

False-Positive Troponin I in a Young Healthy Woman with Chest Pain

Erika N. Ringdahl, MD, and James J. Stevermer, MD, MSPH

Cardiac troponin I (cTnI) is frequently used to help determine whether a patient with chest pain has had cardiac damage. A false-positive finding can result in patients undergoing unnecessary hospitalization and potentially invasive tests. Clinicians need to be aware of the possibility of spuriously elevated troponin I levels.

Case Report

A 43-year-old healthy woman came to the emergency department complaining of a dull ache in her left chest, which radiated to her left shoulder. The pain was minimal but constant and unaffected by exertion or rest. She had no associated diaphoresis, nausea, or vomiting. The patient did not smoke and did not have hypertension, diabetes, or a family history of cardiac disease. Her low-density lipoprotein was less than 130 mg/dL 1 year earlier. Findings of her physical examination, including temperature, blood pressure, pulse, and respiratory rate, were normal. An electrocardiogram was normal and without evidence of ischemic changes. Laboratory studies disclosed the following values: creatine kinase (CK) was 67 U/L (normal 21–215 U/L), with a CK-MB of 0.5 ng/mL (normal 0.0–5.0 ng/mL); and troponin I (AxSYM, Abbott Laboratories, Abbott Park, Ill) was 9.3 ng/mL (normal 0.0–0.4 ng/mL).

Given this single laboratory abnormality, the patient was admitted to the family practice inpatient service. The patient was asymptomatic at admission and remained so throughout the hospitalization. A dipyridamole nuclear scan showed no ischemia, a normal ejection fraction, and normal wall motion. A repeat troponin I measurement later in the day of admission was 9.8 ng/mL. Levels of troponin I remained elevated 1 week (3.3 ng/mL)

and 2 months (4.5 ng/mL) after she was released from the hospital. Her renal function was normal, and rheumatoid factor was not present. Her troponin T level was within normal limits.

Discussion

Several biochemical markers have been developed to aid in the diagnosis of acute coronary syndromes. Lactate dehydrogenase has been used as a marker since 1957,¹ but it is not specific for cardiac tissue. Creatine kinase–MB band (CK-MB) is more specific than lactate dehydrogenase, but because CK-MB is also found to some degree in skeletal muscle, levels can be elevated with muscle disease or trauma.

The troponin complex is located on the thin filament of striated and cardiac muscle and regulates the movement of calcium between actin and myosin. The cardiac troponin is a unique form of troponin found only in myocardial tissue. Cardiac troponin has three components, T, C, and I.² Cardiac troponin T (cTnT) is also found in diseased or regenerating skeletal muscle, and levels can be elevated in patients with muscular dystrophy or polymyositis.³

cTnI is specific to cardiac tissue and is released into serum after myocardial necrosis.⁴ Enzyme-linked immunosorbent assay for cTnI was first available in 1995.⁵ cTnI has become a marker of choice for detecting myocardial damage because of its specificity to cardiac tissue. Currently, there are two major commercial immunoassays that measure cTnI levels. The Access System (Beckman Coulter, Fullerton, Calif) uses monoclonal mouse antibodies as both the capture and the conjugate antibodies. The AxSYM system uses monoclonal mouse antibodies as the capture antibody and goat anti-cTnI as the conjugate antibody.¹ Table 1 lists the primary causes of elevated troponin I.

Nonischemic heart disease can raise cTnI levels. Elevated cTnI levels are found in about one half of younger patients with pericarditis, especially those who have had a recent infection.⁶ Elevated cTnI

Submitted, revised, 7 February 2002.

From the Department of Family and Community Medicine (ENR, JJS), University of Missouri–Columbia. Address reprint requests to Erika N. Ringdahl, MD, MA303 Medical Sciences Building, University of Missouri–Columbia, Columbia, MO 65212.

Table 1. Causes of Elevated Troponin I.

