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False Positive Cardiac Troponin Results in Patients Without Acute Myocardial Infarction

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Abstract

Cardiac troponin I (cTnI) and T (cTnT) are highly sensitive and specific biochemical markers for myocardial necrosis and are generally not elevated in cases other than acute myocardial infarction (AMI) and acute coronary syndrome (ACS). However, if the patient's clinical picture for AMI or ACS do not match an elevated troponin result, the laboratory should suspect a false positive troponin value caused by analytical interferences with this assay. These analytic interferences include fibrin clots, microparticles in sample, hetereophile and human anti-animal antibodies, rheumatoid factor, interference by bilirubin, hemolysis, lipemia, elevated alkaline phosphatase activity, macro immunocomplex formation, and analyzer malfunction. In general, analytical interferences resulting in false positive troponin results are associated with a specific manufacturer's troponin assay and are not encountered in all troponin assays. This review discusses steps which the laboratory should consider taking in the investigation of suspected analytical interference with the troponin assay. Awareness of the possibility of a false positive troponin result may assist the physician in the management of the patient without AMI or ACS and may spare the patient additional diagnostic procedures especially if the troponin result is not consistent with these diagnoses. A false positive troponin result is a reminder that although troponin plays an important role in the diagnosis of AMI and ACS , it should not be the only criterion for establishing these diagnoses.

Cardiac troponin I (cTnI) and T (cTnT) are the most sensitive and specific biochemical markers of myocardial cell damage and have replaced creatine kinase MB as the preferred marker for diagnosis of myocardial injury.[1,2] A consensus document issued by the European and American College of Cardiology Committee for the redefinition of myocardial infarction promoted cardiac troponin I and T as the preferred markers for myocardial damage because of their nearly absolute myocardial tissue specificity, high sensitivity, and the ability of these marker to reflect microscopic zones of myocardial necrosis.[3] Cardiac troponins are recommended as the preferred marker in the evaluation of all patients who present with chest discomfort consistent with acute coronary syndromes (ACS), including ST-segment elevation myocardial infarction, non-ST elevation myocardial infarction, and unstable angina, which are characterized by a common pathophysiology of cardiac ischemia.[4]

A variety of clinical conditions other than myocardial infarction may be associated with elevated cardiac troponin levels; these conditions include acute pulmonary embolism, acute or severe heart failure, myocarditis, sepsis/critically ill patients, acute pericarditis, renal failure, hypovolemia, cerebrovascular accidents, tachyarrythmias, myocardial contusion,[5-7] and takotsubo cardiomyopathy,[8] reversible left ventricular dysfunction associated with emotional stress with evidence of exaggerated sympathetic activation.[8] In addition, false elevations in patients without myocardial infarction may also occur because of analytical interferences with the troponin immunoassay. In this regard, in August, 2005, the Office of In Vitro Diagnostic Device Evaluation and Safety (OVID) of the United States Food and Drug Administration (FDA), using input provided by Advanced Medical Technology Association (AdvaMed) issued an advisory regarding false elevations in cardiac troponin results in response to many manufacturers' and users' reports of false positive troponin levels and to published articles in the medical literature.[9] The purpose of the advisory was to inform laboratories about the possibility of false positive troponin values when this marker is used in the diagnosis of acute myocardial infarction and to recommend steps to be followed by the laboratory to identify and to confirm cases of false positive troponin results.[9]

We present a recent case encountered at our medical facility of a patient with a persistently elevated troponin I value without a clear clinical picture of myocardial infarction to illustrate a false positive troponin I result caused by analytical interference and to discuss the causes for the false positive troponin which may lead to unneeded clinical workup and intervention.

