Elevated Cardiac Troponins—Not Always an Acute Coronary Syndrome

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Health care professionals use sensitive blood tests to quickly diagnose and treat acute coronary syndromes; but without supporting evidence, this diagnosis needs to be made with caution in cases of elevated troponins.

An 85-year-old female with a history of coronary artery disease (CAD) presented to the Emergency Department (ED) with altered mental status. While she was admitted for sepsis and had positive blood cultures for methicillin-resistant *Staphylococcus aureus* (MRSA), the patient was also noted to have an elevated troponin level of 1.32 (higher than the local laboratory normal values). Given the history of CAD with altered mental status, she was placed on an acute coronary syndrome (ACS) protocol with serial electrocardiograms (ECGs) and enzymes. However, her ECG remained normal, and her cardiac troponin levels trended downward in the Intensive Care Unit (ICU) as she recovered from sepsis. Since her transthoracic echocardiogram performed at that time was normal and did not show any regional wall motion abnormality, her troponin enzyme elevations were considered to be secondary to sepsis; however, initial emphasis at admission was on ACS.

DISCUSSION

Cardiovascular disease is a leading cause of morbidity and mortality in the United States. It can be a silent killer or may present as a life-threatening event, such as ventricular fibrillation, sudden death, or acute myocardial infarction (MI) with or without classic signs and symptoms of ACS. Not uncommonly ACS symptoms may be vague. When missed, ACS can lead to a devastating event, such as cardiovascular collapse, death, loss of cardiac muscle, ventricular irritability, and to significant changes in a person's quality of life. Thus, there is a heightened awareness for ACS. These life-threatening events are important, and as such ACS should not be missed when it is presented in the ED or when a person is found unresponsive. The ACS spectrum includes unstable angina, non-ST elevation MI (NSTEMI), and ST elevation MI (STEMI). Since ECG changes may be transient, and patients may have atypical symptoms, sensitive blood tests such as cardiac troponins help identify ACS and have revolutionized cardiology, leading to identification of the smallest amount of myocardial damage in a setting of ACS.

The cardiac troponin biomarkers have revolutionized the diagnostic abilities of physicians in the ambulatory and hospitalized patient settings, including the ED, in recognizing myocardial cell death. Physicians determine the presence of cardiac injury by measuring serum levels of cardiac troponins in order to diagnose and treat true MIs. However, these sensitive biomarkers have also led to increased recognition of myocardial cell injury from causes other than ACS. Thus, these markers may be elevated in a setting associated with occlusion of the coronary vasculature, which is the typical presentation of an ACS, but also can be due to a supply and demand mismatch for the myocardial cells.

The true diagnosis of MI, however, requires the typical rise and fall of the cardiac enzymes with either ischemic symptoms or electrocardiogram (ECG) changes suggestive of ischemia, development of pathological Q waves, or imaging evidence of recent loss of viable myocardium or wall motion abnormalities along with presenting symptoms either typical or atypical. Without this evidence supporting the elevation of troponin as an ACS, the diagnosis of ACS needs to be made with caution.

This case is a reminder to physicians and physician extenders not to exclude non-ACS causes of troponin elevation and to use clinical context and judgment along with diagnostic tests in a case of troponin elevation, especially now when more triaging to fast-track pathways of medical management occurs, such as 23-hour observation and chest pain center units.

Cardiac Biomarkers

Today, cardiac biomarkers, such as troponin (cTnT and cTnI) levels, are commonly used to determine

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whether a patient is presenting with an ACS. ACS is defined by reduced coronary blood flow to the cardiac muscles, which leads to an MI. The spectrum of ACS has a range from unstable angina to a transmural MI or STEMI and includes NSTEMI in the spectrum. Unstable angina is diagnosed by clinical history with possible ST segment, T-wave changes on ECG, or wall motion abnormalities on imaging, but without cardiac troponin elevation. Troponin elevation then changes the diagnosis of unstable angina to NSTEMI or STEMI based on ECG findings. Thus, the clinical presentation, electrocardiographic changes, and biochemical cardiac markers make up the triad of characteristics that determine the diagnosis of ACS and type of ACS.

