Delta Creatine Kinase–MB Outperforms Myoglobin at Two Hours During the Emergency Department Identification and Exclusion of Troponin Positive Non–ST-Segment Elevation Acute Coronary Syndromes

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Study objective: Limited information is available about the diagnostic performance of creatine kinase (CK)–MB and myoglobin levels during the early evaluation of chest pain patients using cardiac troponins as the criterion standard for diagnosing acute myocardial infarction. In this study, we compare the sensitivity and specificity of the baseline, 2-hour absolute, and 2-hour delta values of myoglobin and CK-MB mass assay for detection of acute myocardial infarction using cardiac troponin I (troponin) as the sole marker of myocardial necrosis.

Methods: A prospective observational study was conducted of 975 chest pain patients with a baseline troponin level of 1.0 ng/mL or less (Abbott Axsym Assay) and an initial ECG nondiagnostic for injury. CK-MB, myoglobin, and troponin levels were all measured on the Abbott Axsym immunoassay. Acute myocardial infarction was diagnosed if there was at least 20 minutes of chest pain and any one of the following criteria within 24 hours of ED presentation: a serial increase in troponin to more than 1.0 ng/mL, new Q-wave formation in 2 contiguous leads, or patient death by cardiac or unknown cause. The optimal values of CK-MB and myoglobin were chosen at the most accurate value on the receiver operating characteristic (ROC) curve (ie, value with lowest false-negative and false-positive rate) of the 2-hour absolute and 2-hour delta value for predicting acute myocardial infarction.

Results: Acute myocardial infarction was diagnosed in 44 (4.5%) of the 975 study patients. ROC curve analysis revealed no statistically significant differences in areas for myoglobin and CK-MB values at baseline and 2 hours for determination of acute myocardial infarction. However, the ROC curve area of the delta CK-MB level significantly outperformed the ROC curve area of the delta myoglobin level for early identification of acute myocardial infarction (0.97 versus 0.81; 95% confidence interval [CI] for difference between areas 0.09 to 0.24). At the most accurate cutoff value, a 2-hour delta CK-MB level more than 0.7 ng/mL had a sensitivity of 93.2% (95% CI 81.3% to 98.5%), a specificity of 94.4% (95% CI 92.7% to 95.8%), a positive likelihood ratio of 16.7, and a negative likelihood ratio of 0.07.

Conclusion: A 2-hour delta CK-MB level outperforms myoglobin level in the early identification and exclusion of acute myocardial infarction in non–ST-segment elevation chest pain patients. This finding suggests that myoglobin may no longer be the optimal early marker of acute myocardial infarction when troponins are used as the criterion standard.

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Editor's Capsule Summary

What is already known on this topic

Myoglobin has long been considered the best "early" marker for the diagnosis of acute myocardial infarction.

What question this study addressed

This study evaluated the ability of delta creatine kinase (CK)–MB and delta myoglobin to identify patients with acute myocardial infarction within 2 hours of emergency department arrival, using the new definition of acute myocardial infarction (including cardiac troponin I as the criterion standard).

What this study adds to our knowledge

This study found that a 2-hour delta CK-MB of more than 0.7 ng/dL had a 93% sensitivity and 94% specificity for detection of acute myocardial infarction. Delta CK-MB performed better than myoglobin during this early time frame.

How this might change clinical practice

The difference between CK-MB drawn at the time of arrival and 2 hours later (delta CK-MB) has good sensitivity and specificity for the early detection of acute myocardial infarction. Use of this delta strategy may preclude the need for myoglobin in institutions where multiple cardiac marker strategies are used.

