

Troponin I sensitivity and specificity for the diagnosis of acute myocardial infarction

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This article describes the sensitivity and specificity of troponin I when compared to creatine kinase-MB (CK-MB) and electrocardiography (ECG) for diagnosing acute myocardial infarction (AMI). Two different lower levels for defining positive results with troponin I were evaluated.

A retrospective study of 153 patients who presented to the emergency department of a community hospital supplied the pool of patients for this study. Patients included in this study were those for whom a CK-MB was ordered. The majority of these patients were evaluated for chest pain or symptoms suggesting an acute cardiac event.

Of the 153 patients studied, CK-MB results were positive in 91 (59%) patients; ECG revealed AMI in 72 (47%) patients. There were 103 (67%) patients who had either positive CK-MB or ECG results. Ninety (59%) patients had a troponin I level greater than 2.0 ng/mL, and 18 (12%) patients had a troponin I level between 0.6 and 2.0 ng/mL. Seven patients whose troponin I level was between 0.6 and 2.0 ng/mL had negative CK-MB and ECG results. Therefore, 11 patients with troponin I between 0.6 and 2.0 ng/mL had AMI. Five patients with positive troponin I results (>2.0 ng/mL) had negative CK-MB and ECG results.

When a troponin I level greater than 0.6 ng/mL was used as a positive value, compared to CK-MB and ECG using either time zero or time 6 hours, the sensitivity was 94% and specificity was 81%. When troponin I greater than 2.0 ng/mL was used to define a positive test, the sensitivity was 85% and specificity was 91% when compared to CK-MB and ECG.

(Key words: troponin, acute myocardial infarction, creatine kinase-MB, electrocardiography)

Evaluation of patients for possible acute myocardial infarction (AMI) is frequently difficult. The diagnosis of AMI is generally based on electrocardiographic (ECG) findings and serial cardiac serum enzymes. Creatine kinase-MB (CK-MB), similar to other serum

markers, is not highly specific for cardiac disease. Several conditions that can cause false elevations of CK-MB levels include rhabdomyolysis, renal failure, hypothyroidism, and heart failure.¹⁻³ CK-MB false negatives can be found in patients with lean muscle mass.⁴ This

has stimulated interest in developing more specific cardiac markers, unaffected by these other conditions, for example, troponin I.

Cardiac troponin I is a regulatory protein reported to have a high specificity for cardiac injury due to a unique 31 amino acid sequence at its N-terminal end that provides high potential for obtaining cardiac-specific antibodies.⁵ Troponin I is present in three isoforms: cardiac, skeletal slow-twitch, and skeletal fast-twitch, encoded by three separate genes. However, cardiac troponin I is expressed as a single isoform in adult heart that is not expressed in skeletal muscle.⁶

Several benefits of troponin I have been reported in the literature. It is specific for heart muscle, and the antibodies used in the assay do not react with other troponins.¹ It has a higher discriminator value because it has a 13-fold greater concentration in heart muscle than CK-MB.⁷ When there is skeletal muscle injury, the troponin I level is only elevated if there is concomitant myocardial damage.⁸ Troponin I is not reported to increase in acute or chronic muscle disease,⁹ after physical exercise,⁸ as a result of renal failure,¹⁰ or in patients with hypothyroidism.³ Its serum concentration in AMI is independent of the muscle mass, an advantage for patients with little muscle mass.⁴ The results of the assay are available in the same time frame as CK-MB, with a similar cost per assay as CK-MB.⁷ The rise to a positive value has been reported similar to CK-MB.¹¹ Its long half-life can replace lactate dehydrogenase isoenzymes,¹² which is advantageous in patients who have a delayed presentation for evaluation after an AMI. Specific uses of troponin I already reported are its use in the perioperative patient and potential use in diagnosing cardiac contusion.^{13,14} In a blinded single-center study of critically ill patients, Guest and colleagues found an unexpectedly high incidence of myocardial injury associated with elevated levels of troponin I, and this was not obvious by other biochemical markers.¹⁵ Troponin I has also proven to be a utility for risk stratification.^{16,17}