Area	Condition
Coronary artery syndromes ^{2,4}	Acute myocardial infarction Unstable angina
Noncoronary heart disease	Pericarditis ⁶ Myocardial injury (trauma) Myocarditis ² Congestive heart failure ⁷ Arrhythmia ⁷ Pulmonary embolism ^{7,8}
Renal failure ⁹	
Assay interference	Heterophile antibody ¹ Rheumatoid factor ¹⁰ Specialized fluids (eg albumin, plasmin) ¹¹ Excess fibrin ¹²

levels have also been reported in patients with congestive heart failure, pulmonary embolism, and ventricular arrhythmias.^{7,8} Levels of cTnI might be elevated in patients with renal insufficiency, though for CK-MB elevated levels are more of a problem.²

Heterophilic antibodies can cause false-positive cTnI results. The antibodies bind to the capture and the conjugate antibodies, simulating cTnI. Using antibodies from two different species, as in the AxSYM system, might decrease the impact of the heterophilic antibodies.¹ The increased use of monoclonal mouse antibodies in cancer imaging and treatment increases the chances a person will develop heterophilic antibodies. Persons with more frequent exposure to animal proteins (such as veterinarians, farmers, and pet owners) can also develop heterophilic antibodies.¹³ It has been reported that up to 40% of the general population has heterophilic antibodies,¹⁴ though it is unlikely that these elevations are clinically relevant in most cases. Recently developed enhanced assays can reduce the chance of interference.¹⁵

In a similar fashion, rheumatoid factor can interfere with the immunoassay. Five percent of healthy patients might have circulating rheumatoid factor, and about 1% of patients who have elevated cTnI levels have this elevation purely because of the rheumatoid factor.¹⁰ Because patients with circulating rheumatoid factor can also have myocardial ischemia, in some circumstances it could be a challenge to determine whether the elevated cTnI levels are due to infarction or interference from the

Table 2. Positive and Negative Predictive Value of the Troponin I Test at 6 Hours of Chest Pain.

Predicted Prevalence	Patients Who Will Have Positive Test (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
1%	5.7	13.6	99.8
2%	6.7	24.1	99.5
4%	7.9	39.4	99.0
6%	9.4	50.0	98.5
8%	10.8	57.6	98.0
20%	19.6	79.6	94.5
50%	41.5	94.0	81.2
80%	63.4	98.4	51.9

Note: Sensitivity estimated at 6 hours after the onset of chest pain = 78%, specificity = 95%.^{19,20}

rheumatoid factor. A rheumatoid factor blocking agent can be used to remove this interference.¹⁶

In addition to clinical entities that interfere with the immunoassays, analytical errors contribute to the number of falsely elevated cTnI results. If the specimen is centrifuged before a clot is completely formed, the remaining fibrin can nonspecifically bind the antibody.¹² Blood from patients who have a coagulopathy or who are taking anticoagulants will be less likely to clot completely.¹⁷ Finally, one study showed that malalignment of a solution dispenser produced elevated cTnI levels without registering an error by the instrument.¹⁸ Overall, the Abbott AxSYM system was found to be more likely than the Bayer Immuno I Assay system to have false-positive cTnI results.⁴

Implications for Practice

Clinicians can often estimate the chance that a patient has a given disease before testing for a particular disease. An a priori estimate is helpful when interpreting the test results. Table 2 displays the probability of a positive test (false- and true-positives), the positive predictive value (the probability that a positive result represents true disease), and the negative predictive value (the probability that a negative result excludes true disease) as prevalence is increased within a range of values.

The patient described here had an estimated risk of 4% for serious coronary artery disease, based on her history and normal electrocardiogram.^{21,22} Because it takes time for troponin to be released from injured muscle tissue, the test characteristics of cTnI improve the longer the patient has had symp-

toms before the test sample is drawn. The overall sensitivity and specificity of cTnI, especially after 24 hours, are more than 90%. The estimated sensitivity about 6 hours from onset of symptoms is 78%, and the specificity is 95%.^{19,20} Even with this patient's low risk of coronary artery disease, the chance that the positive cTnI measurement indicated myocardial damage was 40% (positive predictive value). It is worth noting that (at 6 hours after pain onset) more than one half of the positive results do not represent chest pain until the a priori probability exceeds 6%.

Conclusion

This case shows how a spuriously elevated troponin I reading resulted in the hospitalization and additional testing in this healthy 43-year-old woman. When test results do not correspond to the clinical picture, the possibility of a false-positive result must be considered. Testing for clinical entities, such as rheumatoid factor or heterophile antibodies, might be appropriate. It is also important to look for analytical errors by the various instruments. In these cases, clinical pathologists can be quite helpful. In the patient described here, the cause of the persistently elevated test result was never determined.

The accuracy of cTnI as a biochemical marker is helpful in the early evaluation of patients with possible coronary syndromes. The likelihood of an incorrect result is somewhat less than with previous biochemical markers for cardiac ischemia. Clinicians who appreciate the accuracy of this test must still be cognizant of the possibility of inaccurate results and evaluate their patients appropriately.

