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Comparative Analysis of Cardiac Troponin I and Creatine Kinase-MB as Markers of Acute Myocardial Infarction

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Summary

Background: The World Health Organization (WHO) criteria for the diagnosis of acute myocardial infarction (AMI) includes presentation of chest pain over 20 min, evolutionary changes on the electrocardiogram (ECG), and abnormal levels of cardiac enzymes.

Hypothesis: A multicenter study was conducted to evaluate the efficacy of cardiac troponin I (cTnI) in detecting and ruling out AMI.

Methods: The normal range for cTnI in 149 apparently healthy subjects without known history of cardiac or other diseases was 0 to 0.5 ng/ml. Cutoffs of 2.5 ng/ml for cTnI and 5.0 ng/ml for creatine kinase-MB (CK-MB) were used.

Results: The diagnostic sensitivity of blood collected from 291 consecutive patients with suspicion of AMI was 95.0 and 96.4%, respectively, for samples obtained at 4–48 h after AMI onset. CK-MB was more sensitive during the early 4–8 h interval (84 vs. 74%); both had 100% sensitivity from 12–36 h. CTnI remained at 100% for 72 h, while CK-MB declined to 57%. The clinical specificity was 97.4 vs. 85.8%, respectively, on non-AMI patients with cardiac and noncardiac diseases, and those with renal disease.

Conclusion: cTnI is an excellent marker for detecting and ruling out AMI, because it has better specificity and a wider diagnostic window than the accepted standard, CK-MB.

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Introduction

The World Health Organization (WHO) criteria for the diagnosis of acute myocardial infarction (AMI) includes presentation of chest pain over 20 min, evolutionary changes on the electrocardiogram (ECG), and abnormal levels of cardiac enzymes.[1] The standard of reference for the diagnosis of AMI is the assay of creatine kinase (CK)-MB isoenzyme and calculation of the percentage relative to total CK.[2] Whereas the sensitivity of CK-MB for AMI diagnosis is very high, the cardiac specificity is compromised in patients with skeletal muscle trauma, inflammatory and noninflammatory myopathies, chronic renal failure, as well as rare ectopic production in patients with tumors.[3] Therefore the search for the ideal biochemical indicator for myocardial damage continues. Recent interest has focused on proteins of striated muscle. Myoglobin is useful for early detection of myocardial damage, however the specificity is low due to release of this protein from noncardiac muscle.[4] Troponin is a regulatory filament of the thin filament and consists of I, T, and C subunits. The importance of cardiac troponin I (TnI) in the diagnosis of AMI stems from the fact that it has higher absolute cardiac specificity than cardiac troponin T (cTnT).[5] There is about 40% nonidentity between the cTnI and the skeletal isoforms at the amino acid level.[6] The unique stretches of amino acid sequence of cTnI have been exploited for the development of cardiac-specific monoclonal antibodies.[7]

Methods

This study was performed at Hartford Hospital, Hartford, Conn., Medical College of Virginia, Richmond, Va., and The Ochsner Clinic, New Orleans, La., under a protocol approved by their respective institutional review boards. A total of 149 apparently healthy individuals was enrolled across the sites for

determining the normal cTnI range. Blood from 291 consecutive patients with suspected AMI was assayed at various time intervals to determine the sensitivity and specificity of cTnI and CK-MB. Patients in whom AMI was ruled out included those with unstable angina, congestive heart failure (CHF), renal disease, and multiorgan disease. The diagnosis and rule-out of AMI was made by attending physicians, using established WHO criteria, who were blinded to the results of cTnI testing at the time of diagnosis and treatment. Where the final clinical diagnosis was either ambiguous or not available, these patients were excluded from statistical analysis (n = 15).

