Discordant Results of CK-MB and Troponin I Measurements: a Review of 14 Cases

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Abstract. In the course of a clinical comparison involving 204 parallel total creatine kinase (CK), creatine kinase-MB isoenzyme (CK-MB), and cardiac troponin I (cTnl) measurements, 12 patients were identified in whom cTnl was elevated while total CK was normal, as well as 2 patients in whom CK-MB was elevated while cTnl was normal. CK-MB relative index was elevated in 6 of the twelve cTnl–positive patients with normal total CK; only 2 of these patients had a discharge diagnosis of acute myocardial infarction (AMI). All of the 12 patients in this group had medical conditions that are associated with greater risk for acute cardiac events. Both patients with normal cTnl but elevated total CK and CK-MB index had chronic renal insufficiency; one of these patients had a positive stress test and a diagnosis of AMI. The other cTnl–negative patient died 2 days after admission, and autopsy revealed evidence of ischemic changes, but not acute infarction. Significant differences were apparent between traditional CK-MB results and cTnl measurements. Using total CK elevation as a prerequisite for subsequent CK-MB measurement may limit the clinical sensitivity of this enzyme marker for detecting subacute ischemic damage to the myocardium. Elevated total CK and CK-MB isoenzyme without corresponding elevations in cTnl, on the other hand, may reflect changes in enzyme elimination kinetics due to renal failure, or cross-reactivity of the cTnl assay with non-cardiac antigens.

Keywords: Troponin I, total creatine kinase, creatine kinase-MB isoenzyme, acute myocardial infarction

Introduction

Efficient triage of patients with chest pain is an important component of emergency department services, and the use of biochemical markers as diagnostic tools in the evaluation of these patients is an active area of investigation. Since clinical and electrocardiographic findings are often nonspecific, biochemical cardiac markers such as creatine kinase MB isoenzyme and troponin I may be essential in diagnosing non-Q-wave or subendocardial myocardial infarctions.

The troponins are proteins that regulate calcium-mediated contraction of cardiac and skeletal muscle. Troponin I (Tnl) is the regulatory subunit of the troponin complex, which is associated with the actin thin filament within muscle cells. Tnl, in conjunction with Troponin C and Troponin T (TnT), plays an integral role in the regulation of muscle contraction. Although the troponin complex functions similarly in all striated muscle, cardiac muscle contains genetically unique isoforms of both TnT and Tnl (cTnT and cTnl). The cardiac-specific troponin isoforms are epitopically distinct from their skeletal muscle counterparts, and immunoassays have been developed to measure both cTnl and cTnT. Clinical studies have demonstrated the release of cTnl and cTnT into the blood stream within hours following an acute myocardial infarction (AMI) [1,2,3]. Elevated levels of cTnl are detectable in serum within 4 to 6 hr after the onset of chest pain, reach peak concentrations in approximately 12 hr, and remain elevated for 3 to 10 days following [4,5].

Creatine kinase (CK) and its MB isoenzyme (CK-MB) have been used for many years to help diagnose AMI. Total CK activity begins to rise within 2 to 4 hr...
of onset of chest pain, and peak activity is detected within 24 hr. Total CK is a sensitive but non-specific marker for AMI; specificity is enhanced by the measurement of the CK-MB isoenzyme, which accounts for approximately 20% of the CK activity in cardiac muscle. CK-MB activity in serum rises within 4 to 8 hr of the onset of chest pain, peaks at 18 hr, and usually returns to normal levels within 48 to 72 hr. The absence of CK and CK-MB elevations during the two days following the onset of chest pain ordinarily excludes the diagnosis of AMI [5] when electrocardiographic results are equivocal.

