

Cardiac Marker Point-of-care Testing: Evaluation of Rapid On-site Biochemical Marker Analysis for Diagnosis of Acute Myocardial Infarction

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Abstract

Introduction: Up to 40% of patients with acute myocardial infarction (AMI) present with non-diagnostic electrocardiograms (ECGs). The diagnosis in such cases is usually made with the aid of biochemical markers. Newer and more rapid assays for such markers have now enabled testing to be done on-site instead of in the laboratory. This potentially enables the clinician to rapidly diagnose and triage patients. We evaluated the diagnostic precision of this point-of-care testing strategy using one such analyser, the Stratus CS (Dade Behring) in a prospective study. **Materials and Methods:** The study population consisted of 51 consecutive patients admitted for suspected AMI with non-diagnostic ECGs. Two blood samples from each patient were drawn simultaneously on admission. The first sample was assayed for myoglobin, troponin I (TnI) and creatine kinase-MB (CKMB) mass by the point-of-care instrument (Stratus CS), and the second sample was sent for standard testing for AMI, comprising a troponin-T (TnT) qualitative test and the analysis of CKMB by the hospital laboratory. Utilising the recommended cut-off values for the individual assays, the results of these 2 sets of tests were evaluated based on whether they were positive or negative for AMI and compared against the patient's final diagnosis at discharge. Various combinations of markers were assessed. **Results:** On evaluation of individual markers, myoglobin was the most sensitive (75%) at 0 to 6 hours after onset of symptoms, while TnI (95%), TnT (80%) and CKMB-mass (90%) performed better at 7 to 12 hours. Point-of-care testing utilising a combination of markers was highly sensitive and specific. Both dual-marker panels of myoglobin with TnI and myoglobin with CKMB-mass yielded equivalent overall sensitivities and specificities of 90% and 95% respectively. A triple-marker panel of myoglobin, TnI and CKMB-mass had a sensitivity of 93% and specificity of 95%. All point-of-care testing panels had good positive and negative predictive values, and showed comparable diagnostic efficacy with the standard testing presently utilised for the diagnosis of AMI. The average time for results to become available was up to 26 minutes for point-of-care testing and 65 minutes for standard testing. **Conclusion:** Point-of-care testing utilising a panel of 2 or 3 cardiac markers has comparable diagnostic precision to the presently utilised testing strategy for AMI, with earlier availability of results.

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Key words: Acute myocardial infarction, Creatine kinase MB, Myoglobin, Point-of-care testing, Troponin

Introduction

In the present era of revascularisation therapy, rapid and accurate diagnosis of acute myocardial infarction (AMI) is important, as these patients may benefit from early intervention in the form of primary angioplasty, fibrinolysis or anti-thrombotic therapy. The most widely accepted criteria for diagnosis of AMI, laid down by WHO, require the presence of 2 out of 3 elements, namely typical symptoms of chest pain, unequivocal electrocardiographic changes and increased cardiac enzyme activity in blood.¹ The electrocardiogram (ECG) is generally considered the most useful tool for diagnosis and therapeutic decision-making, especially pertaining to early intervention

strategies.^{2,3} However, up to 40% of patients with AMI may present with non-diagnostic ECGs,^{4,6} posing a dilemma for the attending clinician.

Because of the limitations of using clinical features and traditional ECG testing in the early diagnosis of AMI, intense interest has been focused on the role of biochemical markers. The marker most frequently used for AMI diagnosis is creatine kinase-MB (CKMB). However, newer assays for other cardiac markers, such as myoglobin and cardiac troponins I and T (TnI and TnT) have shown much promise and are now considered potential adjuncts or, as in the case of the troponins, even alternatives,⁷ though they have yet to be incorporated into any diagnostic criteria.

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Myoglobin, CKMB and the cardiac troponins are released after an AMI and can be detected in the patient's blood relatively early. Until recently, their usefulness was handicapped by the need for time-consuming laboratory-based assays. However, new rapid analysers capable of measuring these markers individually or collectively as a panel have become available. They can usually give a quantitative result in 10 to 20 minutes and are compact enough to be placed in the Coronary Care Unit or Emergency Department and used by clinical staff. Such point-of-care testing has received much attention as it has the potential to offer the clinician valuable assistance in making real-time clinical decisions that can affect patient care.

We used one such instrument, the Stratus CS (Dade Behring), in a prospective study to evaluate the potential of rapid point-of-care analysis of myoglobin, TnI and CKMB-mass in the identification of AMI for patients with non-diagnostic presenting ECGs.

