CK-2 isoform ratio) is clearly superior, because the likelihood ratios are infinite.

A good test also has a low, i.e., $<<1$, likelihood ratio for a negative test result (defined as the ratio of the probability of a falsely negative test result to the probability of a true-negative test result). During the 0–4, 3–6, and 4–8 h intervals, all three tests possess an equal value for ruling out infarction and this value improves with time (Table 4), whereas at later intervals the consistently best test is the CK-2 mass assay.

During the 0–4 h interval, a likelihood ratio of 1 or just above or below 1 (Tables 3 and 4) for either a positive or negative test result makes very little difference between the pre- and posttest odds for the presence or absence of MI. Therefore, little diagnostic reliance can be placed on such results. These conclusions are derived from data for a test with 95% sensitivity or specificity; different values will be obtained for the likelihood ratios when the values of the test indexes are altered. However, a test with a high sensitivity is used to rule out infarction, whereas a test with a high specificity is used to diagnose infarction, and these two diagnostic functions appear to be essential during the early stages of infarction. In conclusion, therefore, none of the tests—CK-2 mass assay or the CK-3 or CK-2 isoform ratios—possesses diagnostic utility during the first 4 h after the onset of MI; the diagnostic situation improves, but not much, during the 3–6 h period, as shown by the likelihood ratios.

We plotted the decision thresholds for either a constant 95% sensitivity or specificity for the first 24 h after the onset of chest pain for the three tests (Figure 5). Although the decision threshold for a constant specificity remains nearly uniform, the threshold for a constant sensitivity varies with time. For example, the decision threshold for the CK-2 mass assay during the 0–4 h interval is $<1.0 \mu g/L$, whereas by the 12–18 h interval the threshold producing the same 95% sensitivity is 18 $\mu g/L$ (Figure 5A). Similar, although quantitatively different, effects can be seen with the CK-3 and CK-2 isoform ratios (Figure 5, B and C). This observation of the changing decision thresholds after MI was first documented by Van Steirteghem et al. (41) and Werner et al. (42); we subsequently confirmed and extended these observations (8, 43). The consequences of such a change are important but were not described in recent reviews (44, 45). If a constant decision threshold is used, e.g., $<5 \mu g/L$ for the CK-2 mass assay (Figure 5A), there will be 95% sensitivity for the 4–8 h interval. Data from earlier intervals will be interpreted with a much lower sensitivity, whereas data from later intervals will be interpreted with a higher sensitivity. Clearly the diagnostic yield will vary instead of being constant. However, it is not practical to have variable decision thresholds in a routine clinical setting although the provision of appropriate algorithms in all acute-care settings might be worth considering.

In conclusion, our results indicate that the immunological CK-2 mass assay and the electrophoretic CK-isoform assays are ineffective for diagnosing MI within the first 4 h of the onset of symptoms, and all three assays are most effective in the 4–18 h interval. In addition, all three assays are diagnostically quite comparable in the critical 3–6 h interval. The analytical performance of the immunoassay for CK-2 mass is superior to the activity assay for isoforms. Immunoassays for the isoforms have been reported; these assays have high analytical sensitivity and short assay times, but most have high cross-reactivity with other isoforms (46–49). Thus, specific and sensitive immunoassays are needed for the quantification of CK isoforms; these assays may be better diagnostically than the activity assays.

Finally, it is important to stress that Helena Laboratories have upgraded their REP/EDC system with a modified overhead gel dryer and the addition of a copper electrophoresis plate, which is claimed to improve analytical sensitivity for CK isoforms. The system that we used here was not so modified, and thus our results may not represent the current capabilities of the REP/EDC for CK isoform analysis. Nonetheless, we believe there is a good case for further comparisons between CK-2 mass and CK-2 isoform assays to establish their respective clinical utilities in the early diagnosis of MI.

References


