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Original Research Article

Evaluation of Biomarkers in Patients of ACS

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Abstract: Millions of patients present annually with chest pain, but only 10% to 15% have myocardial infarction. Lack of diagnostic sensitivity and specificity of clinical and conventional markers prevents or delays treatment and leads to unnecessary costly admissions. Comparative data are lacking on the new markers, yet using all of them is inappropriate and expensive. The older markers like aspartate amino-transferase, creatine kinase, lactate dehydrogenase etc. lost their utility due to lack of specificity and limited sensitivities. Cardiac troponin levels but negative CK-MB who were formerly diagnosed with unstable angina or minor myocardial injury is now reclassified as non–ST-segment elevation MI (NSTEMI) even in the absence of diagnostic ECG changes. CK-MB is both a sensitive and specific marker for myocardial infarction. Cardiac troponin T is a cardio-specific, highly sensitive marker for myocardial damage. Cardiac troponin I is a contractile protein exclusively present in the cardiac muscle. The absolute cardiospecificity of cTnI allows the diagnosis of myocardial infarction distinct from muscle lesions and non-cardiac surgery.

Keywords: Cardiac markers, Myocardial infarction, ACS, CK-MB, Troponins, sensitivity, specificity.

METHODS AND RESULTS

Diagnostic sensitivity and specificity and frequency of increase in patients with unstable angina were determined for creatine kinase-MB (CK-MB) subforms, myoglobin, total CK-MB (activity and mass), and troponin T and I on the basis of frequent serial sampling for ≤24 hours. It is well known that the clinical signs and symptoms of patients presenting with suspected ACS are frequently vague and non-specific, and mimic a number of other conditions. For this reason, measurement of biomarkers should be obtained in all patients presenting with ACS symptoms. Quantitative measurement of biochemical markers is important for objecting the diagnostic process of the MI work-up, patient's clinical presentation and electrocardiogram (ECG) must be used in addition to biomarkers in the diagnostic evaluation of suspected MI.

Which Biochemical Markers and When?

In brief, cTn is the cornerstone of biochemical marker testing for evaluation of MI in the suspected ACS patient. The data for cTn have been so convincing that it has emerged as the preferred biomarker for use in the diagnosis of MI. Given the high prevalence and increased risk profile of MI, cTn should be available wherever possible. While CK-MB by mass assay is an acceptable alternative. cTn is a structural protein and several hours are usually required for its release into the blood after myocardial necrosis. It is therefore not an early biomarker of myocardial damage. Ideally, the temporal sampling sequence would begin at the time of the acute onset. On the other hand, patients are frequently unable to provide a detail of exact time when the symptoms started. For this reason, the reported time of symptom onset should be noted as well. Serial sampling up to six to nine hours after presentation is necessary to evaluate the MI diagnosis with near precision. However, test can be repeated even when earlier samples are negative and the clinical index of suspicion remains intermediate or high. Given the relatively late release profile for cTn, an early marker of necrosis such as myoglobin may be useful in addition to a cTn for patients who present within the first hours after symptom onset. Also, a

rapid 'rule-in' protocol with frequent early sampling of markers of myocardial necrosis may be appropriate if tied to therapeutic strategies.

What Is the Cardiac Troponin Decision Point (Cut-off) to Use?

NO doubt it indicates the diagnosis of MI. Outcomes show that even a small release of cTn confers a high-risk profile in the setting for ACS. This evidence justifies a low cTn cut-off. The ESC/ACC global task force was the first to designate a low cTn decision point, specified as the 99th percentile of a reference control population.1 The NACB guidelines are in accordance with the notion of a low cut-off. They state that, in the context of ACS, a maximal concentration of cTn exceeding the 99th percentile for a reference control group on at least one occasion during the first 24 hours after the clinical event is indicative of myocardial necrosis consistent with MI. In the event that CK-MB must be utilized, the guidelines state that the maximal concentration must exceed the 99th percentile of values for a sex-specific reference control group on two successive samples.

What is the 'Need for Speed'?

