

Cardiac Troponin-I Assay

Background

Serum levels of cardiac enzymes and isoenzymes are essential to the diagnosis or exclusion of myocardial damage. A new set of serum assays have been developed for the detection of cardiac injury.¹ Cardiac troponin I is specific for cardiac tissue and is detected in the serum only if myocardial injury has occurred. An enzyme immunoassay specific for cardiac troponin I has been developed, clinically validated, and is offered by the UCLA Clinical Laboratories. This test has improved sensitivity and specificity over CK-MB in the diagnosis and exclusion of myocardial injury.^{2,3} The troponin I assay allows early identification and stratification of patients with chest pain suggestive of ischemia, allows identification of patients that present 48 hours to 6 days after infarction, and identifies patients with false positive elevations in CK-MB (such as in rhabdomyolysis).

Clinical Studies of the Troponin Assay

Clinical studies have demonstrated improved time dependent sensitivity and improved specificity for troponin I and T compared to CK-MB.^{1,4} Patients with acute myocardial infarction have a earlier rise in troponin I than CK-MB.^{5,6} Mair et al demonstrated the occurrence of first increase values after myocardial infarction symptom onset.⁵

Troponin	50% patients at 3.8 hours	75% at 4.3 hours	95% at 7 hours
CK-MB	50% patients at 4.8 hours	75% at 5.5 hours	95% at 12 hours

Because Troponin I increases to a first peak value 40 times the detection limit vs CK-MB only 6-9 times there are not the borderline cases where although the CK-MB has started to rise early it has not yet exceeded the upper limit of normal. (hence the need for the 3rd (16 hour) CK-MB measurement). By 6 hours after symptom onset using troponin I there is a 95-99% detection of patients who are ultimately shown to have a myocardial infarction.^{4,7} In addition, the troponin assay is a powerful, independent mortality risk marker in patients who present with acute myocardial infarction.⁸ The troponin T and troponin I assays have equivalent early sensitivities for myocardial injury.⁵

The prognostic value of troponin in unstable angina has also been shown with the troponin assay appearing to be a more sensitive indicator of myocardial cell injury than CK-MB.^{9,10} In one study of 84 patients with resting angina and no elevation of CK-MB, a negative troponin assay predicted a low adverse cardiac event rate 1 of 51 (1.9%) vs an event rate of 10 of 33 (30.3%) for patients with a positive troponin assay.⁹ In the TIMI III study of 1404 patients with acute coronary syndromes, the mortality rate was significantly higher in the patients with troponins I > 0.5 ng/ml (3.7%) than in the patients with levels < 0.5 ng/ml (1.0%) p< 0.001, using the initial version of the assay.¹¹ There were significant increases in mortality with increasing levels of cardiac troponin I (troponin < 0.5 ng/ml, mortality 1.0%; 0.5-1.0 ng/ml, 1.7%; 1.0-5.0 ng/ml, 3.6%; > 5.0 ng/ml, 6.8%). The troponin assay thus detects small amounts of myocardial necrosis missed by CK-MB and predicts which patients will otherwise have adverse outcomes despite ruling out for infarction by CK-MB alone (allowing the physician to identify which patients will benefit from intensified medical therapy and early invasive management). Two negative troponin I assays obtained 6 hours apart had a 99.7% negative predictive value for clinical events at 30 days in a study of 773 patients presenting to emergency medical centers with chest pain.¹² Negative troponins do not, however, exclude coronary artery disease or eliminate the need for further risk stratification with stress testing.

Based on this data, patients that present with chest pain without a diagnostic ECG and that are troponin I assay negative (<0.25 ng/ml) on admission and 6 hours later (and are chest pain free, without dynamic ischemia on ECG) may be considered good candidates for early stress testing and if negative discharge on medical management or direct discharge with outpatient stress testing within 72 hours. Patients who are troponin I positive may be better served to have early catheterization.

Patients that present with a chest pain episode > 48 hours prior to admission may have sustained a MI but would

not be expected to have continued elevation in CK-MB. Troponin I has been shown to be elevated for 4-6 days post MI. This assay allows a simpler and more reliable way to identify patients presenting 2 -6 days post myocardial infarction (as opposed to nuclear medicine scanning or cardiac catheterization).⁴

Patients that have skeletal muscle injury (motor vehicle accident or rhabdomyolysis) often have elevations in CK total and elevations in CK-MB. Attempting to exclude a noncardiac source of CK-MB often leads to further testing such as echocardiography, stress testing, or coronary angiography. Troponin I has been demonstrated to help identify patients with false positive CK-MBs in this setting. In a study of 215 patients without clinical or ECG evidence of cardiac disease, 59% of patients with skeletal muscle injury and 3.8% with renal failure had increased CK-MB levels whereas none of these patients had increased troponin I levels.²

The troponin assay is able to detect small amounts of myocardial necrosis. Elevation in cardiac troponins has been detected in patients presenting with decompensated heart failure, acute myocarditis, and cardiac rejection even in the absence of coronary artery disease. Elevations have also been detected in patients with syncope or prolonged tachyarrhythmias in the setting of left ventricular hypertrophy and/or stable coronary artery disease. In a recent study, small elevations in cTNI was found in 89% of patients hospitalized with acute severe heart failure without increase in CK-MB. An improvement in clinical status was associated with a decline in cTNI concentrations. Those with elevated troponins had increased mortality. Possible mechanisms for the release of cardiac troponins T and I in advanced heart failure may include apoptosis, necrosis due to catecholamine toxicity/free radicals, and/or ischemic necrosis due to abnormalities of coronary microcirculation.