INTRODUCTION

Current recommendations from the National Academy of Clinical Biochemistry are to use an early biochemical marker such as myoglobin in conjunction with a later definitive marker (troponin I [troponin] and T) for the routine diagnosis of acute myocardial infarction.[1] However, prospective studies to date that have demonstrated myoglobin to be a reliable early marker of acute myocardial infarction have used World Health Organization (WHO) criteria or creatine kinase (CK)–MB assay as the criterion standard.[2-5] New recommendations for the serum marker redefinition of acute myocardial infarction suggest using a troponin cutoff value of the 99th percentile or greater of a reference population in which the assay imprecision is 10% or less.[6,7] As a result, a significant number of patients previously classified as having unstable angina will now be classified as having acute myocardial infarction. Estimates of the effect of using this new troponin definition suggest that the number of patients receiving a discharge diagnosis of acute myocardial infarction will increase approximately 25% because of the enhanced ability of troponins to detect microinfarcts.[8-10]

Because myoglobin has an early peak and is cleared rapidly from the circulation, it is unknown whether myoglobin level has the ability to detect microinfarcts in patients presenting early in symptom onset. Theoretically, there may be a subset of patients with microinfarcts in whom the myoglobin is cleared from the circulation so rapidly that a peak is difficult to measure without continual blood sampling.

Previous work has demonstrated that a 2-hour delta CK-MB level reliably identifies and excludes acute myocardial infarction using WHO criteria in conjunction with CK-MB mass assay as criterion standard.[11,12] Studies have also demonstrated the utility of delta myoglobin testing at 1 to 2 hours after baseline in the exclusion of myocardial infarction using CK-MB level as the criterion standard.[13-15] Limited information is available about the diagnostic performance of CK-MB and myoglobin levels during the early evaluation of chest pain patients using low cutoff values of cardiac troponins as the criterion standard for diagnosing acute myocardial infarction. In this study, we compare the sensitivity and specificity of the baseline, 2-hour absolute, and 2-hour delta values of myoglobin and CK-MB mass assay for detection of acute myocardial infarction using cardiac troponin as the criterion standard for serum marker diagnosis of acute myocardial infarction.

MATERIALS AND METHODS

This prospective study was conducted at a university teaching hospital during a 6-month period from July 1999 through December 1999. The institutional review committee approved the study protocol without written informed consent because (1) baseline and 2-hour CK-MB, myoglobin, and troponin level determinations were part of the accepted Erlanger Chest Pain Evaluation Protocol during this study; (2) patient contact for 30-day follow-up was part of our established emergency department (ED) quality improvement process; and (3) patient confidentiality was maintained. The study population was derived from 1,140 consecutive chest pain patients with suspected acute coronary syndrome. Patients were initially evaluated by board-certified emergency physicians or residents from the departments of internal medicine and family practice (under the supervision of the attending emergency physician). All patients underwent an accelerated chest pain evaluation protocol, which consisted of continuous ST-segment monitoring with automated serial 12-lead ECGs, a baseline and 2-hour cardiac serum marker measurement (CK-MB, myoglobin, and troponin levels), and selective nuclear stress testing before the physician made the final disposition decision.[16] Initial exclusion criteria included patients presenting with chest pain in the presence of a tachyarrhythmia (ventricular tachycardia, supraventricular tachycardia, or rapid atrial fibrillation); patients

with pulmonary edema on presentation, requiring mechanical ventilation; patients with chest pain not deemed by physician to warrant cardiac workup; and patients with suspected acute coronary syndrome who did not present with chest pain. Secondary exclusion criteria included an initial ECG diagnostic for injury, baseline troponin more than 1.0 ng/mL, and incomplete serum marker data.