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No doubt, ACS requires prompt recognition, since the beneficial effects of therapies are time sensitive. The diagnosis of an acute MI is confirmed by ECG changes and serum cardiac biomarker elevation. In STEMI, the ECG shows classic ST elevation of at least 1 mm in 2 contiguous leads. NSTEMI does not have ST elevation on EKG but has ST-T abnormalities with positive cardiac biomarkers, including troponins. Diagnosis of STEMI results in prompt activation of cardiac catheterization laboratory for procedure or a consideration of giving intravenous thrombolytics to all patients, without consideration to initial cardiac biomarkers that may be negative. In other words, in case of STEMI, the cardiac biomarkers are drawn, but the results are not acted on or waited for, as the biomarkers, in spite of all their sensitivity, tend to be negative in the first few hours. In cases of NSTEMI, the troponins are negative initially when drawn on early arrival with classic history of unstable angina with or without ECG changes in the form of ST depression or T-wave changes from baseline. In unstable angina, the ECG changes may be transient and troponins are negative. The biomarkers are, therefore, relied on and become positive after 4 to 6 hours of initial presentation of symptoms in cases of ACS, as more cases of unstable angina are now diagnosed with NSTEMI due to increased sensitivity of these troponin biomarkers.

Patients presenting with a poor history are usually taken through multiple blood tests that may also include troponins, which may be positive due to cardiac demand mismatch rather than ACS. It is these types of patients in whom troponin elevations must be viewed with caution. It is true that generally the presence of elevated biomarkers draws attention to definite myocardial injury and needs to be differentiated from ACS. Myocardial injury, without any history of chest pain, or an atypical presentation without ECG changes, cannot be truly defined as ACS. In such cases, other underlying causes for myocardial injury must be investigated. This review draws attention to these non-ACS causes of troponin elevation.

Troponins

Troponin is a regulatory protein complex that participates in muscle contraction between myosin and actin. It is found in cardiac and skeletal muscle, but not in smooth muscle. There are 3 different protein components—T, C, and I—of the troponin complex. Troponin T is located directly over the myosin-binding sites on the tropomyosin, which is wrapped around the actin thin filament. Troponin C binds to calcium and allows troponin T to expose the myosin-binding sites. Troponin I is an inhibitory protein that prevents calcium from binding troponin C. This troponin complex is the primary regulator of calcium-and adenosine triphosphate (ATP)-dependent myocardial contraction. When an action potential passes through the muscle, calcium channels are opened, releasing calcium from the sarcoplasmic reticulum into the sarcoplasm. Calcium then binds to troponin C, altering its shape and exposes the myosin-binding sites. Different types of muscle have their own unique troponin complexes, particularly the troponin C subunit. There are 3 calcium-binding sites on the troponin C subunit of cardiac myocytes, whereas there are 4 in skeletal muscle (Figure 1).

DETECTION OF TROPONINS

Troponins in the blood are detected by immunoassays that use cardiac troponin-specific antibodies and are quantified by the same immunoassay methods. The newest generation of assays testing for cardiac troponins is very sensitive in detecting trace levels of troponin in the blood. When cardiac myocyte injury occurs, cell

membrane is compromised, leading to the release of the intracellular proteins into the bloodstream. Troponin detection in the blood signifies a break in myocardial cell membrane integrity, not a coronary occlusion; the troponin leak may be due to demand mismatch. Hence, a troponin leak occurs due to break in the cell integrity due to other mechanisms as discussed later and not necessarily related to MI secondary to CAD. Cardiac troponin levels measured by immunoassay methods detect the troponin in the bloodstream but cannot define the mechanisms of heart muscle cell injury.

Noncardiac Causes of Troponin Release

Recent papers and studies have shown that noncoronary events and other noncardiac conditions, eg, end-stage renal disease, acute pulmonary embolism (PE), acute pericarditis, neurologic strokes, hypertensive crises, and sepsis have all led to release of troponin in the bloodstream that is readily detectable by laboratory testing.[1] Thus, cardiac troponin levels merely indicate the break of cardiac muscle cell membrane integrity or injury and do not necessarily point to the mechanism of myocardial damage. Hence, when a patient in an ED presents for a noncardiac reason, the patient's troponin level may be elevated due to other causes. While one would intuitively want to rule out cardiac etiology, it is equally important not to overlook the overall patient's clinical picture. A good history and physical examination that focuses on other conditions is important so that the patient's primary clinical diagnosis is not left untreated. In addition, putting emphasis only on a lab value of an elevated troponin may lead to increased hospitalizations and unnecessary cardiac testing when ACS is unlikely to be the cause of an isolated troponin elevation. Thus, as important as it is to not miss an ACS, it is equally important to recognize other causes of elevated troponin.