Use of cTnl or cTnT for the sensitive and specific detection of AMI is becoming commonplace, but the troponins often are used in conjunction with CK-MB. Because they vary in specificity and elimination kinetics, results of troponin and CK-MB measurements do not always agree. In a recent study to assess the addition of cTnl to the chest-pain triage scheme used in a busy emergency department, a group of patients was identified in which there was discordance between CK-MB and cTnl measurements. The clinical histories and pathologic findings were reviewed in an attempt to resolve the observed differences.

Materials and Methods

Specimens were selected from routine submissions to the hospital laboratory for a "Cardiac CK" profile, which includes total CK and CK-MB if the total CK activity is greater than 195 IU/L. Total CK was measured by a modified Rosalki method (Boehringer Mannheim Corporation, Indianapolis, IN, CK/NAC catalog no. 450060, 816360, 917019, 1126005 [R1], and 1126006 [R2]) on a Hitachi 747 multi-channel analyzer. CK-MB mass was measured by a microparticle enzyme immunoassay (Abbott Laboratories, Abbott Park, IL, List no. 7A57, 66-3724/R3) on an Abbott AxSym® immunoassay analyzer. The CK-MB relative index was calculated by dividing the CK-MB mass result (µg/L) by the total CK activity (IU/L) and multiplying the result by 100, in accordance with the manufacturer's product literature. Cardiac Tnl was measured by microparticle enzyme immunoassay (Abbott Laboratories, List no. 3C29, 69-0176/R1) on an AxSym® immunoassay analyzer. In all, 204 specimens were selected without bias for patient type, history, or total CK activity, and cTnl was measured in each specimen. CK-MB was also measured when results were not already available (total CK less than 195 IU/L). For qualitative classification purposes, CK-MB results were considered positive if the total CK was greater than or equal to 195 IU/L (the upper limit of normal, per manufacturer's literature and confirmed by in-house reference range studies) and the CK-MB relative index was ≥ 4.0, the diagnostic threshold used by cardiologists at this institution. If the total CK was < 195, or the CK-MB relative index was < 4.0, the CK-MB result was considered negative. The threshold for positive cTnl results was 2.0 µg/L; this threshold corresponds to the diagnostic cutoff specified in the manufacturer's literature, confirmed in a recent multicenter evaluation of the Abbott cTnl method [7].

Results and Discussion

A matrix that summarizes the comparisons of CK-MB and cTnl results is presented in Table 1. Overall, 35 specimens were positive for both CK-MB and cTnl, while 127 specimens were negative for both cardiac markers. However, two specimens were positive for CK-MB but negative for cTnl, and 40 specimens had positive cTnl results but were negative for CK-MB. Both of the CK-MB positive/cTnl-negative specimens were from patients with significant history of cardiac disease. One of these patients was a 77-year-old male with a history of hypertension, renal failure, and stroke, who expired 6 hr after admission. Autopsy indicated that death was due to cardiogenic shock and aspiration pneumonia; histological examination of cardiac tissue revealed evidence of chronic ischemic changes but not an acute infarction.

Table 1. Matrix of cTnl and CK-MB results. The threshold for positive cTnl was 2.0 µg/L. CK-MB results were considered negative if total CK did not exceed 195 IU/L.

<table>
<thead>
<tr>
<th>CK-MB</th>
<th>Positive</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>cTnl Positive</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>cTnl Negative</td>
<td>2</td>
<td>127</td>
</tr>
</tbody>
</table>
Table 2. Summary of 12 patients with elevated cTnl and total CK <195 IU/L. For patients with multiple cardiac enzyme measurements, the highest total CK is listed. RI = relative index [(CK-MB/total CK) * 100]. CAD = coronary artery disease; HTN = hypertension; CHF = congestive heart failure; PTCA = percutaneous transluminal coronary angioplasty; NIDDM = non-insulin-dependent diabetes mellitus (type 2 diabetes); COPD = chronic obstructive pulmonary disease; CABG = coronary artery bypass graft; CVA = cerebrovascular accident; CRF = chronic renal failure; SLE = systemic lupus erythematosus; ETOH = ethanol; IDDM = insulin-dependent diabetes mellitus (type 1 diabetes).