The baseline ($CK\text{-}MB_0$) and 2-hour ED ($CK\text{-}MB_2$) CK-MB levels were analyzed using the Abbott Axsym Fluorometric Enzyme Immunoassay (Abbott Laboratories, Abbott Park, IL).[17] Analytic sensitivity of the Abbott CK-MB assay (smallest value that can be distinguished from zero) is 0.7 ng/mL, with a within-run precision coefficient of variation of 4.5% for serum samples with a mean concentration of 4.9 ng/mL. Delta CK-MB level was defined as the difference between $CK\text{-}MB_2$ and $CK\text{-}MB_0$ levels. The baseline ($myoglobin_0$) and 2-hour ED myoglobin ($myoglobin_2$) levels were also analyzed using the Axsym Fluorometric Enzyme Immunoassay (Abbott Laboratories).[18] Analytic sensitivity of the Axysm myoglobin level is 1.0 ng/mL, with within-run precision coefficient of variation of 4.6% in samples with a mean concentration of 49 ng/mL. Delta myoglobin level was defined as the difference between $myoglobin_2$ and $myoglobin_0$ levels. All CK-MB values less than 0.7 ng/mL were recorded as 0.7 ng/mL, and all myoglobin values less than 1 ng/mL were recorded as 1 ng/mL because these values correspond to the analytic sensitivity of the respective assays.

Acute myocardial infarction was diagnosed if there was at least 20 minutes of chest pain and any 1 of the following criteria within 24 hours of ED presentation: a serial increase in troponin to more than 1.0 ng/mL, new Q-wave formation in 2 contiguous leads (according to official ECG interpretation), or patient death by cardiac or unknown cause. The troponin value was determined by the Axsym Fluorometric Enzyme Immunoassay (Abbott Laboratories). Analytic sensitivity of the Axysm troponin is 0.3 ng/mL, with within-run precision coefficient of variation of 6.1% in samples with a mean concentration of 2.9 ng/mL.[19] The lowest cutoff value above the 99th percentile with a 10% precision or less is reported to be 0.8 ng/mL.[7] Thirty-day adverse outcome was defined as life-threatening complication, death by cardiac or unknown causes, percutaneous coronary intervention, or coronary artery bypass grafting occurring within 30 days of initial ED visit. Life-threatening complications were defined as ventricular fibrillation, sustained ventricular tachycardia, third-degree atrioventricular block, bradycardic or asystolic arrest, post-ED presentation acute myocardial infarction, cardiogenic shock, or electromechanical dissociation. Thirty-day adverse outcome was determined for all patients by review of inpatient and outpatient medical records, private physician contact for results of office follow-up visits, and patient contact by telephone or mail. For patients lost to follow-up, missed acute myocardial infarction on presentation and 30-day death were determined by review of patient complaints and malpractice allegations and by review of county death records. For reporting of demographic characteristics of patient population, typical risk factors were defined using definitions of Morise et al[20] and ECG findings using definitions of Fesmire et al.[21] Data were recorded on a standardized form and placed in a computer database using SYSTAT 10.0 (SPSS, Inc., Chicago, IL). Receiver operating characteristic (ROC) curves for acute myocardial infarction of the paired serum marker measurements under comparison (ie, baseline, 2-hour, and delta measurements) were compared using MedCalc 4.2 (MedCalc Software, Mariakerke, Belgium).[22] The discriminatory ability of CK-MB and myoglobin levels for acute myocardial infarction was investigated at the most accurate cutoff value on the ROC curve (ie, value with lowest false-negative and false-positive result). Positive and negative likelihood ratios were calculated according to the formula positive likelihood ratio=sensitivity/(1–specificity) and negative likelihood ratio=(1–sensitivity)/specificity.[23] All statistical comparison is presented as 95% confidence intervals (CIs) in preference over *P* values. CIs for difference in areas of ROC curves[24] and CIs for difference in proportions[25] for sensitivities and specificities were calculated with appropriate correction for paired data. CIs for relative risk were calculated by Mietten's test-based method.[26]