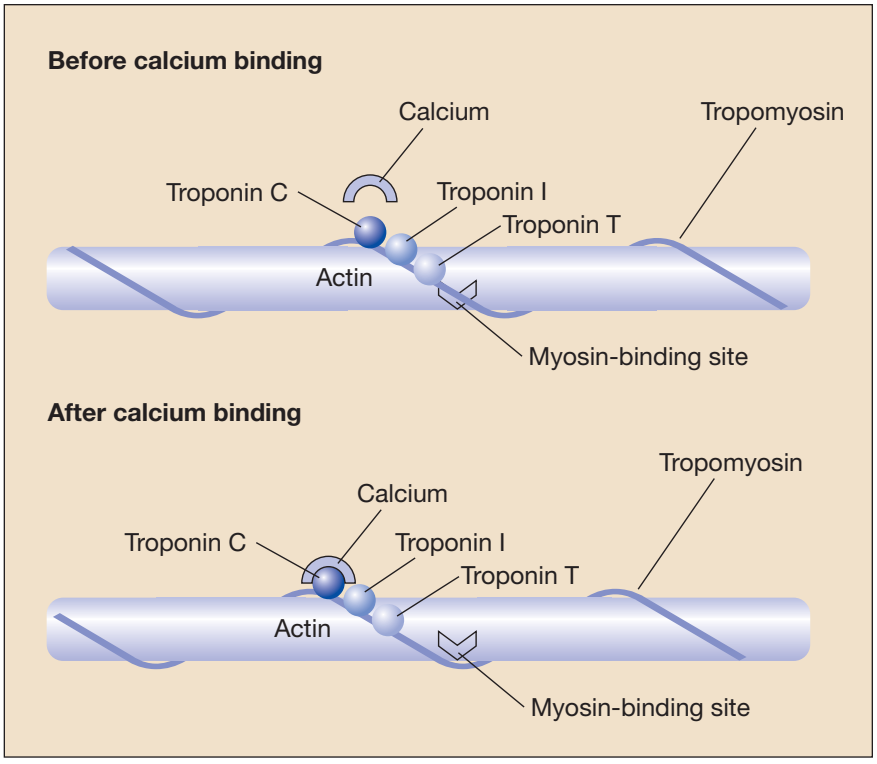

Figure 1. Intracellular proteins involved in muscle contraction before and after calcium binding.

Chest Discomfort as a Presenting Symptom

When a patient complains of chest discomfort, a suspicion of ACS is raised. The differential diagnosis, however, can range from a musculoskeletal pain to an acute MI, or may be a pain referred from a distant area, such as an abdominal organ. Cardiac enzyme levels are measured in these cases when suspicious. In addition, cardiac enzymes are also measured routinely in other atypical presentations that may be considered to be cardiac in origin, including loss of consciousness, dizziness, or dyspnea. This leads to a need for a list of differential diagnoses. In case of CAD, the suspicion for a coronary event is high when a patient has a documented history of CAD and presents with an atypical chest pain; however, the differential diagnoses are generally broad and include musculoskeletal pain, congestive heart failure (CHF) exacerbation, pulmonary event, chronic obstructive pulmonary disease (COPD) exacerbation, hypertensive urgency, infection, vascular event, central nervous system event, or even an abdominal event that need not be overlooked.

Table 1 is a brief summary of the different causes of cardiac troponin elevation, which include many non-ACS causes. There are several conditions that have detectable troponin in the bloodstream in the absence of

Table 1. Major differential diagnosis for cardiac troponin elevation[2]

Cardiac
Acute MI (STEMI, NSTEMI); Prinzmetal angina; CHF; acute aortic dissection; tachycardia; atrial fibrillation; inflammatory response (myocarditis, pericarditis, endocarditis); infiltrative disorders (sarcoidosis, amyloidosis, hemochromatosis); trauma; drug-induced heart failure (chemotherapy); iatrogenic event (cardioversion, surgery); coronary intervention; recent implantable cardioverter-defibrillator firing; hypertensive crisis

Pulmonary
Acute PE; respiratory distress; COPD

Neurovascular
Stroke; intracerebral hemorrhage; subarachnoid hemorrhage

Chronic
End-stage renal failure; hypertension (HTN); diabetes mellitus; hypothyroidism

Other
Sepsis; hypovolemia (dehydration, anemia); critically ill (ICU) patients

ACS or acute MI.[2] These are considered to be due to demand mismatch, myocardial cell irritation, infiltration of the myocardial cells, or direct trauma to the myocardial cell membrane. These conditions, when present, need to be recognized and dealt with when the presentation is somewhat atypical for a coronary event. These causes of troponin elevation have also been classified as MI.[3]

The ultimate interest in elevated troponin in a triage center or ED is not to miss a case that fits in the ACS spectrum that is a primary type of MI; and not a differential diagnosis or secondary types of MIs. Thus, an elevated troponin may steer a physician or a physician extender toward ACS and away from the patient's primary problem on presentation, leading to improper triage, further unwarranted cardiac investigations, and increased hospitalizations. In addition, there are several non-ACS causes that require immediate attention and if overlooked can lead to life-threatening situations.