Serum or plasma samples were obtained relative to the time of onset of chest pain and stored at 4°C for up to 24 h or frozen until analysis. Samples were assayed for cTnI and CK-MB using the Opus Plus analyzer (Behring Diagnostics, Westwood, Mass.). The intra- and interassay precision on control materials was performed on 20 replicates twice daily for 10 days, respectively. The mean, standard deviation, and coefficient of variation (%CV) were calculated with differences between sites evaluated by an analysis of variance (ANOVA) and Tukey's test. Demographic differences were determined using the Kruskal-Wallis test [95% confidence interval (CI) at $p < 0.05$]. Sensitivity and specificity were calculated for cTnI and CK-MB using standard formulae. Receiver operating characteristic (ROC) curves were used to determine the optimum cutoff concentrations. Area under the curve (AUC), standard error (SE), and the 95% CI were determined.[8] The proportion of patients with a diagnosis of AMI, cardiac disease, and noncardiac disease were compared for statistical significance between positive cTnI and CK-MB results (McNemar's test).

Results

ANOVA showed significant differences among the centers for intra-assay precision. Tukey's test showed differences in mean results in at least one center for all controls. The %CV for the three levels of control were 8.5, 6.7, and 4.9%, respectively. We conclude that the results and analysis show acceptable intra-assay precision at all centers. Results of interassay precision showed similar differences among the centers; however, data were within manufacturer's specifications and were acceptable for routine use.

Results of healthy subjects demonstrated a normal range of 0 to 0.5 ng/ml. All samples for cTnI in healthy subjects were < 0.5 ng/ml. Figure 1 shows the ROC curves for cTnI and CK-MB obtained from serial samples drawn at 4–48 h after onset. Diagnostic cutoff concentrations of 2.5 ng/ml for cTnI and 5.0 ng/ml for CK-MB were obtained from these curves. Although the AUC for cTnI was slightly higher (0.9907) than for CK-MB (0.9752), the results were not significantly different. At these respective cutoff values, the sensitivity of cTnI and CK-MB were 95.0 and 96.4%.

Serial sample analysis indicated that both cTnI and CK-MB successfully identified 48 of 49 AMI cases. McNemar's test results by diagnosis between a positive cTnI and a positive CK-MB indicated that the two markers correlated highly for the detection of AMI ($p < 0.001$). The discrepant false negative sample was from a patient with a small Q-wave infarct (CK-MB values of 9.9, 11.7, and 8.4 ng/ml). The diagnostic specificity of cTnI and CK-MB from various patients is listed in Table I. There were 227 patients who did not fulfill the WHO criteria for AMI and in whom it was considered that AMI was

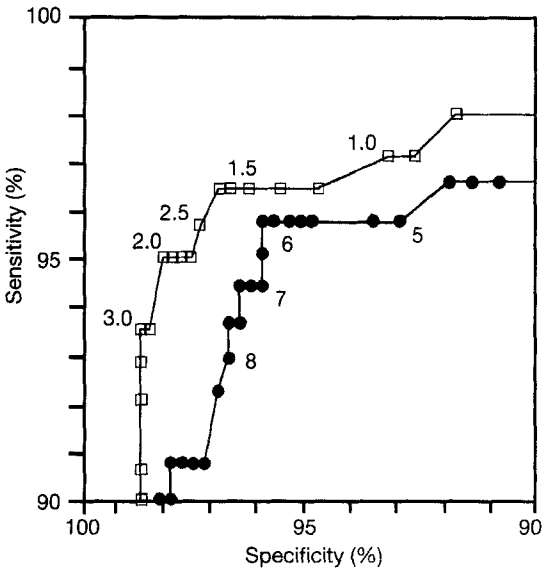

FIG. 1 Receiver operating characteristic curve for cTnI (□) vs. CK-MB (•), using blood collected from 4 to 48 h after onset of chest pain, and all non-AMI data points. Area under the curve, standard error, and 95% confidence interval: 0.9907, 0.839, and 0.826–1.00 for cTnI, and 0.9752, 0.836, and 0.811–1.00 for CK-MB. Results are not significantly different.