RESULTS

During a 6-month period, a total of 1,140 consecutive eligible chest pain patients underwent evaluation for potential acute coronary syndrome. Of these, 30 patients were excluded for having injury on the initial ECG. Sixty-seven patients were excluded for having a baseline troponin level more than 1.0 ng/mL, and 74 patients (6 with acute myocardial infarction) were excluded for having incomplete serum marker data, giving a final study population of 975 patients. Direct 30-day follow-up was obtained for 932 (95.6%) patients, and indirect follow-up was obtained for 43 (4.4%) patients. A total of 44 (4.5%) patients had acute myocardial infarction on ED presentation, and 68 patients had 1 or more 30-day adverse

outcomes: 10 (1.0%) patients with 30-day life-threatening complication, 66 (6.8%) patients with 30-day percutaneous coronary intervention/coronary artery bypass grafting, and 3 (0.3%) patients with 30-day death. Forty-eight percent of the 931 patients without acute myocardial infarction underwent ED nuclear stress testing as part of their initial evaluation. Table 1 lists demographic characteristics of the study patients with and without acute myocardial infarction. Table 2 lists initial ECG findings in patients with acute myocardial infarction and 30-day adverse outcome. The median time from symptom onset until presentation in the 44 acute myocardial infarction patients was 1.5 hours (mean 4.0 hours; 95% CI 2.1 to 5.8 hours). The median time until baseline serum marker was drawn was 20 minutes (mean 23 minutes; 95% CI 18 to 27 minutes) and the median 2-hour delta time was 120 minutes (mean 127 minutes; 95% CI 118 to 136 minutes).

Table 3 represents ROC curve areas for acute myocardial infarction of the 3 paired serum marker measurements under comparison (ie, baseline, 2-hour, and delta) for myoglobin and CK-MB respectively. There were no statistical differences in ROC curve areas for baseline and 2-hour myoglobin and CK-MB values. However, the delta CK-MB level significantly outperformed the delta myoglobin level for early identification of acute myocardial infarction.

Table 4 compares sensitivities, specificities, positive likelihood ratio, and negative likelihood ratio of the baseline and 2-hour marker measurements at manufacturer's recommended cutoffs and of the delta values using institutional cutoffs at the time of the study. Myoglobin level is more sensitive and less specific compared with CK-MB level at baseline and 2 hours, although both markers performed poorly in identifying and excluding 24-hour acute myocardial infarction. Delta CK-MB level was more sensitive and more specific compared with delta myoglobin level.

Table 5 compares sensitivities, specificities, positive likelihood ratio, and negative likelihood ratio of the baseline, 2-hour, and delta marker measurements at the most accurate cutoff value on the ROC curve (ie, value with the lowest false-positive and false-negative rate) for identifying acute myocardial infarction. There were no differences in sensitivity or specificity between CK-MB

Table 1.
Demographic characteristics and inhospital outcome of the 975 study patients with and without acute myocardial infarction on ED presentation.

Population Demographics	Positive AMI, No. (%) (N=44)	Negative AMI, No. (%) (N=931)
Age, y±SD	60.4±14.7	53.3±13.7
Male sex	30 (68.2)	488 (52.4)
Race		
White	40 (90.9)	685 (73.6)
Black	4 (9.1)	240 (25.8)
Other	0	6 (0.6)
Previous myocardial infarction	17 (38.6)	251 (27)
Previous PTCA/CABG	15 (34.1)	198 (21.3)
Hypertension	23 (52.3)	273 (29.3)
Diabetes	10 (22.7)	103 (11.1)
Hyperlipidemia	24 (54.5)	247 (26.5)
Cigarette use	18 (40.9)	238 (25.6)
Family history of coronary artery disease	17 (38.6)	207 (22.2)
Recent cocaine use	0	12 (1.3)

AMI, Acute myocardial infarction; **PTCA,** percutaneous transluminal coronary angioplasty; **CABG,** coronary artery bypass grafting.

Table 2.
Initial ECG findings according to outcome in the 44 patients with acute myocardial infarction on ED presentation and 68 patients with 30-day adverse outcome.