Use of the Troponin I Assay

The troponin I assay should be used in the following clinical presentations:

- 1) Patients who present with chest pain and an ECG that is nondiagnostic for acute myocardial infarction (60% of MI patients) currently are diagnosed by CK-MB assay but in a time frame that is often too late for reperfusion therapy. A STAT troponin I assay (turnaround time < 60 mins) obtained in the Emergency Department at the time of presentation may allow identification of patients having a myocardial infarction earlier when there is greater benefit from primary angioplasty. Patients with a positive troponin I and an appropriate clinical presentation should be considered for direct cardiac catheterization and primary reperfusion therapy, unless contraindicated. Patients with a negative assay should be treated with medical therapy for unstable angina. An intermediate assay result should be viewed as indicating possible myocardial injury, and repeated prior to 6 hours. A negative troponin I assay obtained on arrival to the Emergency Department does not exclude the diagnosis of myocardial infarction or unstable angina nor does it imply that the patient is at low risk.
- 2) Patients admitted for possible myocardial infarction or unstable angina should be ruled out for infarction or high risk unstable angina with the troponin I assay. This involves admission and cardiac monitoring with a second troponin I obtained 6 hours after the initial admission troponin. If there is sufficient concern an additional troponin may be obtained, for example at 3 hours. This does not replace the need for the 6 hour test. The use of the troponin I assay allows for patients with a negative assay 6 hours after admission who are clinically stable to undergo early stress testing and discharge or be directly discharged to undergo stress testing on an outpatient basis within 72 hours. Patients with positive troponin I in the clinical setting of an acute coronary syndrome meet criteria for acute myocardial infarction and should be referred for cardiac catheterization if they are potential candidates for revascularization or treated with intensive medical therapy alone if they are not candidates for revascularization.
- 3) Patients that present with chest pain or abnormal ECG after trauma or surgery and have an elevated CK total and CK-MB may have a non-cardiac source for the CK-MB. The troponin I assay is recommended to determine whether the elevation in CK-MB is a true positive. A negative troponin I assay in this setting excludes myocardial injury and eliminates the need for any further testing such as echocardiography or catheterization, unless otherwise indicated.

4) Patients presenting with chest pain 2 to 6 days prior to admission may have sustained an acute myocardial infarction but the CK-MB should have returned to normal levels in the majority of cases. Troponin I remains elevated for 4-6 days after myocardial infarction and troponin I is the preferred diagnostic test in this setting. A negative troponin I excludes myocardial infarction in the previous 5 days in 96% of cases.

5) Patients with decompensated heart failure, acute myocarditis, cardiac rejection, as well as patients with hypotension, syncope, or prolonged tachyarrhythmia in the setting of left ventricular hypertrophy and/or stable coronary artery disease may have intermediate or positive troponin levels in the absence of an unstable atherosclerotic lesion. Although these troponin elevations are associated with increased cardiac risk, the management strategy should be individualized based on the clinical presentation and other factors.

Warning: a negative troponin I assay does not exclude the diagnosis of unstable angina and does not exclude myocardial infarction of less than 6 hours duration. As with CK-MB, the initial assay should not be used to determine whether to admit or discharge a patient presenting to the emergency department with chest pain. Diagnosis, risk assessment, and the decision as to whether inpatient or outpatient management is indicated should be based on the history, physical examination, and ECG as detailed in the UCLA Unstable Angina Clinical Guidelines. Admission, initiation of therapy, or the filling out of a referral form should not be delayed to await the results of the troponin I assay.

Assay Characteristics

Diagnostic level for increased cardiac risk with the new assay is troponin I \geq 0.25 ng/ml. A level of 0.1 - 0.25 ng/ml is considered intermediate. A level of $<$ 0.1 ng/ml is considered negative. An elevated troponin indicates myocardial necrosis. It can occur in acute myocardial infarction and in other clinical settings where myonecrosis has occurred. The assay identifies patients who are at higher risk for cardiac events and mortality. Each increase of 1.0 ng/ml in the cardiac troponin I level is associated with an increase in the relative risk of mortality.

