Clinical Investigations

Comparison of the Diagnostic Performance of Two Rapid Bedside Biochemical Assays in the Early Detection of Acute Myocardial Infarction

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Summary

Background: New biochemical markers have been recently proposed as potential aids in the diagnosis of myocardial infarction. Assessment of these markers in real time by near-patient testing would allow more rapid decisions regarding critical therapeutic interventions.

Hypothesis: The diagnostic performance of two qualitative, whole blood assays for measurement of myoglobin/creatine kinase (CK)-MB mass (CARDIAC STATus™) and cardiac troponin T (TropT®) was compared. Their potential in optimizing the rule-in of patients with infarction in order to initiate revascularization therapies was also evaluated.

Methods: A group of 101 patients admitted to the hospital within 12 h from onset of symptoms suggestive of myocardial infarction was studied. A first blood sample was drawn in all patients immediately after admission. In patients not receiving reperfusion therapy (n = 61), three additional samples were also obtained 2, 4, and 6 h later.

Results: CARDIAC STATus showed good performance in patients with an admission time > 2 h from onset of pain (diagnostic efficiency, 71–100%). Conversely, TropT was not sensitive enough for acceptable efficiency. In a subset of 39 patients admitted within 6 h who did not meet standard enrollment criteria for thrombolysis, CARDIAC STATus allowed early detection of almost 50% of infarcts, enabling a significant implementation of alternative revascularization therapies.

Conclusions: In patients admitted to the coronary care unit on the basis of case history and clinical examination, CARDIAC STATus assay is more effective than TropT in the early

diagnosis of infarction, providing a valuable aid to cardiologists for confirming a suspected infarction rapidly, thus allowing, if indicated, recourse to revascularization therapy in clinically uncertain cases.

Key words: creatine kinase, diagnosis, cardiovascular, myoglobin, troponin

Introduction

The diagnosis of acute myocardial infarction (AMI) is far more challenging than generally recognized, and clearly there is a need for more rapid and accurate triage and diagnosis of patients with acute chest pain, not only from an economic standpoint but also (and more important) to improve patient care.^{1,2} In particular, the advent of thrombolytic therapy and the clear benefit of early intervention with revascularization procedures have heightened interest in rapid methods to diagnose patients with possible AMI early after arrival at the hospital.³ Symptoms and electrocardiograms (ECG) are frequently both insensitive and inconclusive.⁴ As a result, new biochemical markers have been proposed as potential diagnostic supplement during recent years. Two such proteins, myoglobin and creatine kinase (CK)-MB measured as mass concentration, provide essential information that aids in early diagnosis of AMI.^{5–8} In particular, the use of a combination of the two tests as a single determination recently demonstrated a better predictive capability than either test alone.⁹ On the other hand, cardiac troponin T (cTnT) has been shown to be a sensitive and specific marker for myocardial cell damage and may be a good prognostic indicator in patients with AMI as well as with unstable angina.¹⁰ Assessment of these biochemical markers in real time by simple near-patient testing would allow physicians to make earlier and more rapid decisions about diagnosis and critical therapeutic interventions at the bedside, which could further enhance patient care and reduce costs.¹¹

Because of these premises, rapid assay systems requiring no instrumentation and using whole blood as the primary sample material for measurement of myoglobin and CK-MB mass (CARDIAC STATus™ CK-MB/myoglobin test kit;

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Received: December 5, 1997

Accepted with revision: March 23, 1998

Spectral Diagnostics, Toronto, Canada) and cTnT (TropT[®] rapid assay, Boehringer Mannheim, Mannheim, Germany) have been developed recently.^{12, 13} At present, it is not clear which of these assays is most efficient and should be used for early diagnosis of AMI in clinical practice, because they have not yet been compared in the same cohort of patients. The aim of this clinical study was to compare the diagnostic performance of these two recently introduced, qualitative, whole blood immunoassays in patients admitted to the coronary care unit with chest pain within 12 h from onset of symptoms suggestive of AMI, and to evaluate the potential of the rapid devices in optimizing the rule-in of AMI patients to initiate appropriate revascularization therapy.