Materials and Methods

Patients

We prospectively studied 51 consecutive patients admitted to the Department of Cardiology, National Heart Centre with suspected AMI but non-diagnostic ECGs over a 1-month period. Patients included in the study had typical chest pain at rest, with the onset less than 24 hours before presentation. This time limit was selected as the early institution of new anti-thrombotic therapies, such as glycoprotein IIb/IIIa inhibitors, has recently been shown to be beneficial.^{2,3} The ECG changes included ST segment depression, ST elevation <1 mm, and left bundle branch block. We excluded patients with clear ECG changes of AMI, those who had received intramuscular injections less than a week before, or those with muscle disease or renal failure receiving dialysis.

For each patient, the time of onset of chest pain, ECG changes and results of cardiac marker assays were recorded. The diagnosis of AMI was made by clinicians responsible for the patient based on the history, serial ECG changes and rising and falling pattern of serial laboratory CKMB-mass measurements according to the WHO guidelines. The results of the assays for myoglobin, TnI and CKMB-mass performed by the Stratus CS were not available to the attending clinicians.

Sample Collection

Two samples of blood were collected simultaneously from each patient at admission. The first sample in an evacuated lithium-heparin tube was assayed immediately for myoglobin, TnI and CKMB-mass by the point-of-care instrument (Stratus CS). The second sample was sent for standard testing for AMI, comprising a TnT qualitative test and the analysis of CKMB by the hospital laboratory.

Assays

Myoglobin, TnI and CKMB-mass were analysed using the Stratus CS in the Coronary Care Unit. This was a fluorometric, whole-blood analyser with an incorporated centrifuge designed to function as a point-of-care device. The recommended cut-off values for diagnosis of AMI for the 3 assays were 82 ng/mL, 1.5 ng/mL and 5.0 ug/L respectively, as recommended by the manufacturer. The other sample for CKMB-mass was measured immunochemically by the hospital laboratory using an Axsym analyser (Abbott Diagnostics), with a recommended AMI cut-off value of 5.0 ug/L. Qualitative testing for TnT was performed using a bedside diagnostic kit (Trop T, Roche). For this test, a small aliquot of the patient's blood was placed in the specimen well and the subsequent appearance of a red line in the read zone of the device signified a positive result.

Data Analysis

Utilising the recommended AMI cut-off values for the individual assays, the results of the individual and combined tests were evaluated based on whether they were positive or negative for AMI and compared against the patient's final diagnosis at discharge. The clinical sensitivity, specificity, positive and negative predictive values for the different tests were calculated using standard statistical formulae. Confidence intervals were stated where applicable. The Student's *t*-test was used for comparison of means between groups while the Chi-square test, with Fisher's correction where necessary, was used for categorical data. A *P* value of ≤ 0.05 was considered statistically significant.

Results

Study Population

The patient characteristics are summarised in Table I. Of the 51 patients, AMI was confirmed in 29 patients. ST segment elevation or Q-wave myocardial infarction developed in 3 patients (10%) while the rest were diagnosed with non-Q wave myocardial infarction. One patient underwent primary coronary angioplasty while thrombolytic therapy was administered to another. The third patient declined intervention or thrombolytic therapy. One patient in whom AMI was eventually excluded underwent primary angioplasty as his history was highly suggestive of AMI, and his ECG showed a left bundle-branch block.

Myoglobin

The mean myoglobin level for patients with AMI was significantly higher than for those in whom AMI was excluded (249 ng/mL vs 40 ng/mL, $P < 0.001$). With the manufacturer's recommended cut-off level of 82 ng/mL,

TABLE I: PATIENT CHARACTERISTICS

Characteristic	AMI	No AMI	P value*
Number	29	22	
Age (years) - mean	66	64	<i>P</i> = ns
- range	45–89	39–82	
Males	18	15	
Time from pain onset (h) - mean	8	8	<i>P</i> = ns
- range	2–16	1–24	
ECG - ST elevation	4	6	
- ST depression	22	11	
- LBBB	3	3	
- Normal	0	2	
Myoglobin (ng/mL) - mean	249	40	<i>P</i> <0.001
- range	26–900	10–283	
Troponin I (ng/mL) - mean	7.06	0.20	<i>P</i> <0.001
- range	0.12–31.68	0.01–1.30	
CKMB – Stratus CS (ug/L) - mean	21.6	1.8	<i>P</i> <0.001
- range	1.4–87.0	0.2–15.0	
CKMB – Laboratory (ug/L) - mean	26.2	2.5	<i>P</i> <0.001
- range	2.0–114.0	0.5–6.9	