The consensus among cardiology and emergency medicine (EM) physicians is that cardiac markers should be available within one hour of specimen collection, and optimally within 30 minutes or less. To meet this stringent requirement, several measures are necessary. First, the specimen for analysis should be either anticoagulated whole blood, so that centrifugation and handling is not necessary, or plasma, to avoid a delay due to the clotting process. Second, institutions that cannot consistently deliver cardiac marker turnaround times of approximately one hour should implement point-of-care testing devices.

RESULTS

Of the 155 patients enrolled, myocardial infarction was confirmed by CK-MB mass level in 119 as per shown in Figure 1. In the 119 patients with acute myocardial infarction confirmed by elevated plasma CK-MB mass, the ECG was diagnostic (STsegment elevation) in only 23 cases. Findings in 36 patients, confirmed by CK-MB mass criteria. In 36 also had increased troponin T, troponin I, CK-MB subforms, and total CK-MB activity. Of the remaining 32 patients, 25% had increased troponin T, troponin and myoglobin, and 128 had increased CK-MB subform activity.

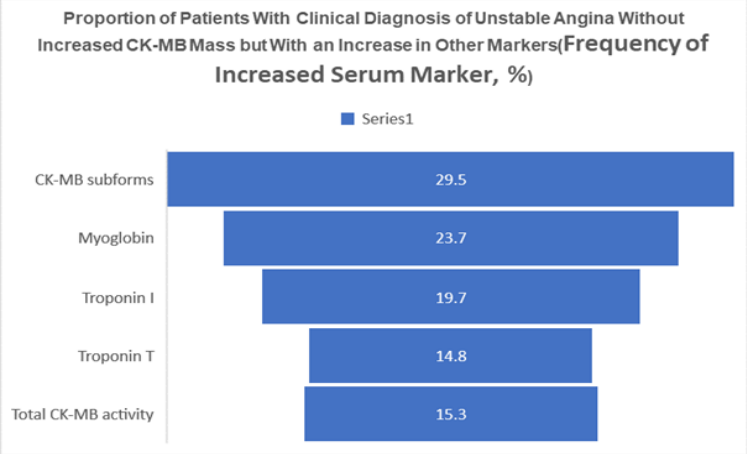

Figure 1

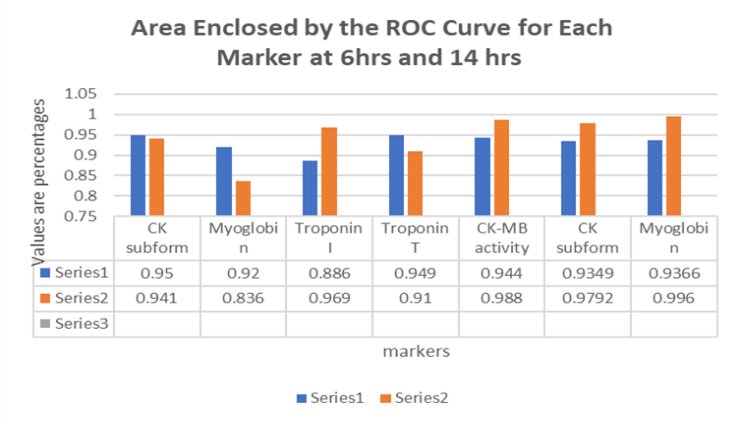

Figure 2

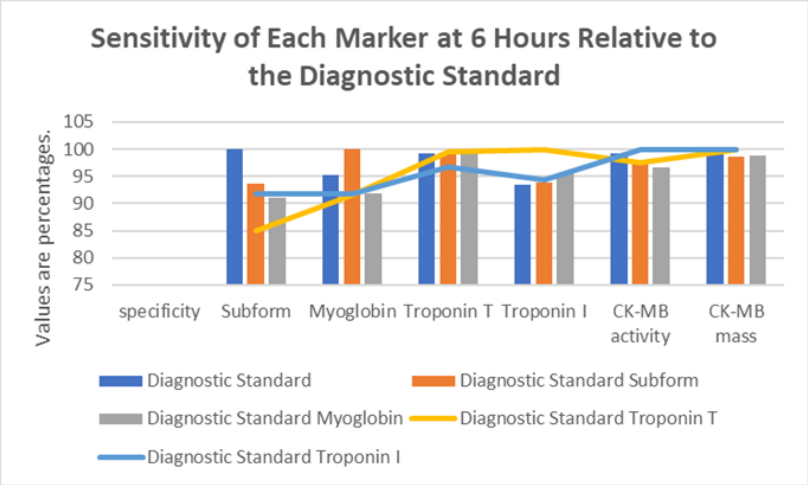

Figure 3

On admission, ECG findings in these 32 patients were T-wave inversion, ST-segment depression (7.8%), Q waves (32.1%), and ST-segment elevation (47.3%). Of the 119 patients with confirmed myocardial infarction, the attending physician diagnosed 29 as having unstable angina 9 anginas, or a noncardiac