Initial ECG Finding	AMI on ED Presentation (% PPV)	30-Day Adverse Outcome (% PPV)
Ischemia (N=9)	1 (11.1)	2 (22.2)
Infarction (N=100)	8 (8)	10 (10)
Bundle branch block (N=65)	3 (4.6)	7 (10.8)
Left ventricular hypertrophy (N=80)	3 (3.8)	3 (3.8)
Normal/nondiagnostic (N=721)	29 (4)	46 (6.4)

PPV, Positive predictive value.

Table 3.
Areas under the ROC curves for the 3 paired serum marker measurements under investigation.

Serum Marker	AMI	Difference Between Areas (95% CI)
$Myoglobin_0$	0.68±0.05	0.02 (95% CI –0.64 to 0.10)
$CK\text{-}MB_0$	0.66±0.05	
$Myoglobin_2$	0.84±0.04	0.05 (95% CI –0.01 to 0.11)
$CK\text{-}MB_2$	0.89±0.03	
Delta myoglobin	0.81±0.04	0.16 (95% CI 0.09–0.24)
Delta CK-MB	0.97±0.02	

CK, Creatine kinase.

and myoglobin levels at baseline. At 2 hours, CK-MB level was more sensitive and equally specific compared with myoglobin level. Delta CK-MB was more sensitive and more specific compared with delta myoglobin.

Nineteen of the 44 acute myocardial infarction patients presented within 1.5 hours of symptom onset. Sensitivity of delta CK-MB level more than 0.7 ng/mL for 24-hour acute myocardial infarction in this subgroup was 94.7% (Figure). The one acute myocardial infarction patient in this subgroup with a negative delta CK-MB level had a peak troponin level of 2.3 ng/mL at 23 hours (CK-MB remained normal; baseline myoglobin 33.5 ng/mL; 2-hour delta myoglobin 11.9 ng/mL) and subsequently underwent inhospital coronary artery bypass grafting. There were 10 patients with acute myocardial infarction and a negative delta myoglobin level. Five of these patients had an abnormal baseline myoglobin level and presented on the decreasing curve of myoglobin (CK-MB and troponin levels increasing). Five more patients had normal baseline and 2-hour myoglobin levels with increasing CK-MB and troponin levels. Combining a positive baseline myoglobin level with positive delta myoglobin level at the most accurate cutoff values increased the sensitivity of acute myocardial infarction to 88.6% (95% CI 75.4% to 96.2%) but decreased the specificity to 65.4% (95% CI 62.3% to 68.5%), thus limiting the clinical usefulness of this combination (positive likelihood ratio 2.6; negative likelihood ratio 0.17). There were 5 acute myocardial infarction patients with negative baseline, 2-hour, and delta myoglobin values. Only 1 of these 5 patients met CK-MB criteria for acute myocardial infarction using the manufacturer's recommended cutoff. Four of these 5 acute myocardial infarction patients had positive delta CK-MB values. The mean peak troponin level in these 5 patients was 2.4 ng/mL, thus suggesting small infarct size.

A delta CK-MB level more than 0.7 ng/mL also outperformed a delta myoglobin level more than 9.4 ng/mL in the risk stratification of patients for adverse outcome. Patients with a positive delta CK-MB level had a 14.1 times relative risk of acute myocardial infarction or 30-day

Table 4.
Sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios for acute myocardial infarction of the paired serum marker measurements under investigation at the manufacturer's recommended cutoffs (for absolute values) and institutional cutoffs (for delta values) for identifying acute myocardial infarction.

Serum Marker	Sensitivity	95% CI*	Specificity	95% CI	+LR	−LR
$Myoglobin_0$ >116.3 ng/mL	22.7 (11.5–37.8)	NC	88.4 (86.2–90.4)	7.7–11.7	2.0	0.87
$CK\text{-}MB_0$ >10.4 ng/mL	0		98.2 (97.1–98.9)		0	1.0
$Myoglobin_2$ >116.3 ng/mL	56.8 (41.0–71.6)	10.7–39.3	89.3 (87.1–91.2)	7.2–11.3	5.3	0.48
$CK\text{-}MB_2$ >10.4 ng/mL	31.8 (18.6–47.6)		98.3 (97.2–99.0)		18.5	0.69
Delta myoglobin ≥40 ng/mL	47.7 (33.0–62.5)	9.4–40.6	96.2 (95.0–97.5)	1.9–4.4	12.6	0.55
Delta CK-MB ≥1.5 ng/mL	72.7 (59.6–85.9)		99.4 (98.8–99.9)		121	0.28

+LR, Positive likelihood ratio; **–LR,** negative likelihood ratio; **NC,** CI not calculable.
*CIs for difference in proportions.