AMI: acute myocardial infarction; CKMB: creatine kinase-MB; ECG: electrocardiogram; LBBB:left bundle branch block; ns: not significant. * Student's *t*-test used for comparison of means between both groups

the overall sensitivity for diagnosis of AMI was 69%, specificity was 91%, positive and negative predictive values 91% and 69%, respectively. Myoglobin was the most sensitive cardiac marker up to 6 hours after the onset of chest pain, with a sensitivity of 75% and negative predictive value of 71%. It, however, fared poorly against the other markers at 7 to 12 hours (Table II).

Troponins I and T

The mean TnI level for patients with AMI was significantly higher than for those without (7.06 ng/mL vs 0.20 ng/mL, *P* <0.001). The qualitative TnT test was also significantly different between the 2 groups (*P* = 0.013). Both troponin assays had poor sensitivity during the first 6 hours after onset of chest pain, but at 7 to 12 hours, TnI was highly sensitive and specific (95% and 100%, respectively) with a negative predictive value of 93% (Table II). TnT appeared to have lower sensitivity (80%), but this difference was not statistically significant (*P* = 0.342 by χ^2 analysis). The difference in overall sensitivity between the 2 tests was also not statistically significant (*P* = 0.564 by χ^2 analysis).

CKMB-Mass

The CKMB-mass measured by both the Stratus CS and laboratory was significantly elevated in patients with AMI compared to those without (Table I). CKMB-mass was more sensitive than the troponins during the first 6 hours after onset of chest pain but less so than myoglobin. At 7 to 12 hours, both CKMB-mass assays were highly sensitive

and specific. Their overall performances as shown in Table II were also similar.

Point-of-Care Testing versus Standard Testing for AMI

For this part of the study, point-of-care testing using the Stratus CS was compared with standard hospital testing for AMI. Three different combinations of cardiac markers were assessed for point-of-care testing. The first testing panel consisted of all 3 markers, while the other 2 panels evaluated 2 dual-marker combinations, pairing myoglobin with TnI or CKMB-mass. A positive result for the triple-marker panel required 2 out of the 3 markers tested to be abnormal while the dual-marker panels required 1 out of the 2 to be abnormal. Standard testing required either a positive CKMB-mass or qualitative TnT result, as per current clinical practice.

The average time taken for the point-of-care results to become available was 26 minutes for the triple-marker panel and 19 minutes for the dual-marker panel as measured immediately after sample collection. By contrast, the average time taken by standard testing was 65 minutes. Using the results of standard hospital testing as the reference, point-of-care testing overall and during the various time-windows showed comparable diagnostic efficacy (Table III). The performance of the various combinations of markers was also comparable to the standard hospital testing strategy. Though there appeared to be somewhat better sensitivity with the triple-marker combination during

TABLE II: CLINICAL SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES FOR INDIVIDUAL CARDIAC MARKERS OF ACUTE MYOCARDIAL INFARCTION

Marker	0-6 hours (n = 14)	7-12 hours (n = 34)	13-24 hours [#] (n = 3)	Overall (n = 51)
Myoglobin				
Sensitivity	75 (45-100)	65 (44-86)	100	69 (52-86)
Specificity	83 (53-100)	100	50	91 (79-100)
PPV	86 (60-100)	100	50	91 (79-100)
NPV	71 (38-100)	67 (47-87)	100	69 (52-86)
Troponin-I				
Sensitivity	25 (0-55)	95 (85-100)	100	76 (60-92)
Specificity	100	100	100	100
PPV	100	100	100	100
NPV	50 (22-78)	93 (80-100)	100	76 (60-92)
Troponin-T				
Sensitivity	25 (0-55)	80 (71-89)	100	66 (47-85)
Specificity	100	93 (86-100)	100	95 (86-100)
PPV	100	94 (88-100)	100	95 (85-100)
NPV	50 (22-78)	76 (66-86)	100	68 (52-84)
CKMB (Laboratory)				
Sensitivity	63 (30-93)	90 (77-100)	100	83 (69-97)
Specificity	100	93 (80-100)	50	91 (79-100)
PPV	100	95 (95-100)	50	92 (82-100)
NPV	67 (37-97)	87 (70-100)	100	80 (64-96)
CKMB (Stratus CS)				
Sensitivity	63 (30-93)	90 (77-100)	100	83 (69-97)
Specificity	100	100	50	95 (86-100)
PPV	100	100	50	96 (89-100)
NPV	67 (37-97)	88 (72-100)	100	81 (65-97)

PPV (Positive predictive value) is the chance of having AMI with a test result above the cut-off value.

