Ninety-Minute Exclusion of Acute Myocardial Infarction By Use of Quantitative Point-of-Care Testing of Myoglobin and Troponin I

James McCord, MD; Richard M. Nowak, MD, MBA; Peter A. McCullough, MD, MPH; Craig Foreback, PhD; Steven Borzak, MD; Glenn Tokarski, MD; Michael C. Tomlanovich, MD; Gordon Jacobsen, MS; W. Douglas Weaver, MD

Background—Diagnostic strategies with ECG and serum cardiac markers have been used to rule out acute myocardial infarction in 6 to 12 hours. The present study evaluated whether a multimarker strategy that used point-of-care measurement of myoglobin, creatine kinase (CK)-MB, and troponin I could exclude acute myocardial infarction in ≤3 hours.

Methods and Results—We prospectively enrolled consecutive patients (n=817) in the emergency department who were evaluated for possible acute myocardial infarction. In patients with nondiagnostic ECGs, we measured CK-MB, troponin I, and myoglobin with a point-of-care device at presentation and at 90 minutes, 3 hours, and 9 hours. Standard central laboratory testing of CK-MB was done at the same time intervals, and triage decisions were made by emergency physicians who were unaware of point-of-care results. Sensitivity and negative predictive value were compared for both the multimarker, point-of-care approach and the central laboratory strategy. Sensitivity and negative predictive value for point-of-care combination of myoglobin and troponin I by 90 minutes was 96.9% and 99.6%, respectively. CK-MB measurements and blood sampling at 3 hours did not improve sensitivity or negative predictive value. Median time from sampling to reporting of results was 71.0 minutes for the central laboratory versus 24.0 minutes for the point-of-care device (P<0.001).

Conclusions—Acute myocardial infarction can be excluded rapidly in the emergency department by use of point-of-care measurements of myoglobin and troponin I during the first 90 minutes after presentation. (Circulation. 2001;104:1483-1488.)

Key Words: myoglobin ■ creatine kinase ■ troponin ■ myocardial infarction

Most patients (~85%) who present to an emergency department (ED) with possible acute coronary syndrome do not have acute myocardial infarction (AMI). For those patients, the obligatory “rule-out” process is both costly and time consuming. Serial cardiac marker testing is essential for accurate evaluation of patients with possible acute coronary syndrome, because ECGs at presentation have been nondiagnostic for 50% of patients with evidence of AMI by serum markers. Furthermore, 2% to 5% of patients with AMI are discharged mistakenly from the ED, often with severe consequences. Use of serial measurements of creatine kinase (CK)-MB for 9 hours has been shown to exclude AMI effectively. Other rapid rule-out strategies have measured either CK-MB or troponin over 6 to 7 hours.

Use of the combination of a marker that appears early (myoglobin) and either CK-MB or cardiac troponin I (cTnI) may facilitate rapid exclusion of AMI and enable discharge of patients who do not require prolonged observation. Myoglobin is advantageous because it appears 1 to 2 hours after symptom onset, and studies have demonstrated its high sensitivity for detection of AMI within the first few hours after presentation. However, use of myoglobin alone has significant limitations. Myoglobin has low specificity for cardiac necrosis in patients with renal failure or skeletal muscle trauma. Also, given that serum myoglobin rises and falls quickly in AMI, a single measurement at presentation may be normal for patients who present early and who present >24 hours after symptom onset. On the other hand, CK-MB and cTnI appear 3 to 6 hours after symptom onset and remain elevated for 24 to 36 hours and 7 to 10 days, respectively.

Point-of-care testing of cardiac markers enables results to be known within 15 to 20 minutes after patient assessment,
potentially reducing time to diagnosis. Prior studies have validated the accuracy of such devices.\textsuperscript{5,10} We hypothesized that a multimarker bedside device that measures myoglobin, CK-MB, and cTnI and that is used at admission and either 90 minutes or 3 hours could equal the diagnostic accuracy of a more-traditional approach that uses central laboratory CK-MB measurements during 9 hours.

Methods

Patients

The survey population consisted of 1024 consecutive encounters of patients who were evaluated for possible AMI in the ED at Henry Ford Hospital from January through May 1999. Patients were included if the emergency physician suspected possible AMI, and a standard cardiac marker panel was ordered from the central laboratory (CK-MB measured 4 times during 9 hours). Patients with ECG findings (ST elevation or left bundle-branch block) that led to reperfusion therapy were excluded.