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The lower level reference positive value for troponin I in serum is not firmly established. This is primarily due to lack of standardization of the procedure for measuring troponin I and limited size of populations studied. A positive test value of 0.6 ng/mL is recommended by the manufacturer (Dade-Behring, Deerfield, Ill). The literature reports various positive levels that differ from 0.6 ng/mL. A study of troponin I in 157 individuals with chest pain indicated a specificity of 99.2% when using a level of 1.5 ng/mL.¹⁸ Another study showed that 99% of 75 healthy blood donors had troponin I levels below 0.26 ng/mL.¹⁹ Using a positive value of 0.4 ng/mL, Antman obtained a negative predictive value of 99%.¹⁶ Adams used 1.5 ng/mL in a study of perioperative AMI,¹³ and Brogan and colleagues used 1.4 ng/mL in an evaluation of patients with cardiac ischemia.²⁰ Zaninotto and others determined a positive value of 1.0 ng/mL for the diagnosis of AMI.¹⁹

Troponin I is not present in healthy patients without acute ischemic syndromes.^{8,21} Keffer noted that troponin I levels can be elevated in coronary ischemia,²² yet the clinician is primarily interested in utilizing the positivity of troponin I when it represents an AMI—the manufacturer's current recommendations for a positive value of greater than 0.6 ng/mL do not take this into account.

For this study, 0.6 ng/mL (as recommended by the manufacturer) was used to represent the lowest positive value for AMI. We arbitrarily chose 2.0 ng/mL as a higher positive level for study purposes, a compromise from the above-reported values. This study evaluates the sensitivity and specificity of troponin I when compared to CK-MB and ECG for diagnosing AMI.

Materials and methods

A retrospective study of the patients who presented to the emergency department of a community hospital was conducted from August 29, 1996 to November 21, 1996. Patients included in this study were those for whom a creatine kinase (CK) was ordered. Blood samples were

drawn into tubes with no preservatives. Whenever a CK assay was ordered, a CK-MB was also performed. The majority of these patients were evaluated for chest pain or symptoms suggesting an acute cardiac event. During this period, approximately 7825 patients came through the emergency department, and a total of 3201 assays were performed for CK and CK-MB on 1479 patients (age, 29 to 103 years; 52% male, 48% female).

Whenever the serum CK-MB was greater than 9 ng/mL, the troponin I assay was done on the same serum specimen. Nine ng/mL was the laboratory's screening value in place for selecting which specimens should have troponin I performed. Serum specimens were obtained at time zero and at 6 hours postpresentation. The troponin I test was performed only when specially trained personnel were available. Due to the limitation of availability of trained personnel, the tests were performed on consecutive patients during the shifts the trained personnel worked and not performed on the days they were off.

A total of 121 patients met the criterion of CK-MB greater than 9 ng/mL to have serum troponin I analyzed. For the control group, an additional 32 randomly chosen patients without cardiac symptoms whose CK-MB was less than 9 ng/mL had troponin I analyzed. In seven patients, time zero data were included in the analysis, but a second ECG and cardiac markers at 6 hours were not performed because the patients were transferred to other facilities before the 6-hour specimen was collected.

No attempt was made to include or exclude patients from this study on the basis of thrombolytic therapy. Results of troponin I assays were never disclosed to the emergency department physician, admitting physician, or consultants during the course of this study.

The catalytic activity of the total CK was measured on the Dimension Analyzer (Dade-Behring), and the CK-MB concentration was measured on the Stratus II Analyzer (Dade-Behring). At our hospital, a CK-MB value greater than 14 ng/mL and its corresponding index

$[(CK-MB \times 100)/\text{total CK}]$ greater than 3.5% in any of the collected specimens was considered positive for AMI. A CK-MB increase by a factor of two from the first test until the second was also considered positive. Either a positive ECG finding or positive CK-MB cardiac marker constituted criteria for AMI.