<table>
<thead>
<tr>
<th>Age (Y)</th>
<th>Total CK (IU/L)</th>
<th>CK-MB (IU/L)</th>
<th>RI (%)</th>
<th>cTnl (μg/L)</th>
<th>Past medical history</th>
<th>Discharge diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>58</td>
<td>78</td>
<td>5.6</td>
<td>7.2</td>
<td>2.4</td>
<td>CAD/HTN</td>
<td>CAD status post PTCA</td>
</tr>
<tr>
<td>65</td>
<td>67</td>
<td>3.2</td>
<td>4.8</td>
<td>2.3</td>
<td>CHF/HTN</td>
<td>Exacerbation CHF/gastroenteritis</td>
</tr>
<tr>
<td>64</td>
<td>32</td>
<td>5.1</td>
<td>15.9</td>
<td>2.5</td>
<td>CAD/NIDDM/COPD/HTN</td>
<td>CAD status post PTCA; stress test positive for ischemia</td>
</tr>
<tr>
<td>69</td>
<td>162</td>
<td>2.4</td>
<td>1.5</td>
<td>2.6</td>
<td>NIDDM/COPD</td>
<td>CAD/CABG x 4</td>
</tr>
<tr>
<td>63</td>
<td>106</td>
<td>6.7</td>
<td>6.3</td>
<td>8.1</td>
<td>CAD; unstable angina</td>
<td>CAD (3 vessel disease; cardiac cath/PTCA</td>
</tr>
<tr>
<td>69</td>
<td>48</td>
<td>6.4</td>
<td>13.3</td>
<td>5.0</td>
<td>Angina/COPD</td>
<td>COPD exacerbation</td>
</tr>
<tr>
<td>58</td>
<td>82</td>
<td>3.0</td>
<td>3.7</td>
<td>4.3</td>
<td>HTN/NIDDM</td>
<td>CVA/syncope/HTN</td>
</tr>
<tr>
<td>71</td>
<td>60</td>
<td>1.6</td>
<td>2.7</td>
<td>4.3</td>
<td>CAD with CABG x 3; unstable angina</td>
<td>status post redo-CABG x 4</td>
</tr>
<tr>
<td>79</td>
<td>162</td>
<td>15.8</td>
<td>9.8</td>
<td>13</td>
<td>CAD/HTN/CHF; NIDDM</td>
<td>CHF/pneumonia/sepsis; CRF/CAD</td>
</tr>
<tr>
<td>69</td>
<td>179</td>
<td>5.7</td>
<td>3.2</td>
<td>39</td>
<td>CAD; CABG (1986)</td>
<td>Acute anterior MI/HTN/CAD</td>
</tr>
<tr>
<td>26</td>
<td>169</td>
<td>6.2</td>
<td>3.7</td>
<td>41</td>
<td>SLE/MI (2 wk prior)</td>
<td>Acute MI/status post-PTCA/HTN</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>6.8</td>
<td>6.9</td>
<td>42</td>
<td>ETOH cardiomyopathy; IDDM</td>
<td>Hypoglycemia</td>
</tr>
</tbody>
</table>
The second patient was a 57-year-old male with a history of coronary artery disease (two previous myocardial infarctions and coronary artery bypass graft surgery), type 1 diabetes mellitus, chronic renal failure, and hypertension. The patient was admitted with shortness of breath, weakness, and chest tightness that had developed over the previous 24 hr. On the basis of positive CK-MB and stress test results, the patient was diagnosed as AMI. In retrospect, the absence of elevated cTnl raises some doubt as to whether an infarction occurred in this patient, but given the history of AMI and bypass graft surgery, it is unlikely that the treatment would have differed had all of the cardiac markers been negative. Both of these patients had chronic renal failure, which can affect the clearance of CK enzymes and produce falsely positive CK-MB results. Immune globulin–CK complexes (macro-CK) have also been described, and the decreased clearance of these macronzymes is another potential cause of idiopathic CK elevations [10]. Because the data review in this study was mostly retrospective, specimens were not retained for additional studies and the possibility of macro-CK complexes could not be investigated.

