Role of Cardiac Troponin I in the Evaluation of Myocardial Injury

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Cardiac troponin I (cTnI) is highly specific for cardiac muscle. In this study, we compared the utility of CK and CK-MB index versus cTnI in the assessment of myocardial infarction in 155 patients being evaluated for myocardial damage. As a cardiac marker for MI, Troponin I seems

to be superior to CK-MB. In the subset of patients with renal disease, cTnI has definite advantages over CK-MB. In addition, the use of cTnI has the potential to replace the measurement of lactate dehydrogenase isoenzymes. *J. Clin. Lab. Anal.* 12:276–279, 1998. © 1998 Wiley-Liss, Inc.

Key words: cardiac markers; cardiac ischemia; renal disease; CK; LDH; troponin I

INTRODUCTION

Troponin I (TnI) is a regulatory protein that is associated with the thin filament of muscle. TnI from cardiac muscle (cTnI) is unique and, unlike CK-MB, does not undergo ontogenic recapitulation (1,2). Thus, cTnI is not produced by regenerating skeletal muscle tissue (3). Subsequent to the development of immunofluorometric-based assays for the determination of cTnI in the serum, several studies have shown cTnI measurement (4,5) to have similar sensitivity as CK-MB (6,7) in the detection of MI.

We undertook this retrospective study to compare the usefulness of serum cTnI determination versus the measurement of CK-MB and CK-MB index in the diagnosis of acute MI. In addition, since cTnI persists up to about seven days in the serum (6,8), we studied the possibility of supplanting serum lactate dehydrogenase isoenzyme analysis by cTnI measurement. We also investigated the use of cTnI in the diagnosis of acute MI in patients with chronic renal failure, a setting in which the rate of falsely positive serum CK-MB is high (9).

MATERIALS AND METHODS

We used serum specimens from a total of 155 patients for whom CK and CK-MB measurements were requested to assess cardiac injury and rule out myocardial infarction.

The study was a retrospective study and the number of specimens collected per patient varied depending on the clinical situation. Generally, specimens were collected on initial evaluation and every 8 hr thereafter if levels were not elevated.

The serum specimens were stored at -20°C , up to 4 weeks until the TnI measurement was made. Specimens are stable for at least 8 weeks when stored at -20°C or below (10). The total CK was measured on the Paramax instrument (Baxter Diagnostics). The method consists of a series of coupled enzymatic reactions leading to the reduction of NADP^{+} to NADPH, which is proportional to CK activity. CK-MB mass was measured by an immunoassay (Stratus CK-MB; Baxter Diagnostics, Miami, FL). CK-MB index was calculated by dividing CK-MB (ng/ml) by total CK (U/L) multiplied by 100. The reference ranges for CK are 61–224 U/L (males), 38–173 U/L (females), CKMB >4.0 ng/ml, and CK Index >2.5 . cTnI was measured by fluorometric enzyme immunoassay on the Baxter Stratus analyzer, which utilizes two monoclonal antibodies directed against two epitopes of the protein.

Histories and charts of patients were reviewed by physicians. WHO criteria were used for diagnosing MI which included presenting symptoms, EKG, and cardiac enzymes. Physical exam findings and various diagnostic imaging studies were also taken into consideration. All patients included in the study were evaluated to rule out MI. Chest pain was a presenting symptom in 34% of cases. The clinical diagnosis upon discharge was used as the final diagnosis.

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Thirty one of the total 155 patients had chronic renal disease by history. Troponin I serum concentrations were also measured in an additional 50 patients who had LDH isoenzymes ordered to further evaluate possible cardiac damage.