Clinical Case

A 57-year-old male with history of heavy alcohol use, tobacco use, hypertension, hyperlipidemia, squamous cell malignancy of the tongue status post chemotherapy and radiation, presented to the VA Boston Healthcare System Emergency Department (ED) with complaint of bilateral lower extremity and scrotal edema with increased abdominal girth for 1 month. The patient denied any fevers, chills, nausea, vomiting, abdominal pain or discomfort, altered sensorium, diarrhea, or hematemesis. He had a temperature of 98.2°F, blood pressure of 109/76, and was noted to have a heart rate in the 110s in the ED. His physical examination was significant for cachexia, no scleral icterus, non-jaundiced, positive caput medusae, tense non-tender abdominal ascites with shifting dullness, hepatomegaly, and resting tremor of hands without asterixis, atrophic arm musculature, lack of hair on distal lower extremities, 3+ tense lower extremity edema to just below the patellae with 2+ pedal pulses, and 2+ scrotal edema. The patient denied any exposure to mice, rodents, or other animals An electrocardiogram revealed sinus tachycardia at 101 beats per minute, slightly prolonged QTc 0.448, low voltage QRS without right ventricular strain pattern, and nonspecific reduced T wave amplitude in the anterior leads compared to 1 month prior. A PA/Lateral chest x-ray revealed clear lungs and no acute cardiopulmonary pathology with normal cardiac silhouette. The patient had a normal CT-pulmonary angiogram that ruled out acute pulmonary embolism. **Table 1**

displays this patient's laboratory findings. In the ED, the patient had a troponin I of 41.0 ng/mL that remained elevated throughout his hospital course, 33.9 to 42.6. Total CK activity was normal, and the CK-MB was negative. Cardiology was consulted, who felt that the patient's story was not consistent with acute coronary syndrome and that "perhaps this was the patient that troponins did not apply." A transthoracic echocardiogram showed normal function, wall thickness, and wall motion without apical ballooning. The patient's plasma was serially diluted with a patient sample with normal troponin I (<0.01 ng/mL) to determine the linearity of the results; the serial dilution demonstrated that the results were non-linear, indicating the presence of interfering antibodies. The manufacturer, Beckman-Coulter Diagnostics, was contacted, and the patient's sample was sent to the reference Beckman-Coulter Laboratory in Chaska, MN, which analyzed the sample for the possible presence of a heterophile antibody. The Beckman laboratory added blockers to the sample and recorded a reduction of the troponin I value from 30.2 ng/mL to 1.04 ng/mL, which was interpreted as the presence of a heterophile antibody.

Biochemistry of Cardiac Troponin

Troponin consists of 3 single chain polypeptides—troponin C, which binds calcium ions; troponin I, which binds to actin and inhibits actin myosin interactions; and troponin T, which binds to tropomyosin and facilitates contraction, which regulate striated muscle contraction.[10] Although troponins are present in skeletal muscle, heart muscle contains cTnI and cTnT isoforms, distinctive for myocardium and encoded by different genes in the 2 types of tissue.[11] cTnI and cTnT may be separated by immunological techniques. Immunoassays utilizing high affinity antibodies specific for cTnI and cTnT have been developed and are now widely available.

In healthy individuals, cTnI and cTnT are undetectable in plasma but are released into the circulation with myocyte damage caused by various conditions including trauma, myocardial necrosis, toxin exposure, and/or inflammation.[11] Most of the cTnI and cTnT is bound to myofilaments, but about 3% to 8% is free in the myocyte cytosol.[12] The initial appearance of troponin in blood following myocyte damage is thought to be caused by release of the unbound cytosolic pool, followed by the more prolonged appearance of troponin from damage to the myofilament structures.[11] Because cTnI and cTnT are not found in any human tissue other than the myocardium, the detection of any increase in cTnI and cTnT are indicative and specific for myocardial damage.[12]

Assays for Cardiac Troponin I and T

Because of international patent restrictions, only one assay for cTnT is available from a single manufacturer (Roche Diagnostics); cTnT demonstrates a high degree of precision at the low end of measurement range and a relatively uniform cutoff concentration.[11] In contrast, at least 18 different commercial assays for cTnI are available on automated and point of care instruments[6]; assays for cTnI demonstrate considerable variation in the cutoff concentrations for the definition of an abnormal concentration of cTnI.[6,13] Thus, if cTnI is used for the diagnosis of myocardial infarction, the clinician should be aware of the cTnI cutoff values specifically associated with the particular assay used by the laboratory. International consensus committees have established that an elevated value for cardiac troponin be defined as a value exceeding the 99th percentile of a reference control group and that imprecision be defined as a coefficient of variation of ≤10%.[3]