The serum troponin I concentration was measured on the Stratus II Analyzer. The performance characteristics (linearity, minimum detection limit, standard deviation, etc.) of the assay were close to those of other investigators.^{11,12}

ECGs were interpreted with the physician blinded to the results of the enzymes and clinical data and were considered positive for AMI using the MILIS criteria.²³ These criteria include any of the following:

- ☐ new or presumably new Q waves of at least 30-ms duration and 2-mm depth (10 mm = 1.0 mV),
- ☐ new or presumably new ST-segment elevation or depression of at least 1 mm (ST-segment elevations were measured 0.02 seconds, and ST-segment depressions 0.08 seconds after the J point) in at least 2 of the 3 diaphragmatic leads (II, III, aVF), in at least 2 of the 6 precordial leads, or in leads I and aVL, or
- ☐ new left bundle branch block.

Results

Of the 153 patients studied, CK-MB results were positive in 91 (59%) patients. ECG revealed AMI in 72 (47%) patients. There were 103 (67%) patients who had either positive CK-MB or ECG results.

There were 90 (59%) patients with a troponin I level greater than 2.0 ng/mL and 18 (12%) patients with troponin I between 0.6 and 2.0 ng/mL. Seven patients whose troponin I was between 0.6 and 2.0 ng/mL had negative CK-MB and ECG results. Therefore, 11 patients with troponin I between 0.6 and 2.0 ng/mL had an AMI. Five patients with positive troponin I results (>2.0 ng/mL) had negative CK-MB and ECG results.

When a troponin I level greater than 0.6 ng/mL was used as a positive value, compared to CK-MB and ECG using

either time zero or time 6 hours, the sensitivity was 94% and specificity was 81%. When troponin I greater than 2.0 ng/mL was used to define a positive test, the sensitivity was 85% and specificity was 91% when compared to CK-MB and ECG.

The five patients whose troponin I results were positive but who had negative CK-MB and ECG results underwent an implicit chart review. Three of these patients presented at least a day after onset of their symptoms. The seven patients whose troponin I levels were between 0.6 and 2.0 ng/mL but who had negative CK-MB and ECG results also underwent implicit chart review. One patient had signs of acute ischemia on their ECG (T wave inversion and slight ST depression not seen on a prior ECG). Three patients had heart failure. One patient expired from aspiration pneumonia, and one patient who was admitted for an acute stroke expired from cardiopulmonary arrest. No clinical impressions were documented for AMI in any of these cases. Two charts were not available for review.

Discussion

Because there is a lack of agreement in the literature for a positive value for troponin I and its clinical impact,²⁴ the current study retrospectively evaluated data for two different positive values. The sensitivity of troponin I being positive at 0.6 ng/mL was 94%, and 85% when a troponin I level greater than 2.0 ng/mL was used to define a positive value. The specificity of troponin I being positive at 0.6 ng/mL was 81%, and 91% when a troponin I level greater than 2.0 ng/mL was used to define a positive value. As noted above, others have reported a much higher specificity.¹⁸ This may be due to presentation time from time of onset of symptoms in this particular suburban population. As mentioned, this study was performed using the Dade-Behring system. This may limit the ability to extrapolate the results to other systems.

Based on the current study and review of the literature, the authors believe that troponin I should be serially assayed as

other markers (two specimens at 6 hours apart) to rule in AMI. There were several patients with positive troponin I results whose CK-MB and ECG results were negative. Assuming the above-mentioned references truly represent troponin I as a reliable test for diagnosing AMI, it is worthwhile to measure both CK-MB and troponin I levels to decrease the number of AMIs missed by one marker alone.