RESULTS

Troponin I vs. CKMB Index

For a diagnosis of MI in our patient population, a Troponin I value of 0.3 ng/ml–0.6 ng/ml seems to be the best cutoff range (Fig. 1). The sensitivity for the detection of MI is essentially the same for a cut off of 0.3 ng/ml and 0.6 ng/ml. However, the specificity for detecting the presence of MI was approximately 7% greater when a cutoff of 0.6 ng/ml was used vs. the lower cutoff of 0.3 ng/ml. As the cutoff increase above 0.6 ng/ml, the specificity increases but the sensitivity markedly decreases. As the Troponin I level decreases, 0.3 ng/ml or 0.1 ng/ml, the sensitivity increases only slightly but the specificity is much less. Furthermore, the negative predictive value for Troponin I at 0.6 ng/ml is 98%. The 27 patients who had cTnI values >0.6 ng/ml but did not have the clinical diagnosis of MI had a variety of disorders, primarily cardiac ischemia (based on clinical evaluation and impression). As compared to CKMB, a Troponin I value of greater than 0.6 ng/ml is more

sensitive (90% vs. 81%) but slightly less specific (80% vs. 84%) than CKMB Index.

Troponin I in Patients With Renal Disease

Troponin I serum levels can be helpful in patients with elevated CKMB Indexes due to renal disease. Table 1 shows that, in our study, half of the renal patients with elevated CKMB indexes had troponin values less than 0.6 ng/ml. In seven patients, Troponin I was elevated but CKMB index was not. A chart review showed that 60% of the patients with elevated Troponin I values but normal CKMB indexes had evidence of cardiac ischemia. In addition, pre- and post-dialysis cTnI levels were determined on three chronic renal patients with normal cardiac function. The results show elevated CKMB levels while in all cases cTnI was not detected (Table 2). Although CKMB/Total CK indexes were not calculated in these patients, we have noted other renal patients with elevated indexes but undetectable cTnI (Table 1).

Troponin I vs. LDH Isoenzymes

Since Troponin I remains elevated in the serum up to seven days following a MI, we investigated the possibility of replacing LD Isoenzyme analysis with the measurement of cTnI. We performed serum cTnI measurements for those patients

Fig. 1. ROC curve for Troponin I

TABLE 1. Cardiac Markers in Patients With Chronic Renal Disease^a

Number of patients	CKMB index	Troponin I	Clinical diagnosis of MI	No MI
6	+	+	3 + 1	2
6	+	—	0	6
7	—	+	0	7
12	—	—	0	12

^aTotal number of patients in study with chronic renal disease: 31.

in whom an LD isoenzyme analysis was requested. Our data is shown in Table 3. All eight of the patients with a final diagnosis of MI were detected by Troponin I at a level greater than 0.6 ng/ml. Only six of the eight were detected by LDH Isoenzyme analysis. Since LDH rises later than Troponin I, the time of blood draw following a suspected cardiac event is important. We postulate that some of the discrepancies shown in our study between the LD and Troponin I levels were probably due to the time of the blood draw. Because Troponin I appears at the same time as CK-MB (4 hr after infarct) and remains elevated as long as LDH, the ability of the test to identify patients with MI is less dependent on the time of blood draw.

DISCUSSION

Some of the characteristics of an ideal myocardial injury marker are: cardiac specificity, rapid appearance in the serum, substantial elevation for a long period of time, and ease and rapidity of the analytical assay. Our study was undertaken to investigate the utility of cTnI from this perspective: cTnI is cardiac-specific, appears in serum as rapidly as CK-MB, and remains in the serum as long as elevation of LD-1 persists. Limitations of the CK-MB assay include those patients who arrive in the emergency department after 36 hr of onset of myocardial infarction, and patients with renal failure and rhabdomyolysis due to trauma or perioperative conditions. From our studies, the optimum TnI cutoff value for the detection of MI was 0.6 ng/ml. Compared with CK-MB, cTnI was superior in the assessment of myocardial injury including ischemia when the cutoff value of 0.6 ng/ml was used. Various clinical studies have used a number of different cut-

TABLE 2. Cardiac Markers in Renal Patients Pre- and Post-Dialysis^a

Patient	Pre/post dialysis	CKMB (ng/ml)	Troponin I (ng/ml)
1	Pre	19.5	0
	Post	2.8	0
2	Pre	1.6	0
	Post	1.3	0
3	Pre	4.4	0
	Post	4.7	0

^aAll patients without MI.