Are results of troponin I assays from different manufacturers comparable? The results are not comparable because there is no standardization or consensus for troponin I results. The lack of comparability has been a source of confusion and irritation to clinicians.[14] Studies have shown that troponin I results may vary by a factor of 100 fold from one assay and manufacturer to

Table 1_Patient's Test Results

Test	11/23/05	11/24/05	11/25/05	11/28/05	Reference Range
Troponin I (cTnI)					
Beckman Access	41.0	37.9	33.9	42.6	0 – 0.5 ng/mL
cTnI (Abbott I-STAT)		<0.01			0 – 0.5 ng/mL
cTnI (Bayer)		<0.01			0 – 0.1 ng/mL
cTnT (Roche)		<0.01			0 – 0.1 ng/mL
CK, Total		20			32 – 237 U/L
CK-MB		0			0 – 5.0 ng/mL
Alkaline phosphatase		401			30 – 115 U/L
AST		60			10 – 45 U/L
ALT		21			7 – 52 U/L
Bilirubin, total		1.1			0.2 – 1.2 mg/dL
Protein, total		4.4			8.5 mg/dL
Albumin		2.1			3.5 – 5.0 g/dL
Alpha 1 Globulin		0.29			0.19 – 0.50 g/dL
Alpha 2 Globulin		0.54			0.46 – 1.20 g/dL
Beta Globulin		0.42			0.56 – 1.18 g/dL
Gamma Globulin		1.08			0.67 – 1.67 g/dL
IgA		314			82 – 453 mg/dL
IgG		988			751 – 1560 mg/dL
IgM		349			46 – 304 mg/dL
Rheumatoid Factor		<20			0 – 20 IU/mL
Antigliadin IgG		2			0 – 19 Units
Antigliadin IgA		3			0 – 19 Units

another.[15] The reason for some variability in cTnI results is that cTnI is susceptible to proteolytic degradation leading to the appearance in serum of a wide diversity of peptides with different stabilities. Some cTnI epitopes remain unaltered while other epitopes are lost or altered in the degradation process.[15,16] This variability in proteolytic degradation results in different recoveries for different cTnI assays.[15,16] In addition, the antibody used by a particular manufacturer may be directed against different epitopes of troponin I, which result in assay-to-assay variation in detected levels of cTnI.[15,16] Hence, for a given patient sample, the chosen analytical method can produce wide variations in cTnI. Therefore, it is important that clinicians understand that when utilizing cTnI for the diagnoses of AMI or ACS, they should refer to the cutoff value established for the particular assay used in their laboratory.

Recently in 2004, the National Institute of Standards and Technology introduced a new standard reference material for human cardiac troponin (SRM 2921) in the form of a complex with other troponin proteins extracted from human heart tissue.[17] This material is considered to be the best common calibrator to be used to standardize the different troponin I assays.[17] The availability of this material should improve the accuracy of troponin I assays and assist in the future standardization of troponin I determinations.

Analytical Interfering Factors Associated With Falsely Elevated Troponin I Results

Table 2 summarizes some causes of false positive troponin results which are seen in immunoassays for cTnI and cTnT.

Interfering Antibodies, Heterophile, and Human Anti-Animal Antibodies

Heterophile antibodies are antibodies that are produced against poorly defined antigens and are generally weak antibodies with multispecific activities.[18] The general term "heterophile" antibodies is sometimes used interchangeably to refer to heterophile antibodies, human anti-animal antibodies, rheumatoid factor, and other autoantibodies.[9] Human anti-animal antibodies are antibodies with strong avidities, are produced against well-defined antigens, and develop as a result of treatment or exposure to animal immunoglobulins.[19] Circulating human anti-animal antibodies may have specificities for a wide range of animal proteins such as mouse, rabbit, rat, and others.[19] Circulating heterophile and human anti-animal antibodies may be acquired from iatrogenic and non-iatrogenic causes; these include the use of mouse monoclonal antibodies for therapeutic and imaging purposes, blood transfusions, vaccination against infectious diseases, exposure to microbial antigens, animal husbandry or the keeping of animals as pets, transfer of dietary antigens across the gut wall in celiac diseases, and autoimmune diseases that may give rise to autoantibodies such as rheumatoid factor.[19]