For patients with possible acute coronary ischemic syndromes, troponin levels between 0.6 and 2.0 ng/mL should probably be considered, indeterminate for AMI. When the level is greater than 2 ng/mL, it probably represents an AMI.

The main limitation of the current study is its size. Larger studies to evaluate the sensitivity and specificity for AMI using troponin I at lower levels are needed. Also, since this study was performed, the manufacturer changed its recommendation to include obtaining the blood specimen in a lithium/heparin-prepared collection tube. This avoids micro-clots, which may have caused false-positive values.

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References

1. Bhayana V, Henderson AR: Biochemical markers of myocardial damage. *Clin Biochem* 1995;28:1-29.
2. LeMar HJ, West SG, Garrett CR, Hofeldt FD: Covert hypothyroidism presenting as a cardiovascular event. *Am J Med* 1991;91:549-552.

3. Cohen LF, Mohabeer AJ, Keffer JH, Fialal I: Troponin I in hypothyroidism. *Clin Chem* 1996;42:1494-1495.

4. Dorogy ME, Hooks GS, Cameron RW, Davis RC: Clinical and angiographic correlates of normal creatine kinase with increased MB isoenzymes in possible acute myocardial infarction. *Am Heart J* 1995;130:211-217.

5. Vallins WJ, Brand NJ, Dabhade N, Butler-Browne G, Yacoub MH, Barton PJR: Molecular cloning of human cardiac troponin I using polymerase chain reaction. *FEBS Lett* 1990;270:57-61.

6. Sasse S, Brand NJ, Kyprianou P, Dhoot GK, Wade R, Arai M, et al: Troponin I gene expression during human cardiac development and in end-stage heart failure. *Circ Res* 1993;72:932-938.

7. Keffer JH, Baillie EE, Christenson RH: Major advances in measurement of myocardial injury: A practical guideline. ASP National Meeting, Fall 1996, San Diego, Calif.

8. Adams JE, Bodor GS, Davila-Roman VG, Delmez JA, Apple FS, Ladenseon JH, et al: Cardiac troponin I. A marker with high specificity for cardiac injury. *Circulation* 1993;88:101-106.

9. Bodor GS, Porterfield D, Voss EM, Smith S, Apple FS: Cardiac troponin I is not expressed in fetal and healthy or diseased adult human skeletal muscle tissue. *Clin Chem* 1995;41:1710-1715.

10. Bhayana V, Gougoulis T, Cohoe S, Henderson AR: Discordance between results of serum troponin T and troponin I in renal disease. *Clin Chem* 1995;41:312-317.

11. 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.

12. Jaffe AS, Landt Y, Parvin CA, Abendschein DR, Geltman EM, Ladenson JH: Comparative sensitivity of cardiac troponin I and lactate dehydrogenase isoenzymes for diagnosing acute myocardial infarction. *Clin Chem* 1996;42:1770-1776.

13. Adams JE, Sicard GA, Allen BT, Bridwell KH, Lenke LG, Davila-Roman VG, et al: Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. *N Engl J Med* 1994;330:670-674.

14. Adams JE, Davila-Roman VG, Bassey PQ, Blake DP, Ladenson JH, Jaffe AS: Improved detection of cardiac contusion with cardiac troponin I. *Am Heart J* 1996;131:308-312.

15. Guest TM, Ramanathan AV, Tuter PG, Schechtman KB, Ladenson JH, Jaffe AS: Myocardial injury in critically ill patients. A frequently unrecognized complication. *JAMA* 1995;273:1945-1949.

16. Antman EM, Tanasitovic MJ, Thompson B, Schactman M, McCabe CH, Cannon CP, et al: 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.

17. Galvani M, Ottani F, Ferrini Donatella F, Ladenson JH, Destro A, Baccos D, et al: Prognostic influence of elevated values of cardiac troponin I in patients with unstable angina. *Circulation* 1997;95:2053-2059.