cause (58.5%). In Figure 2, the diagnostic sensitivity and specificity of each marker are compared with CK-MB mass as the diagnostic standard at selected intervals from onset of chest pain. The markers for early diagnosis, CK-MB subforms and myoglobin, exhibited sensitivities of 91% and 78%, respectively, at 6 hours from onset, with similar specificities of '89%. In contrast, total CK-MB mass, total CK-MB activity, and troponin I and T had sensitivities of only 66.0%, 74.5%, 57.5%, and 61.7%, respectively. The sensitivity and specificity of CK-MB subforms from the first sample were 48.7% and 87.6%, respectively, which were similar to those of myoglobin, 48.7% and 87.7%. The sensitivity and specificity of CK-MB subforms from the combined first and second samples were 81.6% and 84.4%, respectively; for myoglobin, they were 76.3% and 83.5%. The overall sensitivity and specificity, together with the 95% confidence limits for each marker at 6 hours from onset, are shown in Figure 1. The results of using CK-MB subforms, myoglobin, troponin T or I, or total CK-MB activity as the diagnostic standard in contrast to CK-MB mass are shown in Figure 3. The CK-MB subforms were the most sensitive diagnostic markers within 6 hours of onset of symptoms, followed by myoglobin, regardless of which marker was used as the diagnostic standard. It is of interest that the sensitivities of CK-MB subforms for early diagnosis with total CK-MB activity or cardiac troponin T as the standard were virtually identical (82% and 84%). The specificity for early diagnosis was very high for all markers regardless of the marker used as the standard.