Materials and Methods

Patients

In all, 101 consecutive patients with chest pain (74 men and 27 women) admitted during a 6-month period to the coronary care unit of our hospital on suspicion of AMI were recruited for the trial upon receipt of informed consent. Patients who had experienced suspected cardiac symptoms or discomfort for at least 20 min at rest within the previous 12 h were eligible. Exclusion criteria were trauma chest pain (x-ray confirmed), acute pulmonary edema on admission, and inability or refusal to give informed consent. The median time from onset of symptoms to hospital admission was 3 h (range 0.5–12 h). The definitive diagnosis of AMI was made according to at least one of the following criteria: (1) time-dependent cardiac enzymes (total CK and CK-MB activities, determined by another laboratory), increase > 50% over the baseline individual value and subsequent fall, independent of the upper reference limit; and (2) evolution of typical changes in at least two leads of the ECG. If Q waves > 0.04 s appeared, or if an R-wave increment leading to an R/S ratio > 1 in leads V₁ and V₂ developed, it was called a Q-wave AMI; if, in the absence of these signs, ST-segment depression > 1 mm 0.08 s after the J point or ST-segment elevation > 1 mm persisted for at least 24 h, it was called non-Q-wave AMI. For purposes of analysis, patients were divided into two groups based on the presence of an AMI (43 with Q-wave and 32 with non-Q-wave infarction) or absence of AMI (*n* = 26). The study was conducted in a single blinded fashion, that is, the cardiologists involved had no access to the individual values of each cardiac marker evaluated in an individual patient, so that the marker values cannot alter the patient diagnosis and management.

Sample Protocol

A first venous whole blood sample, collected in lithium heparin-containing tubes (Sarstedt, Numbrecht, Germany), was drawn in all 101 patients immediately after admission. Forty study patients with AMI received reperfusion therapy soon after admission. Since it is well recognized that reperfusion alters the release kinetics of cardiac markers into the blood, no further samples were obtained in this group. The re-

maining 61 patients, conservatively treated or with a lower suspicion of infarction, had three additional samples obtained 2, 4, and 6 h later. When all the specimens of the same case were available, the rapid tests were performed by an experienced laboratory technician without further delay.

Assay Methods

The CARDIAC STATus CK-MB/myoglobin test kit is a solid-phase immunochromatographic assay that qualitatively detects abnormal concentrations of myoglobin and (or) CK-MB (mean reactive cutoff value: 45 µg/l and 6 µg/l, respectively).¹² Assay results, that is, positive or negative, are read within 15 min after adding 150 µl of whole blood. The results were considered positive even if the signal line was only faintly detected. Previously established overall accuracy of the CARDIAC STATus test to detect abnormal marker concentrations was shown to be 94 and 88% for myoglobin and CK-MB, respectively.¹² Two models for evaluation of CARDIAC STATus diagnostic performance were used: (1) referring patients with at least one positive test (myoglobin or CK-MB) to the positives (Model 1), and (2) referring them to the negatives (Model 2).

The TropT rapid assay is a chromatographic dry-stip assay using two different cTnT-specific monoclonal antibodies.¹³ The results are read visually within 20 min (mean reactive cutoff value: 0.30 µg/l).¹⁴ In this study, even a weak signal line was considered as a positive result.

Statistical Analysis

Patients were grouped into time intervals based on the number of hours from the onset of chest pain to admission (first sample) and, when additional samples were obtained, that is, in patients not treated with therapeutic revascularization, into specimen number. A two-by-two contingency table relating the number of patients with a positive rapid assay result to the number who fulfilled the protocol definition of AMI was created for each time interval or sample number analyzed, and the sensitivity and specificity of the results of the rapid assays were calculated. The efficiency of the test was defined as the number of true-positive plus true-negative results divided by the total number of results. The 95% confidence intervals for the population proportions were calculated from the sample proportions by using the appropriate upper-tail probability.¹⁵ Positive and negative likelihood ratios [sensitivity/(1-specificity); (1-sensitivity)/specificity] were also calculated. Differences between the efficiency of the rapid assays in various times or samples after the onset of symptoms were calculated with the chi-square test for differences in proportions. A *p* value < 0.05 was considered statistically significant.