18. Tucker JF, Collins RA, Anderson AJ, Hauser J, Kalas J, Apple FS: Early diagnostic efficacy of cardiac troponin I and troponin T for acute myocardial infarction. *Acad Emerg Med* 1997;4:13-21.

19. Zaninotto M, Altinier S, Lachin M, Carraro P, Plebani M: Fluoroenzymometric method to measure cardiac troponin I in sera of patients with myocardial infarction. *Clin Chem* 1996;42:1460-1466.

20. Brogan GX, Hollander JE, McCuskey CF, Thode HC, Snow J, Sama A, et al: Evaluation of a new assay for troponin I vs creatine kinase-MB for the diagnosis of acute myocardial infarction. *Acad Emerg Med* 1997;4:6-12.

21. Wu AH, Feng YJ, Contois JH, Pervaiz S: Comparison of myoglobin, creatine kinase-MB, and cardiac troponin I for diagnosis of acute myocardial infarction. *Ann Clin Lab Sci* 1996;26:291-300.

22. Keffer JH: The cardiac profile and proposed practice guideline for acute ischemic heart disease. *Am J Clin Pathol* 1997;107:398-409.

23. Zoltan G, Rutherford J, Roberts R, Muller J, Jaffe A, Rude R, et al: Electrocardiographic, enzymatic and scintigraphic criteria of acute myocardial infarction as determined from study of 726 patients (a MILIS study). *Am J Cardiol* 1985;55:1463-1468.

24. Selker HP, Zalenski RJ, Antman EM, Aufderheide TP, Bernard SA, Bonow RO, et al: An evaluation of technologies for identifying acute cardiac ischemia in the emergency department. A report from a national heart attack program working group, other biochemical markers. *Ann Emerg Med* 1997;29: 63-69.

Review article

Role of antileukotriene agents in asthma therapy

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Leukotrienes are proinflammatory mediators with special significance in asthma. Released by numerous cell types, particularly after exposure to allergens, leukotrienes cause a potent contraction of bronchial smooth muscle, resulting in reduced airway caliber. Further, they cause plasma to leak from the vessels, resulting in edema, and enhance the secretion of mucus—both events that increase airway obstruction. Thus, leukotrienes have been a target of basic research in asthma. To date, a number of antileukotriene agents have been developed, and three are currently being used in clinical practice in the United States: zafirlukast and montelukast act by antagonizing the leukotriene receptor, and zileuton inhibits leukotriene synthesis. Studies have shown that these agents improve asthma symptoms, pulmonary function, and patient quality of life. Antileukotriene agents have generally been associated with a low incidence of side effects and good tolerability. Currently recommended for mild-to-moderate, persistent asthma, these agents have enabled patients to reduce their use of corticosteroids.

(Key words: asthma, zafirlukast, montelukast, zileuton, leukotrienes, receptor antagonists, synthesis inhibitors)

The recent characterization of the pathophysiology of asthma has led to the development of new modes of therapy.¹ In particular, studies of leukotrienes and their role in asthma have prompted great interest in agents that affect leukotriene activity.²⁻⁴ This article describes the role of leukotrienes in asthma, the biological effects of antileukotriene agents, and the clinical role of these compounds in patients with asthma.

The most important advance in our understanding of asthma has been a recognition of the major role played by

airway inflammation; thus, research has focused on control of inflammatory mechanisms. Important inflammatory events associated with asthma include the recruitment of eosinophils into the airway tissues⁵ and the activation and degranulation of mast cells.⁶ Antigens cause mast cells to become activated and degranulate when they bind to antigen-specific receptors on the cell membrane. Degranulating mast cells release a number of inflammatory mediators, including histamine, proteinase acid hydrolases, major basic protein, and eosinophilic cationic protein. Activated mast cells also synthesize and release proinflammatory cytokines, including interleukins, tumor necrosis factor, interferon, and granulocyte-macrophage colony stimulating factor, which promote chemotaxis of neutrophils and eosinophils to the region, enhancing the

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