A full 9 hours of cardiac marker testing was not completed in 206 patients. These patients were excluded from the analysis, because after early clinical observation and additional evaluation, such testing was felt to be clinically unwarranted (ie, patient had a noncardiac diagnosis, such as musculoskeletal pain, pneumonia, or pulmonary embolism). Of these patients, 116 were discharged home and 90 were admitted to hospital. At 30 days, 2 deaths had occurred among these 206 patients: 1 cardiac death in a patient discharged from the ED and 1 noncardiac death in a patient admitted to a medical floor. One additional patient was excluded because of lost data. Thus, 817 patient encounters were studied, as follows: 1484 Circulation (1999) AMI (n = 817) AMI (n = 65) No AMI (n = 752) P

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
<th>All (n = 817)</th>
<th>AMI (n = 65)</th>
<th>No AMI (n = 752)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean ± SD</td>
<td>64 ± 16</td>
<td>69 ± 14</td>
<td>63 ± 16</td>
<td>0.006</td>
</tr>
<tr>
<td>Men</td>
<td>374 (46)</td>
<td>31 (48)</td>
<td>343 (46)</td>
<td>0.747</td>
</tr>
<tr>
<td>Women</td>
<td>443 (54)</td>
<td>34 (52)</td>
<td>409 (54)</td>
<td>0.747</td>
</tr>
<tr>
<td>Black</td>
<td>664 (81)</td>
<td>54 (83)</td>
<td>610 (81)</td>
<td>0.291</td>
</tr>
<tr>
<td>White</td>
<td>129 (16)</td>
<td>7 (11)</td>
<td>122 (16)</td>
<td>0.291</td>
</tr>
<tr>
<td><strong>Past medical history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>266 (33)</td>
<td>17 (28)</td>
<td>249 (34)</td>
<td>0.336</td>
</tr>
<tr>
<td>CABG surgery</td>
<td>92 (12)</td>
<td>8 (13)</td>
<td>84 (11)</td>
<td>0.652</td>
</tr>
<tr>
<td>Percutaneous coronary intervention</td>
<td>166 (21)</td>
<td>9 (15)</td>
<td>157 (22)</td>
<td>0.218</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>224 (28)</td>
<td>24 (39)</td>
<td>200 (27)</td>
<td>0.045</td>
</tr>
<tr>
<td>Muscle trauma</td>
<td>29 (4)</td>
<td>4 (7)</td>
<td>25 (3)</td>
<td>0.187</td>
</tr>
<tr>
<td>Chronic renal insufficiency*</td>
<td>201 (25)</td>
<td>23 (35)</td>
<td>178 (24)</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Values are all n (%) unless otherwise indicated.

*Serum creatinine ≥ 1.5 mg/dL.

AMI was defined as follows: (1) ≥ 1 CK-MB value higher than upper reference range (9 ng/mL) as measured in the central laboratory over the 9-hour sampling period and (2) agreement between 2 cardiologists working independently (after the pattern of change in CK-MB and medical records of all patients were reviewed) that AMI had occurred. In case of disagreement, a third cardiologist adjudicated the case. All other final diagnoses were determined by the discharging physician as documented in the medical record. ECGs were interpreted by physicians blinded to the clinical cases by use of the Thrombolysis In Myocardial Infarction (TIMI) study group\textsuperscript{11} classification.

Biomarker Analytical Techniques

CK-MB was measured in the central laboratory with the AxSYM analyzer (Abbott Laboratories). Point-of-care testing was performed with 6 drops of whole blood and a fluorescence immunoassay for simultaneous quantitative determination of CK-MB, myoglobin, and cTnI (Triage Cardiac Panel, Biosite Diagnostics). After addition of the sample, cells are separated from the plasma through a filter in the device. A predetermined quantity of plasma is allowed to react with fluorescent antibody conjugates within the reaction chamber. Analytical sensitivities for CK-MB, myoglobin, and cTnI are 0.75, 2.70, and 0.19 ng/mL, respectively.\textsuperscript{12}

Statistical Analysis

Group comparisons were made by use of the $\chi^2$ test, Wilcoxon rank sum test, or t test as appropriate. A 2-sided $\alpha$ level of 0.05 was used to determine significance. Receiver-operating characteristic curve (ROC) analysis was performed on each of the 3 markers measured by the bedside device as predictors of final diagnosis of AMI. Cutoff values with the largest sum of sensitivity plus specificity for all time points combined were chosen. By use of these optimal values, resulting sensitivity, specificity, and positive and negative predictive value estimates were obtained for each individual time point and
marker and for the various time points and marker combinations. For marker combinations, if any test was abnormal, the combination was considered positive, and only if all tests were negative was the combination considered negative.