TABLE 3. Correlation of LD Isoenzyme Analysis and Troponin I

Number of Patients	LDH 1/2 prominence	Troponin I (cutoff 0.6 ng/ml)	Clinical diagnosis of MI	No MI
8	+	+	6	2
3	+	—	0	3
7	—	+	2	5
32	—	—	0	32

off values including 0.6 ng/ml, 1.5 ng/ml, and 3.1 ng/ml. Some references feel that any detectable (>0 ng/ml) level of cTnI is abnormal and indicates cardiac damage.

One reason for the lower specificity shown by cTnI as compared to CKMB is the fact that Troponin I can be elevated in patients with cardiac ischemia. As is the case with Troponin T (11), recent studies have shown that patients without MI but with an elevated serum Troponin I level had an increased risk of subsequently developing a significant cardiac event (12). However, unlike Troponin T, Troponin I is cardiac specific and is neither re-expressed in regenerating skeletal muscle nor is it elevated in patients with chronic renal disease (4,13–17). In our recent studies evaluating the ontogenic aspect, cTnI is absent in cord blood while CK-MB is present (unpublished observation). For these reasons, we feel that cTnI may be a more specific marker than Troponin T in the detection of cardiac injury.

CKMB is elevated in many circumstances other than cardiac injury, e.g., rhabdomyolysis, renal disease, and degenerative diseases of skeletal muscle. In the setting of chronic renal failure and rhabdomyolysis, cTnI measurement provides a distinct advantage over CK-MB or CK-MB index measurement. Furthermore, as other recent studies have shown (18) our results suggest that cTnI measurement can replace LD isoenzyme analysis. In situations where LD isoenzyme analysis and cTnI were discordant, it was mostly due to inappropriate collection time for LD isoenzyme analysis (too early). From the laboratory's perspective, the Troponin I assay is less time-consuming than LD Isoenzyme fractionation and thus translates into faster turnaround time.

At first glance, it appears that measurement of cTnI may result in many false positive tests. Whether these apparent false positive results truly are false positive is somewhat questionable. Currently the diagnosis of MI is based on a combination of clinical history, external electropotential tests, and various cardiac enzymes (CK/CKMB and LDH). Evaluation of tests with potentially greater sensitivity and specificity than the current "gold standard" evaluation is always extremely difficult. What if the new test, in this case cTnI, were able to detect cases of MI that current tests could not? Most statistical applications are based on the selection of a gold standard test to which the new test is compared. However, if the new test has potential to be the new gold standard, then the evalua-

tion may be misleading. In the case of MI, many patients present atypically. These patients often do not have the classic findings associated with MI. This makes evaluation of a new, potentially more sensitive and specific test extremely difficult. Thus, the apparent false positive results may be true positive. The results may only appear false based on less sensitive and specific current standards. Some of the patients with apparent false positive cTnI levels did manifest cardiac ischemia on additional evaluation. This suggests that the other cardiac enzymes (CK/CKMB and LD) were falsely negative.

In patients with Non-Q wave MI or silent MI, all of the typical clinical and diagnostic parameters are not seen. Thus, certain diagnosis of MI in these patients is difficult. In this study, we used the final discharge diagnosis to determine the sensitivities and specificities of Troponin I in detecting patients with MI. Similarly, the sensitivities and specificities of CKMB were also determined. However, unlike Troponin I, CKMB was one of the parameters used in determining the ultimate diagnosis. This could bias the study somewhat in favor of CKMB. In a study such as this where the "gold standard" is possibly not the most definitive, it is very difficult to determine the true statistical significance of the parameter in question (in this case Troponin I). It is possible that Troponin I could be more specific than CKMB.

Cardiac troponin I may be superior to CKMB and LDH isoenzymes in the detection of MI. In patients with chronic renal disease, cTnI measurement appears to have advantages. The separation of patients with elevated Troponin I due to ischemia as opposed to MI remains a challenge.

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