Results

Table I compares the performance characteristics and the diagnostic values of the CARDIAC STATus and TropT rapid

TABLE I Diagnostic value of the CARDIAC STATUS and the TropT rapid test for detecting acute myocardial infarction (AMI) on admission sample

	Hours from onset of chest pain											
	0-2 (n = 41; AMI = 73%)			>2-4 (n = 31; AMI = 77%)			>4-6 (n = 15; AMI = 67%)			>6 (n = 14; AMI = 78%)		
	SENS	SPEC	EFFY	SENS	SPEC	EFFY	SENS	SPEC	EFFY	SENS	SPEC	EFFY
(and 95% confidence interval)												
CARDIAC												
STATUS	50%	64%	54%	92%	100%	94%	100%	60%	87%	100%	100%	100%
(Model 1)	(31-69)	(31-89)	(37-69)	(73-99)	(59-100)	(79-99)	(69-100)	(15-95)	(60-98)	(72-100)	(29-100)	(77-100)
CARDIAC												
STATUS	27%	73%	39%	63%	100%	71%	80%	100%	87%	91%	100%	93%
(Model 2)	(12-46)	(39-94)	(24-56)	(41-81)	(59-100)	(52-86)	(44-97)	(48-100)	(60-98)	(59-100)	(29-100)	(66-100)
TropT	7%	100%	32%	13%	100%	32%	40%	100%	60%	73%	100%	79%
	(1-22)	(71-100)	(18-48)	(3-32)	(59-100)	(17-51)	(12-74)	(48-100)	(32-84)	(39-94)	(29-100)	(49-95)
P value ^a			NS			0.020			<i>d</i>			<i>d</i>
P value ^b			0.045			<0.0001			<i>d</i>			<i>d</i>
P value ^c			NS			0.0023			<i>d</i>			<i>d</i>

^aSignificance of the difference between CARDIAC STATUS Models 1 and 2.

^bSignificance of the difference between CARDIAC STATUS Model 1 and TropT.

^cSignificance of the difference between CARDIAC STATUS Model 2 and TropT.

^dChi-square test is inaccurate for calculation of the significance of the difference in this case (number of cases too small).

Abbreviations: SENS = sensitivity, SPEC = specificity = EFFY = efficiency, NS = not significant.

tests using the first blood sample obtained on admission from all 101 patients studied. Because the release of markers after AMI is dependent on the time elapsed since onset of necrosis, we related the diagnostic properties of the markers to the time interval between onset of chest pain and admission. While CARDIAC STATUS indicated promising performance in patients with an admission time >2 h from onset of pain, TropT showed no acceptable efficiency, especially in patients with early (<6 h after onset) hospital admission. In general, the specificity of TropT was high, but its overall sensitivity was too low for considerable support of medical decision making at patient presentation. CARDIAC STATUS was positive in six patients without AMI using evaluation Model 1. Three of these patients were also positive using CARDIAC STATUS Model 2 and four showed ST-segment depression >0.1 mV in at least three leads of the presenting ECG and were diagnosed with unstable angina; thus, there was a high probability that myocardial damage was present in these patients. The remaining two (2%) were false-positive results in patients without apparent acute coronary syndromes.

Table II summarizes separately the performance of the tests in patients who did not receive revascularization therapy and had serial blood samples collected. In the first three samples, the performance of CARDIAC STATUS was significantly better than that of TropT, while both tests had similar efficiency at the fourth retest, 6 h after admission. Model 1 showed higher sensitivity at admission (83%), whereas in the following samples Model 2 showed the best compromise between sensitivity and specificity. It should be noted that the global efficiency of CARDIAC STATUS assay did not increase after the

second sample collected 2 h after admission, diminishing the utility of additional blood sampling.