Table 5.
Sensitivity, specificity, positive likelihood ratios, and negative likelihood ratios for acute myocardial infarction of the paired serum marker measurements under investigation at the most accurate 2-hour and delta cutoff values (ie, values with lowest false-negative and false-positive result) for identifying acute myocardial infarction.

Serum Marker	Sensitivity (95% CI)	95% CI*	Specificity (95% CI)	95% CI*	+LR	–LR
$Myoglobin_0$ >70.8 ng/mL	47.7 (32.5–63.3)	−7.4 to 25.5	77.1 (74.3–79.8)	−1.6 to 4.2	2.1	0.68
$CK\text{-}MB_0$ >2.9 ng/mL	38.6 (24.4–54.5)		78.3 (75.5–80.9)		1.7	0.78
$Myoglobin_2$ >70.8 ng/mL	75.0 (59.7–86.8)	5.1–26.7	79.3 (76.5–81.8)	−1.5 to 4.3	3.6	0.32
$CK\text{-}MB_2$ >2.9 ng/mL	90.9 (78.3–97.4)		77.9 (75.1–80.5)		4.1	0.12
Delta myoglobin >9.4 ng/mL	77.3 (62.1–88.5)	1.9–29.9	83.8 (81.3–86.1)	7.9–13.1	4.8	0.27
Delta CK-MB >0.7 ng/mL	93.2 (81.3–98.5)		94.4 (92.7–95.8)		16.7	0.07

*CIs for difference in proportions.

adverse outcome (95% CI 9.5 to 20.8) compared with a 5.0 times increased relative risk for patients with a positive delta myoglobin level (95% CI 3.3 to 7.5). Table 6 lists relative risk of a positive CK-MB level and positive delta myoglobin level for the individual adverse outcome variables.

LIMITATIONS

Limitations of this study are due to the small sample size of acute myocardial infarction patients once patients with a diagnostic baseline ECG or baseline troponin level more than 1 ng/mL were excluded. However, the fact that CK-MB and myoglobin tests were performed for each patient (ie, paired data as opposed to unpaired data) strengthens the significance of the statistical findings. Another limitation of our study is use of modified WHO criteria for diagnosis of acute myocardial infarction. However, the fact that we used troponin as the criterion standard eliminates incorporation bias because our definition of acute myocardial infarction is independent of the markers under investigation. Furthermore, our cutoff value of 1.0 ng/mL for the Axsym Troponin I assay is extremely close to the suggested cutoff value of 0.8 ng/mL for this assay using suggested European Society of Cardiology/American College of Cardiology diagnostic criteria.[6,7] Selection bias was minimized by focusing only on the chest pain population and by excluding patients on presentation who already met study criteria for acute myocardial infarction. However, 43 patients with indirect follow-up were included in the database, thus potentially overestimating the sensitivities of our tests. Another limitation of this study is that physicians were not blinded to the results of the baseline and 2-hour cardiac marker values. Obviously, these values influenced the subsequent diagnostic evaluation and potentially inflated the estimates of diagnostic characteristics. A final limitation is that this was a single-center derivation study, with all assays being run on a single instrument, and results may not apply to other institutions.

Table 6.
Relative risk (RR) for a delta CK-MB more than 0.7 ng/mL and delta myoglobin more than 9.4 ng/mL for 24-hour acute myocardial infarction and 30-day adverse outcome.