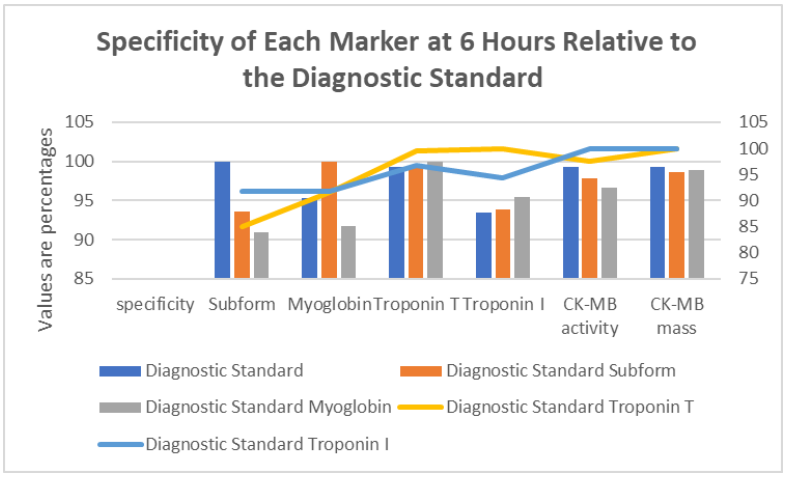

Figure 4

The most reliable marker for late diagnosis with the diagnostic standard of total CK-MB mass was total CK-MB activity, exhibiting 96% sensitivity and 98% specificity at 10 hours [2]. Troponin I exhibited a sensitivity and specificity of 96% and 93%, but not until 18 hours from onset. At 10 hours, troponin T had a specificity of 96% and a sensitivity of 87%, which remained the same throughout the subsequent interval. The sensitivities of CK-MB subforms and myoglobin decreased significantly after 10 hours from onset of symptoms. The sensitivity and specificity of each marker for late diagnosis with CK-MB subforms, myoglobin, troponin T or I, or total CK-MB activity as the diagnostic standard are shown in Figure 4. There were 99 patients in whom all markers were increased. It is noteworthy that all patients

presenting with infarction and ST-segment elevation exhibited an increased in all markers. With CK-MB mass as the diagnostic standard, 119 patients were identified as having an infarction compared with 23 identified with CK-MB subforms, 12 with CK-MB activity, 231 with troponin I, 166 with troponin T, and 276 with myoglobin. Most of these patients had a clinical diagnosis of unstable angina in which CK-MB mass was not increased but other markers were. In 512 patients, none of the markers was increased, and none of these patients was diagnosed as having an infarction by the study criteria. The specificity for total CK-MB activity, troponin I, troponin T, or CK-MB mass was virtually identical, varying from 95% to 99% with each of the other markers used as the standard. The specificity of the CK-MB subforms or myoglobin was slightly less at 93% and 90%, respectively. The total area enclosed by each ROC curve for each marker is included in Figure 5. The diagnosis of unstable angina was made in 203 (21.3%) patients. Pertinent clinical characteristics are given in Figure 6.