Lower limit of detection is 0.04 ng/ml. The assay is linear up to 50 ng/ml. The 97.5 percentile for apparently healthy adults is 0.06 ng/ml. Collect blood in a 4 ml sodium heparin plastic tube without gel separator (deep green cap)-- a minimum of 3 ml of blood is required. Moderately hemolyzed specimens are acceptable. The test is available only on a STAT basis with a maximum 60 minute turn-around time. A troponin I level \geq 2.0 ng/ml will be treated as a panic value and will be called back. Direct laboratory cost is \$11.08. (for comparison, CK-MB cost is \$11.08)

Diagnosis of Acute Myocardial Infarction

Criteria for acute, evolving or recent MI. Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI:

Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:

ischemic symptoms;

development of pathologic Q waves on the ECG;

ECG changes indicative of ischemia (ST segment elevation or depression);

coronary artery intervention (e.g., coronary angioplasty)

Diagnostic Algorithms (Acute Coronary Syndromes)

- Patient with chest pain suspicious for unstable angina or acute myocardial infarction
ECG → diagnostic for AMI → direct cath

	→ nondiagnostic	→ troponin I (serum assay sent from ER STAT)
Troponin I	→ positive	→ direct cath
	→ negative	→ unstable angina management

- Patient admitted for unstable angina/rule out infarction who remains clinically stable
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|--------------|-----------------------|--|
| ECG | → evolving infarction | → direct cath |
| | → nondiagnostic | → troponin I (serum assay sent at 6 hours from admit) |
| → troponin I | → positive | → direct cath or intensive medical treatment |
| | → negative | → early inpatient stress testing or discharge for outpt stress within 72 hours |

Intermediate troponin result patients would be viewed as at possible increased risk and inpatient stress testing would be recommended

- Patient with chest pain or abnormal ECG after trauma or surgery or suspected of having false positive CK-MB (skeletal muscle injury, hypothyroidism, renal failure)

Troponin I	→ positive	myocardial injury
	→ negative	excludes injury, false positive CK-MB

- Patient presents having had chest pain 2 - 6 days prior to evaluation

Troponin I	→ positive	myocardial injury or infarction
	→ negative	myocardial infarction in time period 7 hours - 6 days unlikely

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Implemented: March 6, 1996 Revised: June 26, 1998 New Assay Revision: March 6, 2000

References

1. Apple FS, Voss E, Lund L, Preese L, Berger CR, Henry TD: Cardiac troponin, CK-MB and myoglobin for the early detection of acute myocardial infarction and monitoring of reperfusion following thrombolytic therapy. *Clin Chim Acta* 1995;237:59-66

2. Adams JE, 3d, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenson JH, Jaffe AS: Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993;88:101-106
3. Mair J, Dienstl F, Puschendorf B: Cardiac troponin T in the diagnosis of myocardial injury. *Crit Rev Clin Lab Sci* 1992;29:31-57
4. Mair J, Wagner I, Jakob G, Lechleitner P, Dienstl F, Puschendorf B, Michel G: Different time courses of cardiac contractile proteins after acute myocardial infarction. *Clin Chim Acta* 1994;231:47-60
5. Mair J, Morandell D, Genser N, Lechleitner P, Dienstl F, Puschendorf B: Equivalent early sensitivities of myoglobin, creatine kinase MB mass, creatine kinase isoform ratios, and cardiac troponins I and T for acute myocardial infarction. *Clin Chem* 1995;41:1266-1272
6. Katus HA, Remppis A, Neumann FJ, Scheffold T, Diederich KW, Vinar G, Noe A, Matern G, Kuebler W: Diagnostic efficiency of troponin T measurements in acute myocardial infarction. *Circulation* 1991;83:902-912
7. Adams JE, 3rd, Sicard GA, Allen BT, Bridwell KH, Lenke LG, Davila-Roman VG, Bodor GS, Ladenson JH, Jaffe AS: Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med* 1994;330:670-674
8. Ohman EM, Armstrong PW, Christenson RH, Granger CB, Katus HA, Hamm CW, O'Hanesian MA, Wagner GS, Kleiman NS, Harrell FE, Califf RM, Topol EJ: Cardiac troponin T levels for risk stratification in acute myocardial ischemia. GUSTO IIA Investigators. *N Engl J Med* 1996;335:1333-1341
9. Hamm CW, Ravkilde J, Gerhardt W, Jorgensen P, Peheim E, Ljungdahl L, Goldmann B, Katus HA: The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146-150
10. Mair J, Wagner I, Puschendorf B, Mair P, Lechleitner P, Dienstl F, Calzolari C, Larue C: Cardiac troponin I to diagnose myocardial injury. *Lancet* 1993;341:838-839
11. Antman EM, Tanasijevic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, Fischer GA, Fung AY, Thompson C, Wybenga D, Braunwald E: Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-1349
12. Hamm CW; Goldmann BU; Heeschen C; Kreyman G; Berger J; Meinertz T: Emergency room triage of patients with acute chest pain by means of rapid testing for cardiac troponin T or troponin I. *N Engl J Med* 1997;337:1648-53.
13. Heeschen C; Goldmann BU; Langenbrink L; Matschuck G; Hamm CW. Evaluation of a rapid whole blood ELISA for quantification of troponin I in patients with acute chest pain. *Clinical Chemistry* 1999; 45:1789-96.