Results

Patient Characteristics
Table 1 shows demographics and medical histories of the study population. Final diagnoses (Table 2) included 65 patients with AMI. Median time from symptom onset to presentation was 4.3 hours for the entire group (Figure 1) and 3.9 hours in patients with AMI. Dispositions from the ED included admission to the telemetry unit n = 376 (46%), to the short-stay observation unit n = 262 (32%), to the cardiac intensive care unit n = 93 (11%), and to other medical beds n = 86 (10%). ECG findings in patients with AMI included nondiagnostic ST-T changes n = 43 (66%), ST-segment depression ≥1.0 mm n = 11 (17%), ST-segment elevation ≥1.0 mm n = 8 (13%), and normal n = 3 (5%).

Diagnostic Accuracy of Point-of-Care Biomarker Combinations
ROC analysis for point-of-care measurement of myoglobin, cTnI, and CK-MB is shown (Figures 2 through 4). Calculated optimum cut-point levels and corresponding coefficients of variation for myoglobin, CK-MB, and cTnI were 200 (11%), 6.0 (12%), and 0.4 (12%) ng/mL, respectively. The combination of cTnI and myoglobin results obtained at 0 and 90 minutes yielded highest negative predictive value (99.6%) and sensitivity (96.7%) for determination of AMI during the first 3 hours (Table 3). Neither use of CK-MB nor additional 3-hour sample improved negative predictive value or sensitivity. Of 65 patients with AMI, 55 (85%) had abnormal myoglobin or cTnI at baseline, and 8 additional patients were identified as having abnormal myoglobin or cTnI at 90 minutes. Thus, 63 (97%) of the 65 AMI patients had abnormal cTnI or myoglobin levels within 90 minutes.

The 2 individuals with AMI not identified early did not show elevated levels of CK-MB until 9 hours. The first patient was a 56-year-old female with a history of hypertension who had vomiting, diarrhea, and abdominal pain. She first complained of intermittent chest discomfort lasting 10 minutes in the triage area just before the initial blood draw. ECG showed T-wave inversion in leads V1 through V3, and coronary angiography demonstrated normal coronary arteries. The second patient was a 52-year-old woman with a history of diabetes mellitus and hypertension who complained of intermittent “chest heaviness” that lasted 10 to 15 minutes and had started 6 hours before presentation. Coronary angiography showed a 90% stenosis in the left anterior descending artery.

Patients with creatinine levels ≥1.5 mg/dL (n = 178) had significantly higher baseline myoglobin levels compared with those with lower creatinine values (330 versus 123 ng/mL; P < 0.001); patients who stated a history of recent muscle trauma (n = 25) did not have significantly higher myoglobin levels (197 versus 153 ng/mL; P = 0.538). Specificity of myoglobin on admission for patients with creatinine levels <1.5 mg/dL was 89% (n = 564), whereas specificity was only 35% for patients with creatinine levels ≥1.5 mg/dL. Median
time for results was 24.0 minutes by the bedside device and 71.0 minutes by the central laboratory ($P<0.001$).

**Discussion**

Current protocols to exclude AMI typically measure individual cardiac markers over 6 to 12 hours. The largest study to date that involved cardiac marker combinations (>6000 patients) demonstrated that measurement of CK-MB and myoglobin at 0 and 1 hour had a sensitivity of only 72% for AMI.\textsuperscript{13} The present study demonstrates that AMI can be excluded more rapidly by use of a combination of normal cTnI and myoglobin values done at 0 and 90 minutes after ED admission. This has significant implications. For example, of the 262 patients admitted to the observation unit, 194 (74%) had negative cardiac bedside myoglobin and cTnI values at 0 and 90 minutes and were possible candidates for earlier stress testing or discharge.