Of the 40 specimens that were positive for cTnl but had normal CK-MB results, 23 had elevated total CK, while the remaining 17 had total CK less than 195 IU/L. Because total CK returns to normal more slowly than CK-MB following AMI, patients with positive cTnl and elevated total CK, but normal CK-MB, most likely are in the 24 to 72 hr period following an ischemic cardiac event. Troponin-positive patients with normal CK-MB and total CK, however, represent a group that is more difficult to explain, especially when the specimens were collected within 12 hr of the onset of symptoms.

The 17 cTnl–positive/CK–negative specimens were from 12 patients. The results of cTnl and total CK measurements in these patients, as well as pertinent clinical histories, are summarized in Table 2. Three patients had cTnl levels >10 times the upper limit of normal, whereas the remaining nine patients had more modest elevations in cTnl. No correlation was observed between total CK and cTnl in these patients.

All three patients with >10 times normal cTnl concentrations had significant cardiac disease: Two had histories of coronary artery disease, and the third had ethanol cardiomyopathy. During hospitalization, two of these patients were diagnosed with myocardial infarction. It is unknown whether these diagnoses were based on electrocardiographic or other clinical findings; the cTnl results were not available to the clinicians since the method was under evaluation at the time. One of these patients had a diagnosis of AMI two weeks earlier, demonstrating the length of time that cTnl can remain elevated after acute ischemic damage. The release of cTnl from the contractile apparatus (which constitutes 95% of cellular cTnl) continues for several days during the cellular repair process following AMI, resulting in prolonged elevations of cTnl levels in the circulation [11,12]. In addition, the clearance of cTnl has been shown to vary depending on the type of infarction; cTnl remains elevated longer after a Q-wave than non–Q-wave myocardial infarction [1].

The third patient in which cTnl was dramatically elevated was a 49-year-old male diabetic with alcoholic cardiomyopathy. The medical record did not contain any reference to current or past AMI, and the patient was discharged after insulin treatment. The cTnl results, however, suggested that some cardiac damage might have occurred, perhaps consistent with the history of alcoholic cardiomyopathy. There also have been reports that attribute false elevations of cTnl to incomplete separation of serum; fibrin in the sample may cross-react with the anti–cTnl antibodies [13].

Among the nine patients with modestly elevated (<10 times normal) cTnl, review of the histories revealed a wide variety of diseases that are associated with greater risk for adverse cardiac events. Five of these patients had a previous diagnosis of coronary artery disease, one had a history of coronary artery bypass graft surgery, five were hypertensive, and two had congestive heart failure. Three of these nine patients had undergone percutaneous transluminal coronary angioplasty (PTCA). Elevations in cardiac markers following PTCA have previously been reported. In a study of 74 patients undergoing elective PTCA, the majority had elevated levels of CK-MB, cTnl, and cTnT during the first day after the procedure [14,15,16]. Some of the patients had cTnl and cTnT elevations that persisted for several days.

Although the total CK was not elevated, five of the nine cTnl–positive/CK–MB–negative patients had an abnormal CK-MB index. The value of CK-MB measurements when total CK is normal has not been
Discordant results of CK-MB & troponin I assays

Fig. 1: Total CK (diamonds), CK-MB (squares), CK-MB index (triangles), and cTnl (circles) results in serum specimens from a 79-yr-old diabetic female with hypertension, congestive heart failure, and chronic renal insufficiency. Each result is shown as the log of the ratio of the observed value to the upper limit of the normal range (total CK = 195 IU/L; CK-MB = 7 IU/L; CK-MB index = 4.0%; cTnl = 2.0 μg/L).