NPV (Negative predictive value) is the chance of not having AMI with a test result equal or less than the cut-off value.

All values are expressed in percentages.

Numbers in brackets represent the 95% confidence interval for each result.

[#] Numbers in this group are too small for statistical analysis.

the first 6 hours after onset of chest pain (88% vs 63%), this was not statistically significant ($P = 0.569$ by χ^2 analysis).

Discussion

Newer biochemical markers of AMI are becoming increasingly available. Many have comparable, and some even better diagnostic precision than CKMB, long considered the gold standard. The recent development of rapid immuno-assays has made point-of-care testing a reality, and results can now be available within minutes instead of hours. This would enable biochemical markers to serve as an aid to patient management rather than to merely establish a diagnosis of AMI after management decisions have been made.

The choice of a marker or combination of markers is important. The various markers differ in size, tissue abundance, sensitivity and specificity, as well as time until elevation, peak and return to normal.⁸ Myoglobin, the

smallest of the cardiac markers, is released more rapidly from necrotic myocardium than other markers. Its serum levels become abnormal within 2 to 3 hours after AMI, reaching a peak at about 6 to 10 hours.^{8,9} Hence, its sensitivity in the first few hours after AMI exceeds that of all the other markers, ranging from 50% to 100% in several studies.¹⁰ It also has fairly high specificity (77% to 95%) and predictive accuracy, if patients with trauma and renal failure are excluded.^{11,12} This is well corroborated by our study (Table II). Its sensitivity after the initial few hours is much less due to its rapid kinetics, and it returns to normal levels after 24 hours.⁸

The troponins are regulatory proteins found in skeletal and cardiac muscle, being present primarily on the actin filaments of the contractile apparatus.⁸ Their main function is to regulate the force and velocity of muscle contraction. The troponin complex consists of 3 subunits (T, C and I). TnT anchors the Tn complex to the tropomyosin, TnC binds to calcium ions and initiates the contractile response,

TABLE III: CLINICAL SENSITIVITY, SPECIFICITY AND PREDICTIVE VALUES FOR POINT-OF-CARE TESTING (USING STRATUS CS) VERSUS STANDARD TESTING FOR DIAGNOSIS OF AMI

Time after Onset (hours)	POC (Myo+TnI+CKMB)	POC (Myo+TnI)	POC (Myo+CKMB)	Standard testing	P value*
0-6 (n = 14)					
Sensitivity	88 (66-100)	75 (45-100)	88 (66-100)	63 (30-93)	ns
Specificity	100	100	100	100	ns
PPV	100	100	100	100	ns
NPV	86 (60-100)	75 (45-100)	86 (60-100)	67 (37-97)	ns
7-12 (n = 34)					
Sensitivity	95 (85-100)	95 (85-100)	90 (77-100)	95 (85-100)	ns
Specificity	100	100	100	93 (80-100)	ns
PPV	100	100	100	95 (85-100)	ns
NPV	93 (80-99)	93 (80-100)	88 (72-100)	93 (80-100)	ns
13-24 (n = 3) [#]					
Sensitivity	100	100	100	100	ns
Specificity	50	50	50	50	ns
PPV	50	50	50	50	ns
NPV	100	100	100	100	ns
Overall (n = 51)					
Sensitivity	93 (84-100)	90 (79-100)	90 (79-100)	86 (73-99)	ns
Specificity	95 (86-100)	95 (86-100)	95 (86-100)	91 (79-100)	ns
PPV	96 (89-100)	96 (89-100)	96 (89-100)	93 (83-100)	ns
NPV	91 (79-100)	88 (75-100)	88 (75-100)	83 (68-98)	ns

CKMB: creatine kinase MB; Myo: myoglobin; ns: not significant; POC: point-of-care testing; TnI: troponin I

All values are expressed in percentages.

Numbers in brackets represent the 95% confidence interval for each result.

Standard testing utilises CKMB mass and qualitative troponin-T test.