Patients with only elevated myoglobin at 0 or 90 minutes require additional cTnI measurement at 6 to 9 hours to confirm myocardial necrosis and eliminate false-positives. Patients with renal insufficiency have higher myoglobin levels and, therefore, a higher false-positive rate. In the present study, history of muscle trauma was not associated with higher myoglobin levels and is probably explained by either patient reporting of all muscle contusions, even minor ones, or by our use of a cut-off value for myoglobin of 200 ng/mL, which is a higher value than in other reports.\textsuperscript{14}

The combination of cTnI and myoglobin had a higher cumulative negative predictive value and sensitivity for AMI within 90 minutes compared with CK-MB and myoglobin. Benamer et al\textsuperscript{15} showed that troponin T elevation identified more patients with AMI compared with CK-MB in a chest pain unit setting within the first 4 hours of presentation. Troponin measurement also detects patients with AMI who present late and is superior to CK-MB for risk stratification of patients with acute coronary syndrome.\textsuperscript{5,16} Patients with acute coronary syndrome and troponin elevation but normal CK-MB values have higher-risk coronary anatomy (complex lesions, multivessel disease, and thrombus) at heart catheterization.\textsuperscript{17}

Our present study used CK-MB as the standard for diagnosis of AMI, but troponin probably has superior diagnostic and prognostic usefulness. Troponin now is recognized as the preferred cardiac marker among consensus documents that concern management of unstable angina and non–ST segment elevation myocardial infarction\textsuperscript{18} and redefinition of AMI.\textsuperscript{19} Even low levels of troponin that are below typical cutoff values to define myocardial necrosis appear to have prognostic significance for future cardiac events.\textsuperscript{20} We believe that the combination of myoglobin and troponin measurement should supplant CK-MB in the routine initial assessment of patients with possible acute coronary syndrome in the ED. CK-MB may have a role in clarifying the clinical situation in the setting of reinfarction or troponin elevation of unclear origin.

High early sensitivity for AMI at 90 minutes in our present study is at variance with some prior trials. Our patient population may have some unique characteristics. Median

**TABLE 3. Diagnostic Usefulness of Biomarker Combinations**

<table>
<thead>
<tr>
<th>Point of Care</th>
<th>Time 0</th>
<th>0, 90 min</th>
<th>0, 90 min, 3 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>Sensitivity</td>
</tr>
<tr>
<td>Myo</td>
<td>70.8 (58–81)</td>
<td>75.6 (72–79)</td>
<td>84.6 (74–92)</td>
</tr>
<tr>
<td>CK-MB</td>
<td>75.4 (63–85)</td>
<td>84.7 (82–87)</td>
<td>83.1 (72–91)</td>
</tr>
<tr>
<td>cTnI</td>
<td>64.6 (52–76)</td>
<td>87.6 (85–90)</td>
<td>76.9 (65–86)</td>
</tr>
<tr>
<td>Myo, CK-MB</td>
<td>83.1 (72–91)</td>
<td>70.2 (67–73)</td>
<td>92.3 (83–98)</td>
</tr>
<tr>
<td>Myo, cTnI</td>
<td>84.6 (74–92)</td>
<td>66.8 (63–70)</td>
<td>96.9 (89–100)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Point of Care</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myo Negative</td>
<td>96.8 (95–98)</td>
<td>20.1 (15–26)</td>
<td>98.2 (97–99)</td>
<td>21.4 (16–27)</td>
<td>98.3 (97–99)</td>
<td>20.4 (16–26)</td>
</tr>
<tr>
<td>CK-MB</td>
<td>97.5 (96–99)</td>
<td>29.9 (23–38)</td>
<td>98.3 (97–99)</td>
<td>29.8 (23–37)</td>
<td>98.9 (98–100)</td>
<td>29.9 (24–38)</td>
</tr>
<tr>
<td>cTnI</td>
<td>96.6 (95–98)</td>
<td>31.1 (23–40)</td>
<td>97.5 (96–99)</td>
<td>24.2 (18–31)</td>
<td>98.5 (97–99)</td>
<td>20.2 (16–25)</td>
</tr>
<tr>
<td>Myo, CK-MB</td>
<td>98.0 (96–99)</td>
<td>19.4 (15–25)</td>
<td>99.0 (98–100)</td>
<td>19.7 (15–25)</td>
<td>99.0 (98–100)</td>
<td>19.0 (15–24)</td>
</tr>
<tr>
<td>Myo, cTnI</td>
<td>98.0 (96–99)</td>
<td>18.1 (14–23)</td>
<td>99.6 (98–100)</td>
<td>17.3 (14–22)</td>
<td>99.5 (98–100)</td>
<td>15.2 (12–19)</td>
</tr>
</tbody>
</table>