In symptomatic patients with diagnostic ECG, there is no need to wait for results of a biochemical test; these patients are immediately strong candidates for thrombolytics according to standard guidelines. For this reason, we focused on the performance of the rapid tests in a subset of 39 patients admitted within 6 h who did not undergo thrombolysis because of the lack of standard enrollment criteria to evaluate the possible potential of the rapid devices in optimizing the rule-in of patients with AMI to initiate a more appropriate therapy (Table III). Patients with possible contraindications to the revascularization therapy or ST-segment depression only at ECG were excluded.¹⁶ The likelihood ratio for a positive CARDIAC STATUS assay result at patient admission was 2.8 using the evaluation Model 1 and 3.4 using Model 2. The likelihood ratio for a positive TropT result could not be calculated because of 100% specificity. The likelihood ratio for a negative rapid assay result declined from 0.82 (TropT) to 0.33 (CARDIAC STATUS Model 1).

Discussion

With the advent of a more interventional approach to the management of acute coronary syndromes and the need to conserve resources by rapid triage of patients through the intensive care system, a premium must be placed on diagnostic tests that can be used in the initial evaluation of the patients as an indication for intervention or triage.^{2,11} Central to this con-

TABLE II Diagnostic value of the CARDIAC STATus and the TropT rapid test in the subgroup of patients ($n = 61$, prevalence of myocardial infarction 57.4%) who did not receive revascularization therapy, studied with four consecutive samples obtained at admission and 2, 4, and 6 h later

	1st blood sample ($n = 61$)			2nd blood sample ($n = 61$)			3rd blood sample ^a ($n = 57$)			4th blood sample ^a ($n = 57$)		
	SENS	SPEC	EFFY	SENS	SPEC	EFFY	SENS	SPEC	EFFY	SENS	SPEC	EFFY
	(and 95% confidence interval)											
CARDIAC												
STATus	83%	77%	80%	94%	62%	80%	94%	67%	82%	97%	58%	81%
(Model 1)	(66–93)	(56–91)	(68–89)	(81–99)	(41–80)	(68–89)	(80–99)	(45–84)	(70–91)	(84–100)	(37–78)	(68–90)
CARDIAC												
STATus	60%	88%	72%	86%	85%	85%	88%	88%	88%	82%	88%	84%
(Model 2)	(42–76)	(70–97)	(59–83)	(70–95)	(65–96)	(74–93)	(72–97)	(68–97)	(76–95)	(64–93)	(68–97)	(72–92)
TropT	31%	100%	61%	51%	88%	67%	64%	83%	72%	70%	83%	75%
	(17–49)	(87–100)	(47–73)	(34–69)	(70–98)	(54–79)	(45–80)	(63–95)	(58–83)	(51–84)	(63–95)	(62–86)
P value ^b			NS			NS			NS			NS
P value ^c			0.017			NS			NS			NS
P value ^d			NS			0.019			0.036			NS

^aVariation in patient sample numbers resulting from failure to collect the 3rd and the 4th specimen in four patients.^bSignificance of the difference between CARDIAC STATus Models 1 and 2.^cSignificance of the difference between CARDIAC STATus Model 1 and TropT.^dSignificance of the difference between CARDIAC STATus Model 2 and TropT.

Abbreviations as in Table I.

cept is the development of rapid, whole-blood bedside assays for serologic markers of myocardial necrosis. In particular, two new test devices—CARDIAC STATus CK-MB/myoglobin and TropT rapid assay—were recently developed to provide a reliable and convenient method of measuring cardiac markers in whole blood and to allow an almost instantaneous analysis of clinical findings, biochemical test results, and ECG recordings at the patient's bedside.^{12–14} Here, a comparison of the diagnostic performance of these two tests in the same group of patients with suspected early AMI was

made. To the best of our knowledge, this is the first study that explicitly compares the two most recent cardiac marker testing bedside technologies for making early diagnosis of AMI.