Immunoassays for cTnI often employ 2-site (sandwich) or competitive reactions which contain 2 antibodies specific at 2 sites for the measured analyte. The first antibody, the "capture" antibody, initially binds to any cTnI in the sample. The second antibody, the "label" antibody is then added after a wash phase and binds any "captured" cTnI, providing a detectable signal that can be measured to quantify the cTnI concentration after a final wash phase. Human anti-animal and heterophile antibodies, which are specific for the F_c portion of the assay species immunoglobulin and may crosslink the capture or label antibodies in the absence of the intended analyte, may cause a positive assay response.[20] Because of this potential interference, manufacturers generally add non-specific blocking antibodies of the assay species, which are intended to limit the effect of any heterophile antibodies present in the sample. However, in some cases when sufficient quantities of interfering antibodies are present, analytical errors may occur.

The prevalence of anti-animal and anti-mouse antibodies is unknown and estimates vary widely (between <1% to 80%).[19] A commonly cited prevalence of 40% for heterophile antibodies for interference in 2 site immunoassays was found in 1986 in 188 subjects.[21]

What can be done to reduce or to remove interfering antibodies from troponin assays? The laboratory can use the following methods to reduce or remove the effect of interfering antibodies from troponin assays:

- The specimen can be analyzed on a different manufacturer's assay system.
- Heterophile blocking reagents can be used (Scantibodies Laboratories, Inc).
- Add endogenous immunoglobulin-free serum samples to the specimen to remove endogenous immunoglobulins, (ie, use normal animal sera as blocking reagent).

Rheumatoid Factor

Rheumatoid factor (RF) may also be a cause of interference with cTnI immunoassays. It has been estimated that approximately 5% of healthy patients have a positive RF.[22] Positive RF has been found in varying percentages in other connective disease disorders such as systemic lupus erythematosis, systemic sclerosis, polymyositis, and Sjögren's Syndrome.[23] In the presence of RF, false positive cTnI results may be found in varying percentages depending on the immunoassay used (0.9% to 1.8% for the Abbott AxSYM system and 0.5% to 1.0% for the Bayer Immuno I analyzer).[22] Use of a polyclonal antisera to RF has been shown to eliminate the false positive interference with the MEIA assay for cTnI on the Abbott AxSYM analyzer.[24] However, a recent study for cTnI in patients with rheumatoid factor found that 11.5% were heterophilic false positive results and that (even after pre-treatment with heterophile blocking agents) 50% of the false positive results were not corrected.[25]

Fibrin Interference

Excess fibrin has been reported to be a cause of falsely elevated cTnI results with the Abbott AxYSM analyzer, a finding attributed to non-specific binding of the antibody to fibrin or the trapping of the indicator enzyme by fibrin in the separation matrix in incompletely clotted serum specimens.[26] False

Table 2_Causes of False-Positive Troponin Results

Heterophile antibodies
Human anti-mouse antibodies
Autoantibodies
Fibrin clots
Rheumatoid factor
Microparticles in specimen
Interference by endogenous components in blood (bilirubin, hemoglobin, lipemia)
High concentration of alkaline phosphatase
Immunocomplex formation
Analyzer malfunction

positive cTnI results in 2.2% of patient specimens were also found by Roberts and colleagues with the Dade Stratus II immunoassay analyzer in incompletely clotted serum specimens, a problem remedied by the routine use of plasma samples for all troponin determinations.[27]

Hemolysis Interference

A recent study showed that hemolysis can lead to false positive cTnI results using the Ortho Vitros ECi analyzer but demonstrated no interference with the Beckman Access 2 method.[28] The false positive rate attributable to hemolysis for the Vitros ECi analyzer was 4.1%, 7.5%, and 16.0% respectively at the cutoff concentrations of 0.12, 0.08, and 0.038 µg/L.[28]