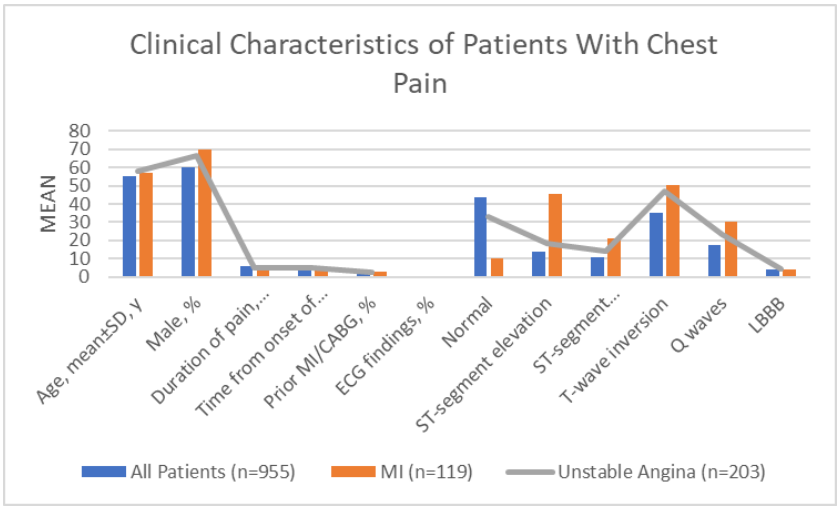

Figure 5

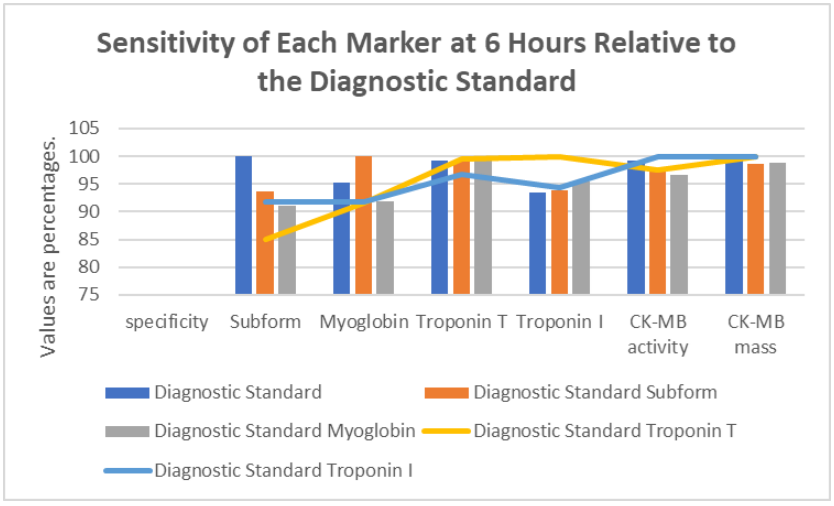

Figure 6

DISCUSSION

In this multicenter, double-blind, prospective study with consecutive enrollment of 155 patients, 12.5% had myocardial infarction and 21% had unstable angina. The most sensitive early marker for myocardial infarction (6 hours after onset) was CK-MB subforms (91%), followed by myoglobin (78%). The negative predictive value of CK-MB subforms at 6 hours was 97%, which is very important given that the probability of infarction in this population is only '10%. Total CK-MB (activity or mass), troponin I, and troponin T were reliable late markers, with CK-MB activity having a sensitivity and specificity of 96% and 98%, respectively, at 10 hours from onset; for troponin I, sensitivity and specificity were 96% and 93%, but not until 18 hours. This is the first study to compare the diagnostic accuracy of all the markers. CK-MB mass was selected as the diagnostic standard because it has been the diagnostic standard worldwide for .2 decades and because extensive clinical and experimental evidence indicate increased plasma CK-MB reflects infarction.

Despite claims [1, 6] that the cardiac troponins may be released with ischemia, experimental studies to determine whether their release reflects myocardial ischemia, necrosis, or both are lacking. There are no published studies in which all the markers are compared in relation to onset of symptoms. Other studies have consistently shown CK-MB subforms to be the most sensitive and specific marker within 6 hours of onset of symptoms [1, 2]. The addition of myoglobin to CK-MB subforms did not increase diagnostic sensitivity. In 55 patients, de Winter *et al.*, 19 noted myoglobin to be a sensitive early marker of myocardial infarction, whereas troponin T was a late marker, similar to total CK-MB. Brogan *et al.*, 20 showed that troponin I and CK-MB had similar sensitivities and specificities in 171 patients. A recent study of just unstable angina showed that troponin T and I were increased in 24%.22 In TIMI IIA (622 patients with unstable angina), 23 troponin T was increased in 19.5%, similar to our results. The sensitivity of CK-MB subforms was greater, being increased in 29.5%. Myoglobin was increased in 25, and troponin I was increased in 26. Most additional patients had a clinical diagnosis of unstable angina. Thus, the CK-MB mass assay is less sensitive than CK-MB activity, CK-MB subforms, or the troponins. These results indicate that CK-MB enzymatic activity is a more appropriate assay than CK-MB mass. However, the mean time from onset of symptoms to therapy was 9 hours, which is probably too late to be effective. An early diagnosis (80% within 1 hour after admission) can now be made in these individuals, and an appropriate trial with fibrinolytic therapy should be performed to test the hypothesis that thrombolysis is beneficial in non–Q-wave myocardial infarction. In the selection of a single assay, CK-MB subforms provide the earliest diagnosis; total CK-MB activity, derived from it, is the most sensitive for late diagnosis. If one prefers a combination of assays, then CK-MB subforms, in combination with troponin I or T, are recommended. Sampling for 24 hours provides a baseline for subsequent procedures, detection of early reinfarction, and a rough estimate of infarct size from the peak serum activity.

SUMMARY AND PATH FORWARD

cTn measurements are an essential part of the MI evaluation and should be measured in all patients with signs and symptoms of ACS. Sampling is necessary at presentation and at six to nine hours, and in some cases again at 12–24 hours. The troponin cut-off that should be used is the 99th percentile of a reference control population. cTn results should be available within one hour after specimen collection, and optimally in 30 minutes or less. Use of anticoagulated whole blood or plasma facilitates shorter turnaround times, and point-of-care testing is an attractive alternative when turnaround times are suboptimal.

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