During the first 12 h after the onset of symptoms, CARDIAC STATus performed better than TropT with respect to sensitivity. Patients with suspected AMI who have a negative CARDIAC STATus test during this period can be diagnosed with great certainty as having no AMI. Generally, combination of CK-MB with myoglobin showed acceptable performance for both evaluation models, both according to Model 1 (at least one of the tests positive was required as a diagnostic sign) and to Model 2 (only cases with both tests positive were taken as a diagnostic sign), even if, as expected, Model 1 showed earlier sensitivity. Regarding TropT, the level of performance of this assay in our patients was not acceptable for clinical use; in particular, we did not find it helpful because it was too insensitive. As previously shown,^{17, 18} the diagnostic sensitivity of cTnT measurement was acceptable only after about 10 h from the onset of AMI. Thus, for this test, it is expected to have the best performance in a later time period. Furthermore, the TropT rapid assay employed in this study was the first commercial version of the device. Quite recently, Boehringer Mannheim developed a second-generation assay with greater sensitivity for cTnT, probably improving the clinical performance of the test.¹⁹

We also analyzed a subgroup of 39 patients with a doubtful evidence of AMI, in whom rapid assays for cardiac markers could have influenced patient management. The CARDIAC STATus assay, using evaluation Model 2, allowed early (< 6 h) detection of almost 50% of AMI that would otherwise have gone without revascularization therapy. As indicated by the

TABLE III Diagnostic value of the CARDIAC STATus and TropT rapid test for detecting acute myocardial infarction (AMI) in the subgroup of patients admitted within 6 h from the onset of symptoms (median time, 2.5 h; range 0.5–6 h) who did not undergo thrombolysis ($n = 39$, AMI prevalence 43.6%)

	SENS	SPEC	EFFY	(and 95% confidence interval)	
				LR(+)	LR(−)
CARDIAC STATUS (Model 1)	76% (50–93)	73% (50–89)	74% (58–87)	2.81	0.33
CARDIAC STATUS (Model 2)	47% (23–72)	86% (65–97)	69% (52–83)	3.36	0.62
TropT	18% (4–43)	100% (85–100)	64% (47–79)	"	0.82

^aLR(+) for TropT could not be calculated because of 100% specificity.

Abbreviations: LR(+) = likelihood ratio-positive test result, LR(–) = likelihood ratio-negative test result. Other abbreviations as in Table I.

likelihood ratio data presented, a positive CARDIAC STATUS assay result, even shortly after the onset of chest pain, increased the probability of the patient having an AMI by more than threefold compared with the pretest odds of an AMI being present. Thus, the introduction of the use of CARDIAC STATUS in association with other standard enrollment criteria could result in more efficient use of appropriate therapy in patients with suspected AMI, giving an additional help for the correct implementation of revascularization treatment.

Our study does suffer from some limitations. First, the patient population selected had a particularly high rate of AMI, and none of the 101 patients fulfilling the inclusion criteria for suspected acute coronary syndromes showed concomitant muscular disease. Therefore, it should be stressed that careful exclusion of patients with concomitant skeletal muscle damage is an essential prerequisite to obtain CARDIAC STATUS results such as ours. Also, the high-risk patient group examined makes extrapolation of results to immediate care areas such as emergency medicine departments difficult. In addition, the bedside tests evaluated were performed by laboratory technologists. Consequently, there is the possibility that their performance could be less effective in the hands of nurses and other health care workers. A preliminary report showed, however, that, when performed by coronary care unit nurses, bedside assays displayed the same diagnostic characteristics of quantitative laboratory determinations of the markers.²⁰

Conclusion

Our data indicate that in patients admitted to the coronary care unit on the basis of case history and clinical examination, CARDIAC STATUS assay is more effective than TropT in the early diagnosis of AMI, thus providing a valuable aid to cardiologists for confirming a suspected AMI rapidly and allowing, if indicated, the recourse to the revascularization therapy in clinically uncertain cases.

Acknowledgments

The authors thank Francesca Stefini and Cristina Serena for technical assistance. They are also indebted to the nursing staff of the coronary care unit for assistance in the collection of the blood samples.

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