Myo indicates myoglobin. Values are all % (95% CI). If any value of a combination of markers was positive, the combination was considered positive. All values had to be negative for the combination to be considered negative.
time from symptom onset to presentation was 4.3 hours, which is longer than in other reports; this, in turn, may have improved sensitivity. However, 30 (46%) of AMI patients presented <4 hours after symptom onset, and 19 (30%) presented within 2 hours. In these groups, sensitivity was 96.7% and 94.4%, respectively. Furthermore, many other trials did not report the combined sensitivity of a multimarker approach, but instead cited only sensitivity of various individual markers over time. Studies that used a multimarker strategy have reported high early sensitivity. Kontos et al reported sensitivity of 85% for the combination of CK-MB and myoglobin on admission and 100% at 4 hours. Jernberg et al similarly described sensitivity of 88% for CK-MB and myoglobin at 0 hours and 99% at 3 hours. Maisel et al reported sensitivity of 88% for myoglobin and cTnI measured over 2 hours, with a negative predictive value of 99%. Finally, the particular assay used in the present study may have some unique characteristics. Lack of standardization of cTnI assays has led to interassay variability, which has resulted in >20-fold differences in measured values. Serum troponin exists in various complex and free forms. The assay used in the present study measures all forms of cTnI in an equimolar fashion, which differentiates it from other assays. Clinical implications of detecting different forms of cTnI, if any, presently are unknown.

Point-of-care testing of cardiac markers also offers some additional unique benefits. Recently published guidelines recommend a 30-minute turnaround time for cardiac markers in patients being evaluated for possible acute coronary syndrome in the ED. Even when we focused on this problem, only 3% of the results measured by the central laboratory met this goal compared with 68% when markers were measured at patient bedside. Transport time, sample handling, and making the physician aware of the result are all logistic hurdles that make this 30-minute goal difficult to accomplish with a central laboratory strategy. Point-of-care testing permits shortening of turnaround time from blood draw to physician decision making, and time to treatment may be important for patients with non–ST elevation AMI.

A limitation of the present study is that predetermined values were not evaluated; instead, ROC analysis–determined values optimized to fit the data were used. These values generated from this particular population may not be ones that can be extrapolated to other settings. However, the calculated value for cTnI (0.4 ng/mL) is exactly the same as the manufacturer’s recommended value; the calculated value for CK-MB (6.0 ng/mL) is similar (manufacturer’s value, 4.3 ng/mL). Only the calculated myoglobin value (200 ng/mL) is substantially different (manufacturer’s value, 107 ng/mL).

Another limitation is that blood samples were not drawn in 206 patients during the entire 9 hours. However, including the available laboratory values of these patients in our calculations did not significantly change baseline specificity of cTnI and myoglobin: 87.8% versus 87.6%, and 76.6% versus 75.6%, respectively. Also, caution should be exercised when a 90-minute rule-out protocol is used in patients who present to hospital within 1 to 2 hours after symptom onset or in those who have transitory symptoms. Although 19 (30%) AMI patients presented within 0 to 2 hours after symptom onset, only 5 did so within 1 hour. The 2 patients with AMI not identified at 90 minutes described intermittent symptoms that lasted only 10 to 15 minutes. Patients that present <1 hour after symptom onset probably require additional blood sampling and observation.

In conclusion, our present study of a large number of ED patients with possible AMI has shown the following: (1) that myoglobin and cTnI measurements during the first 90 minutes rapidly and accurately excluded AMI with this particular assay and (2) that more rapid turnaround time of cardiac marker results was achieved with point-of-care technology, which may lead to more rapid patient triage and treatment.

Acknowledgments
The present study was supported by an unrestricted research grant from Biosite Diagnostics, San Diego, Calif. We thank the entire staff of the ED at Henry Ford Hospital for their help and cooperation during the trial period. Special thanks go to Michele Whitican, RN, and Angelina Stone, RN, who worked diligently to ensure successful completion of the study, and to Gloria Sabo for her patience and superb manuscript preparation.

References


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