Alkaline Phosphatase Interference

cTnI may be effected by high concentrations of alkaline phosphatase (ALP) as reported in a study using the Dade Stratus cTnI fluorometric enzyme immunoassay, which uses ALP as the substrate[29]; in the presence of an ALP value of 129 U/L, the observed cTnI concentration was falsely elevated to 4.3 ng/mL, and at ALP values of 445 and 913 U/L, respectively, the cTnI values were falsely elevated to 20.4 and 41.0 ng/mL, respectively.[29] In the same study, no interference by high concentrations of ALP were found for the microparticle immunoassay assay (Abbott Laboratories) or the chemiluminescent assay (Bayer Diagnostics) for cTnI.[29]

Immunocomplex Formation Interference

A case of a false-positive troponin I attributed to a macrocomplex was reported in 2002, in which the authors suggest the possibility that a modified molecule of cTnI induced the immunocomplex formation with a molecular mass similar to that of apolipoprotein B-100 (~500 kDa)[30] leading to interference with the measurement of cTnI.

Instrument Malfunction

Malfunction of the immunoassay analyzer itself may be a cause of false elevations in cTnI. Galambos and colleagues found several cases of false positive cTnI results because of a temporary malfunction of the Abbott AxSYM analyzer and recommended that, after maintenance of the instrument, quality control specimens be analyzed.[31]

Prevalence of False Positive cTnI Values

Because of the many manufacturers of troponin I assays, it is difficult to estimate the prevalence of false positive cTnI results since false positives depend on the manufacturer, the specific immunoassay analyzer used, and each laboratory's definition of positive versus negative cTnI levels. One study of false positive cardiac troponin I (Beckman Access analyzer) in a routine clinical population found the overall false positive prevalence of 3.1%.[32] Other studies have found prevalence of false positives of 0.17% (Dade Dimension),[33] 0.5%-1.0% (Bayer Immuno 1),[22] 0.9%-1.8% (Abbott AxSYM),[22] and 0.19% (Abbott AxSYM).[34]

Although the true prevalence of false positive troponin results is difficult to estimate, the issuance of the FDA advisory in August of 2005 in direct response to numerous adverse event reports of false positive troponin values sent by manufacturers and users of troponin assays as well as reports in the medical literature indicate that the problem of troponin false positive troponin results is significant and that it should be brought to the attention of all laboratory professionals and clinicians involved in the care of the patients.[9]

Manfacturers' Improvements in Troponin Assay Kits

Continued improvements in assay kits incorporating more effective blocking agents to reduce or eliminate the effect of interfering antibodies have improved the performance of assays for cTnI and led to fewer false positive cTnI results. For example, Abbott Diagnostics reformulated their troponin kit to decrease the interferences with the assay in response to numerous cases of false positive troponin I results using the Abbott AxSYM instrument in the literature.[33,34]

Laboratory Approaches to a False Positive Cardiac Troponin Value

Good communication between the medical and clinical laboratory staff is critical for identifying erroneous troponin results because it is the clinician who will be the first to recognize and to bring to the laboratory's attention that the elevated troponin value does not match the clinical picture of AMI or ACS. If the patient's clinical picture is not consistent with the finding of an abnormal troponin value, the laboratory should investigate the possibility that the troponin value is falsely elevated and should approach this problem in the following manner[9]:

- Check the sample for possible micoparticles or clots (possibility of fibrin interference). Recentrifuge specimen and re-assay.
- Request a repeat blood draw and retesting of the patient to confirm the initial positive troponin value.
- Check for hemoglobin (hemolysis), lipemia, high bilirubin interference.
- Dilute sample with a zero calibrator or with a negative troponin patient sample to check for linearity of results to access presence of interfering heterophile antibodies.
- Re-assay sample with another manufacturer's assay system or submit specimen to another laboratory using a different assay for troponin.
- Check for possible instrument malfunction.
- Consider use of blocking antibodies to pre-treat sample before retesting.
- Save sample and submit to manufacturer for work up and consider alerting the FDA of the false positive troponin result.

Importance of Awareness of False Positive Troponin Results

Awareness of the possibility of a false positive troponin result may assist the physician in the management of the patient without AMI or ACS and may spare the patient additional diagnostic procedures especially if the troponin result is not consistent with these clinical diagnoses. A false positive troponin result should serve to remind the clinician and the laboratory that although the troponin test assay may play an important part in the diagnosis of ACS, other diagnostic modalities including careful clinical history and the electrocardiogram may assist in confirming this diagnosis. LM

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