References

1. Volk AL, Hardy R, Robinson CA, Konrad RJ. False-positive cardiac troponin I results - Two case reports. *Lab Med* 1999;30:610-2.
2. Coudrey L. The troponins. *Arch Intern Med* 1998;158:1173-80.
3. Bodor GS, Survant L, Voss EM, Smith S, Porterfield D, Apple FS. Cardiac troponin T composition in normal and regenerating human skeletal muscle. *Clin Chem* 1997;43:476-84.
4. Parry DM, Krahn J, Leroux M, Dalton J. False positive analytical interference of cardiac troponin I assays: an important consideration for method selection. *Clin Biochem* 1999;32:667-9.
5. 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. *Clin Chem* 1999;45:1789-96.
6. Bonnefoy E, Godon P, Kirkorian G, Fatemi M, Chevalier P, Touboul P. Serum cardiac troponin I and ST-segment elevation in patients with acute pericarditis. *Eur Heart J* 2000;21:832-6.
7. Heeschen C, Goldmann BU, Moeller RH, Hamm CW. Analytical performance and clinical application of a new rapid bedside assay for the detection of serum cardiac troponin I. *Clin Chem* 1998;44:1925-30.
8. Douketis JD, Crowther MA, Stanton EB, Ginsberg JS. Elevated cardiac troponin levels in patients with submassive pulmonary embolism. *Arch Intern Med* 2002;162:79-81.
9. Mockel M, Schindler R, Knorr L, et al. Prognostic value of cardiac troponin T and I elevations in renal disease patients without acute coronary syndromes: a 9-month outcome analysis. *Nephrol Dial Transplant* 1999;14:1489-95.
10. Krahn J, Parry DM, Leroux M, Dalton J. High percentage of false positive cardiac troponin I results in patients with rheumatoid factor. *Clin Biochem* 1999;32:477-80.
11. Lagneau F, Beyne P, Letteron P, Laperche T, Marty J. Fluid therapy directly interferes with immunoassay for cardiac troponin I. *Intensive Care Med* 1999;25:625-7.
12. Abbott AxSYM system. Package insert: troponin-I. List No. 3C29. Abbott Park, Ill: Abbott Laboratories, 1997.
13. Fitzmaurice TF, Brown C, Rifai N, Wu AH, Yeo KT. False increase of cardiac troponin I with heterophilic antibodies. *Clin Chem* 1998;44:2212-4.
14. Boscato LM, Stuart MC. Incidence and specificity of interference in two-site immunoassays. *Clin Chem* 1986;32:1491-5.
15. Yeo KT, Storm CA, Li Y, et al. Performance of the enhanced Abbott AxSYM cardiac troponin I reagent in patients with heterophilic antibodies. *Clin Chim Acta* 2000;292:13-23.
16. Dasgupta A, Banerjee SK, Datta P. False-positive troponin I in the MEIA due to the presence of rheumatoid factors in serum. Elimination of this interference by using a polyclonal antisera against rheumatoid factors. *Am J Clin Pathol* 1999;112:753-6.
17. Roberts WL, Calcote CB, De BK, Holmstrom V, Narlock C, Apple FS. Prevention of analytical false-positive increases of cardiac troponin I on the Stratus II analyzer. *Clin Chem* 1997;43:860-1.
18. Galambos C, Brink DS, Ritter D, Chung HD, Creer MH. False-positive plasma troponin I with the AxSYM analyzer. *Clin Chem* 2000;46:1014-5.
19. Tucker JF, Collins RA, Anderson AJ, Hauser J, Kalas J, Apple FS. Early diagnostic efficiency of cardiac

- troponin I and troponin T for acute myocardial infarction. *Acad Emerg Med* 1997;4:13–21.
20. Apple FS, Maturen AJ, Mullins RE, et al. Multi-center clinical and analytical evaluation of the AxSYM troponin-I immunoassay to assist in the diagnosis of myocardial infarction. *Clin Chem* 1999; 45:206–12.
 21. Pryor DB, Harrell FE Jr, Lee KL, Califf RM, Rosati RA. Estimating the likelihood of significant coronary artery disease. *Am J Med* 1983;75:771–80.
 22. Pryor DB, Shaw L, McCants CB, et al. Value of the history and physical in identifying patients at increased risk for coronary artery disease. *Ann Intern Med* 1993;118:81–90.