Numbers in this group are too small for statistical analysis.

* Chi-square test used for comparison between groups.

and TnI inhibits actin-myosin interaction and the contraction process. Both TnT and TnI have a specific cardiac form, making them ideal markers for myocardial damage.⁸ The release kinetics of both markers are broadly similar, both attaining abnormal serum levels within 6 hours and reaching a peak in 10 to 24 hours. However, TnI returns to baseline within 5 to 7 days while TnT can be detected up to 14 days post-event.¹³⁻¹⁵ As their release is slower than myoglobin and CKMB, their early sensitivity is relatively poor.^{8,16} However, their performance after 6 hours is excellent, with some studies claiming nearly 100% sensitivity, specificity and negative predictive values.¹⁷⁻¹⁹ In our study, TnI showed excellent sensitivity (95%) after 6 hours, while TnT appeared to perform less well (Table II). The difference, though not statistically significant, could be due to the TnT test being a qualitative test and therefore more susceptible to variations in interpretation. Our results with the qualitative TnT test, however, compare well with a recently published trial which demonstrated a sensitivity of 70% at 6 hours post-presentation.²⁰ Excellent specificity was also shown by both assays, but our study excluded patients with muscle disease or renal failure, both of which have been reported to cause elevated TnT but not TnI results.²¹⁻²³

CKMB has long been the classical marker for AMI, and the CKMB-mass assays show good sensitivity and specificity. Serum levels become abnormal 4 to 6 hours after myocardial damage and reach a peak in 12 to 24 hours.⁸ CKMB-mass is thus less sensitive than myoglobin but slightly superior to the troponins in the first few hours. Its performance in the subsequent hours improve dramatically, till past its peak level.^{16,24} This is shown in our study, which also demonstrates excellent correlation between the Stratus CS and hospital laboratory assays in the diagnosis of AMI (Table II).

As the individual markers have different characteristics and each offer certain advantages, a logical approach would be to use some of these markers in combination to facilitate the diagnosis of AMI. Strategies combining an early but less sensitive marker such as myoglobin with a late but specific marker such as CKMB or a troponin have been recommended in recently published guidelines.^{3,25,26} Studies utilising a combination of myoglobin and CKMB-mass have reported excellent results, with overall sensitivity of 80% to 100% and specificity of 84% to 100%.^{27,28} This is reproduced in our study, where a similar panel showed a sensitivity of 90% and specificity of 95%. A combination

of myoglobin and TnI also showed equivalent results (Table III). We also utilised a combination of 3 markers (myoglobin, TnI and CKMB-mass) and this combination likewise showed excellent sensitivity (93%), specificity (100%) and predictive accuracy (Table III). These results are comparable to very recently published studies.²⁹ Including a troponin assay in the panel of markers is also desirable because of its prognostic value, as elevated troponin levels have been shown to be good predictors of short-term,³⁰⁻³² as well as medium-term³³ cardiac events and mortality. There is also increasing evidence that treatment with newer anti-thrombotic agents such as glycoprotein IIb/IIIa inhibitors³⁴ and low molecular weight heparin³⁵ significantly improves outcome in such patients.

As shown in Table III, a point-of-care testing strategy utilising various combinations of cardiac markers has at least an equivalent sensitivity, specificity and predictive accuracy as the current methods for diagnosis of AMI. The advantage of this strategy lies in the increased speed with which results are available for clinical decision-making.³⁶ It allows the clinician to make the diagnosis of AMI earlier, and potentially allows for faster triaging of patients and earlier institution of appropriate therapy.³⁷

Study Limitations and Future Issues

This study is limited by a relatively small sample size, which dilutes the impact of the results. Secondly, the possibility of inter-observer variation should be considered with the qualitative TnT assay, though all personnel involved in performing this test have had experience with it and the difference in results compared to the quantitative TnI assay was not statistically significant.

Though point-of-care testing strategies have a definite advantage in terms of rapid availability of results, evidence is presently still lacking regarding its impact on therapeutic outcome. A subsequent larger study is being planned to evaluate this issue.

Conclusion

Point-of-care cardiac marker testing has diagnostic precision comparable to the traditional testing strategies for AMI, with more rapid availability of results. As individual cardiac markers have different and very specific properties, a combination panel of 2 or 3 markers offers the best performance. Future studies evaluating point-of-care testing strategies should now focus on their impact on real-time clinical decision-making, as well as on clinical outcomes and cost-effectiveness.

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