well established. Some investigators have suggested that the total CK activity should exceed twice normal before establishing the diagnosis of an AMI [17,18,19]. Although it is generally accepted that the specificity of CK-MB index is lower when total CK is normal than in specimens with elevated total CK activity, some patients may have very low baseline total CK due to wasting or low muscle mass. In one study of patients with normal total CK, elevated CK-MB indexes were associated with older age, more intense monitoring and therapy during longer stays, and sustained higher in-hospital mortality rate, compared to patients with normal CK-MB indexes [20]. In these patients, the CK released from the cardiac muscle during AMI may be insufficient to produce an overall elevation in total CK, but a relative increase in CK-MB can still be detected. Fig. 1 shows the cTnl, total CK, CK-MB, and calculated index for sequential specimens collected from a 79-year-old diabetic woman with hypertension and congestive heart failure. The pattern of decreasing total CK, elevated cTnl, and elevated CK-MB is consistent with AMI that did not produce an elevated total CK.

There is mounting evidence that cardiac troponins are more sensitive for subacute cardiac ischemia than conventional enzyme markers. Studies examining the prognostic use of biochemical markers in patients with coronary artery disease and unstable angina have demonstrated that mild elevations in cTnl and cTnT are associated with increased risk for cardiac events over a 30-day to 1-year period [21-23]. Although follow-up information was not available for the patients included in this study, the presence of other risk factors in the group of CK-MB-negative/cTnl-positive patients suggests that the cTnl results may be due to ischemic changes that were not detectable by enzyme
or electrocardiographic results. Several investigators have used the term "microinfarction," or non-Q-wave infarction, to describe subacute ischemia. Patients with suspected microinfarctions might be candidates for more aggressive intervention and follow-up.

The sensitivity of cTnl for subacute myocardial ischemia has prompted clinical consideration of reversible vs irreversible myocardial damage. Myocardial function is rapidly compromised by severe ischemic events, causing loss of contractility within 60 sec and histologically identifiable changes (eg, myofibrillar relaxation, glycogen depletion, cellular and mitochondrial swelling) within a few min [6]. However, all of these changes are potentially reversible, and cell death is not immediate. Only severe ischemia lasting at least 20 to 40 min or longer leads to necrosis of cardiac myocytes [24]. Modest elevations of cTnl with normal total CK may result from the release of unbound cytosolic troponin from cardiomyocytes prior to cellular necrosis. This pattern has been observed in trauma patients without either cardiac wall motion abnormalities or specific EKG changes; in these cases cTnl showed limited increases and for a shorter duration, compared with results typically observed during AMI [25]. Myocardial hypoxia occurs in severe hypotensive episodes, and elevated cTnl is frequently noted in these patients without otherwise detectable cardiac injury [4,26,27].

The use of biochemical markers for the diagnosis of AMI continues to be a diagnostic challenge, particularly in patients admitted to the emergency department with uncertain and transient clinical manifestations, and for whom it is important to rule out a diagnosis of AMI. The availability of several biomarkers has allowed laboratorians and clinicians to revise and compare diagnostic strategies for diagnosing AMI, but a consensus on the most cost-effective approach to using cardiac markers remains elusive. Keffer [28] has proposed a practice guideline for acute ischemic heart disease, and the National Academy of Clinical Biochemistry has also published recommendations for the use of cardiac markers [29]. However, despite the greater cardiac specificity of troponins, many clinicians continue to rely on CK-MB measurements, often in conjunction with cTnl or cTnT, for the early diagnosis of AMI. Although the results of CK-MB and cTnl measurements in patients presenting with chest pain often concur, discordance is occasionally observed and must be interpreted with respect to the clinical history and the differences in sensitivity and specificity of the two cardiac markers.

References
10. Lee KN, Csako G, Bernhardt P, Elin RJ. Relevance of macro creatine kinase type 1 and type 2 isoenzymes to...