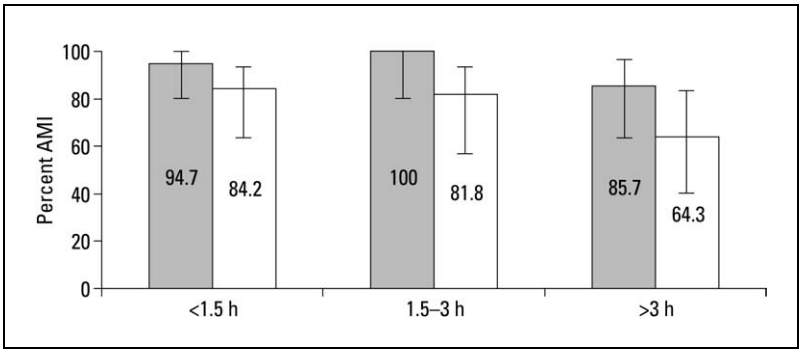
Adverse Outcome	Delta CK-MB, RR (95% CI)	Delta Myoglobin, RR (95% CI)
24-h AMI (N=44)	128 (40.4–406)	14.5 (7.3–28.9)
30-d PCI/CABG (N=66)	10.1 (6.5–15.4)	3.8 (2.4–6.0)
30-d life-threatening complication (N=10)	9.4 (2.8–31.8)	10.0 (2.6–38.1)
30-d death (N=3)	18.7 (1.7–205)	NC*

PCI, Percutaneous coronary intervention.
*Relative risk not calculable; 0% death rate in negative delta myoglobin patients versus 1.6% in positive delta myoglobin patients.

DISCUSSION

Multiple rapid protocols using myoglobin in conjunction with troponins have been demonstrated to have a high negative predictive value for acute myocardial infarction.[3-5] Ng et al[4] report on the findings in 1,285 ED patients with suspected acute myocardial infarction who presented at a Veterans Affairs hospital and underwent CK-MB, myoglobin, and troponin testing at baseline and 30, 60, and 90 minutes as measured by the Triage Cardiac Panel (Biosite Diagnostics, San Diego, CA). Acute myocardial infarction was diagnosed in 66 (5.1%) patients using WHO criteria in conjunction with CK-MB mass more than 8.9 ng/mL as measured by the Opus Dade-Behring assay (Glasgow, DE). At 90 minutes, an abnormal troponin level in conjunction with an abnormal delta myoglobin level (increase ≥25%) had a sensitivity for acute myocardial infarction of 94%, specificity of 98%, and negative predictive value of 99.7%. However, only 29% of the patients in this study presented

Figure.
Relationship from time of symptom onset for detection of acute myocardial infarction by the delta CK-MB (shaded box) and delta myoglobin (white box) measurements at the most accurate cutoff values.



within 6 hours of symptom onset, and 98% were male patients, thus limiting extrapolation of these data to the typical ED setting.