TABLE I Diagnostic specificity of cTnI and CK-MB in non-AMI patients (n = 232)[a]

Site	Cardiac diseases (%)	Noncardiac diseases (%)	Renal and cardiac diseases (%)
Hartford, Conn.			
cTnI	48/52 (92.3)	11/12 (91.7)	2/2 (100)
CK-MB	45/52 (87.2)	10/12 (83.3)	2/2 (100)
Richmond, Va.			
cTnI	66/67 (98.5)	17/17 (100)	7/7 (100)
CK-MB	64/67 (95.5)	16/17 (94.1)	6/7 (85.7)
New Orleans, La.			
cTnI	37/37 (100)	31/31 (100)	2/2 (100)
CK-MB	27/37 (72.9)	22/31 (71)	1/2 (50)
All sites			
cTnI	151/156 (96.8)	59/60 (98.3)	11/11 (100)
CK-MB	136/156 (87.2)	50/60 (83.3)	9/11 (81.8)

[a] Overall specificity 97.4% for cTnI, 85.9% for CK-MB ($p < 0.01$).
Abbreviations: cTnI = cardiac troponin I, CK-MB = creatine kinase-MB.

ruled out. The overall specificity of cTnI was 97.4% (221/227) compared with 85.8% (195/227) for CK-MB. For patients with skeletal muscle injury, CK-MB was increased in 10 of 60 patients (17%) compared with only 1 of 60 (1.7%) for cTnI. The two markers correlated highly for cardiac disease without AMI ($p < 0.001$) and noncardiac disease ($p < 0.01$).

The sensitivity and specificity of cTnI and CK-MB were also analyzed according to time of collection from onset. The sensitivity of CK-MB was better than cTnI at 4–8 h (84 vs. 74%) and 8–12 h (94 vs. 88%). Both cTnI and CK-MB were 100% sensitive from 12–36 h. Whereas the sensitivity of cTnI for AMI rule-in remained at 100% for up to 72 h, the sensitivity of CK-MB declined to 57% at 48–72 h. The specificity of cTnI and CK-MB was comparable for patients with cardiac diseases with no AMI as indicated. In patients diagnosed with noncardiac disease, cTnI showed 100% specificity at all time intervals compared with CK-MB with a specificity of 86% at 0–4 h and 80% at 24–36 h.

Discussion

Analysis of serial samples from patients with AMI showed that the sensitivity of CK-MB and cTnI was comparable. For these markers to attain ideal sensitivity, it is imperative that diagnosis is made on results of serial samples. As the early release kinetics of both CK-MB and cTnI are comparable (peak values around 4–8 h), the utility of a cTnI marker for very early myocardial damage is similar to that of CK-MB. The advantage of cTnI over CK-MB is the broader diagnostic window (up to 7 days). The sensitivity of cTnI in our study was 100% at 72 h, whereas CK-MB had poor sensitivity from 48 h onward. Incorporation of a test for myoglobin in a panel with cTnI could be a useful diagnostic protocol for AMI diagnosis. The fact that myoglobin appears in serum as early as 2 h following injury could be used as an early marker for myocardial damage if skeletal muscle injury or renal disease is excluded.

In ruling out AMI, cTnI was more specific than CK-MB. In all six of the false positive cases for cTnI, there was a discrepancy between CK-MB and cTnI values compared with the final clinical diagnosis. We observed no nonspecific elevation of cTnI in patients without AMI, unlike that reported for cTnT.[9] CTnI is not expressed in human skeletal muscle during development or during regenerative muscle diseases such as polymyositis and Duchenne muscular dystrophy.[10] In each of the false positive cases there was a history of cardiac disease (e.g., CHF, hypertension, recent bypass surgery), and minor myocardial injury may have been present. Are these slight to modest cTnI elevations in patients with known cardiac disease truly false? It may be possible that such injury could be an indicator for high risk, and these patients could be candidates for interventional therapy. Studies on cTnT[11] and cTnI[12] in patients with unstable angina provide impetus to this hypothesis.

Conclusion

Measurement of cTnI in blood is more specific than CK-MB for diagnosis of acute myocardial infarction and more sensitive for detection of minor myocardial injury, and it is suggested that this test will eventually replace the need for measurement of CK-MB.

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