In a similar study, McCord et al[5] reported a 90-minute acute myocardial infarction exclusion protocol using CK-MB, myoglobin, and troponin levels as measured by the Triage Cardiac Panel (Biosite Diagnostics) in 817 ED patients (65 acute myocardial infarction patients) with suspected acute myocardial infarction. Acute myocardial infarction was diagnosed if CK-MB level was 9 ng/mL or greater as measured by the Abbott Axsym assay (Abbott Laboratories) in 1 or more samples during the first 9 hours of presentation and expert cardiology agreement that acute myocardial infarction had occurred. Using this definition, myoglobin level in conjunction with troponin level had sensitivity for acute myocardial infarction of 96.9%, specificity of 59.7%, positive predictive value of 17.3%, and negative predictive value of 99.6% (positive likelihood ratio 2.4; negative likelihood ratio 0.05). In a follow-up study on the same patient population, McCord et al[27] reported findings of serial measurements of the Triage Cardiac Panel for detecting adverse events at 30 days, defined as myocardial infarction (84 patients; 56% with positive baseline troponin level) or death (43 patients). In this retrospective analysis, myocardial infarction was diagnosed if troponin levels were more than 1.0 ng/mL (Abbott Axsym Fluorometric Enzyme Immunoassay; Abbott Laboratories) in 1 or more samples during the first 9 hours of presentation and cardiology experts agreed that acute myocardial infarction had occurred. The combined sensitivity of myoglobin- and troponin-level measurements outperformed the combined sensitivity of CK-MB and troponin level at baseline, 90 minutes, 3 hours, and 9 hours. At 9 hours, the combined sensitivity of myoglobin and troponin levels for adverse events was 94%, with a specificity of 50%. Myoglobin level was also more sensitive than CK-MB level for detection of acute myocardial infarction at baseline, 90 minutes, and 3 hours compared with CK-MB. The authors conclude that there is no incremental benefit in obtaining CK-MB in addition to myoglobin and troponin levels in evaluation of chest pain patients. The differences in the study protocol of McCord et al[27] and patient population, as well as different assays used in the ED, limit any comparisons between the study of McCord et al[27] and the present report.

Current recommendations from the National Academy of Clinical Biochemistry are to use an early biochemical marker such as myoglobin in conjunction with a later definitive marker (troponin or troponin T) for the routine diagnosis of acute myocardial infarction.[1] These recommendations derive from studies using WHO criteria or CK-MB assay as the criterion standard for diagnosing acute myocardial infarction. Recently, the European Society of Cardiology and American College of Cardiology have redefined the criteria for acute myocardial infarction as a typical increase and gradual decrease (troponin) or more rapid increase and decrease (CK-MB) of biochemical markers of myocardial necrosis, with at least 1 of the following: ischemic symptoms, development of pathological Q-waves, ECG changes indicative of ischemia, or coronary intervention. These new guidelines recommend troponin and troponin T as the preferred marker of necrosis and suggest using a cutoff value of the 99th percentile or greater of a reference population in which the troponin assay has an imprecision of 10% or less for the serum marker diagnosis of acute myocardial infarction.[6] Because of the inability of the majority of currently available troponin assays to meet the suggested requirements of the European Society of Cardiology/American College of Cardiology recommendations, Apple et al[7] have proposed using the lowest cutoff value of the 99th percentile or greater in which the assay imprecision is 10% or less. It is estimated that use of this new definition of troponin will result in an increase in the number of patients given a diagnosis of acute myocardial infarction by approximately 25% to 195%, depending on what cutoff value is used.[8-10] Impact of this new diagnosis on ability of myoglobin level to detect acute myocardial infarction early in symptom onset is unknown. Our data suggest that myoglobin measurements at baseline and 2 hours are insufficient to detect acute myocardial infarction early in symptom onset using troponin as the criterion standard. There were 5 acute myocardial infarction patients in our study with negative baseline, 2-hour absolute, and 2-hour delta myoglobin values. Four of these 5 acute myocardial infarction patients had positive delta CK-MB values. The mean peak troponin level in these 5 patients was 2.4 ng/mL, suggesting small infarct size. We believe that myoglobin levels peaked in the middle of our 2-hour measurement window in these 5 patients or that myoglobin was being cleared from the serum as fast as its level was increasing. A large study using the protocol of Ng et al[4] (30-, 60-, and 90-minute sampling) would help to answer this question.

In conclusion, a 2-hour delta CK-MB level outperforms myoglobin level in the early identification and exclusion of acute myocardial infarction, effectively risk-stratifies patients for 30-day adverse outcome, and could preclude myoglobin level in cardiac testing. Larger studies are

needed to verify these results using current European Society of Cardiology/American College of Cardiology redefinition of acute myocardial infarction as the criterion standard, as well as to determine whether delta measurements with newer-generation troponins are sufficient for identification and exclusion of acute myocardial infarction early in symptom onset.

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