NON-ACS CAUSES OF TROPONIN REQUIRING IMMEDIATE ATTENTION

There are a few important non-ACS causes of cardiac troponin elevation that require immediate attention and treatment:

Acute aortic dissection

Aortic dissections can present with chest discomfort and dyspnea, mimicking the symptoms of ACS. Although the quality or type of pain is different, most chest pain presentations in the ED are initially evaluated with an ECG, which is required by the standard of care guidelines to meet benchmarks for chest pain evaluation in the ED. Troponins are obtained for triage into possible low- and high-risk patients with chest pains. Those with elevated troponins are usually admitted to chest pain units or for care in coronary care units; the low-risk ones are triaged in the ED to observation units, if one is available, for early discharges. In cases of aortic dissection, the most significant risk is extension of dissection and bleeding, which can cause the blood pressure (BP) to drop and lead to poor perfusion to end organs and major morbidity or mortality. Aortic dissection may cause some coronary compromise, leading to troponin elevation, while increasing morbidity and mortality.[4] Chest X-rays done in the ED are often nondiagnostic.[5] In such cases, aggressive antiplatelet or antithrombotic therapy, which is the standard therapy in ACS, may be more harmful than beneficial.

Pulmonary embolism (PE)

Patients with a PE can present with chest pain, tachycardia, and diaphoresis. ECG and troponin levels are routinely checked in such cases. PE and other pulmonary-related diseases (eg, pulmonary hypertension, severe COPD exacerbation, pneumonia, etc) can cause strain on the right heart from increased pulmonary artery pressure, leading to a troponin leak.[6] Although some of these pulmonary conditions are severe enough to damage myocardial cells, treatment should be focused on the underlying pulmonary cause.

A handful of other medical conditions may present with an isolated elevation of troponin without other common signs associated with ACS.

Troponin leaks from supply-demand mismatch

The most common noncoronary cause of elevated troponin is demand ischemia. Demand ischemia, or increased demand from the cardiac cells, is not classified as an ACS. Common causes include tachycardia, hypovolemia, anemia, and HTN. These conditions are seen in patients with a multitude of systemic disorders, including renal failure, cardiomyopathies, infiltrative disorders, or systemic diseases, such as hypothy-

roidism, HTN, and diabetes mellitus, which may affect the diastolic properties of the ventricles.

Hypovolemia and anemia. The total blood volume nutrients and oxygen supply are decreased to meet the demand of the organs and circulatory area. This may lead to a decreased systemic BP as well as poor organ perfusion and oxygenation of vital tissues, including myocardial cells.[7] The body tries to compensate and keeps up with demand for nutrients and oxygen by increasing the heart rate to maintain cardiac output. By increasing the heart rate, the myocardial contractility increases, using more energy and, hence, requiring more oxygen.[8] Thus, the combination of decreased supply and increased demand causes a supply-demand mismatch of oxygen and other nutrients for myocardial tissue, leading to cell injury.

Tachycardia. Persistent tachycardia from numerous etiologies causes strain on the heart, resulting in a measurable troponin leak in the bloodstream. Common causes include pain, sympathetic overactivity, recreational drug use, or even abrupt drug withdrawal especially beta-blocking agents. In addition, patients with atrial fibrillation can present with a detectable troponin in the bloodstream, possibly also due to tachycardia-induced heart failure.[8,9] Any cause of tachycardia may lead to a measurable troponin in the bloodstream. Tachycardia is one of the most common causes of a troponin leak in patients who had a normal coronary angiogram.[8]

HTN. Poorly controlled HTN over time can lead to myocardial strain. This is mainly due to long-term effects of systemic HTN that include hypertrophy of the left ventricle, development of hypertensive cardiomyopathies, and remodeling of the myocardium. Left ventricular hypertrophy happens when the left ventricle works harder to pump blood into the systemic circulation and against the raised systemic resistance.[6] Thus, myocardial cells require more nutrients and oxygen and absence of adequate oxygenation and nutrients may lead to cell membrane damage. Hypertrophied myocardium with the same amount of supply of oxygen thus has to support higher demand when heart rate or BP rises. In some cases, this supply-demand mismatch can cause nonocclusive injury and ischemia of the myocardial cells with possibly detectable troponins in the bloodstream.

Detectable troponin due to pulmonary causes

The cardiac and pulmonary circulations are dependent on each other; changes in one can lead to an effect on the other as well. Pulmonary pathology influences the right-sided cardiac chambers, while the left chamber of the heart influences the pulmonary pathophysiology. COPD exacerbation leads to an increased risk of morbidity and mortality from cardiovascular conditions as COPD places increased burden on the right side of the heart secondary to changes in pulmonary artery pressures.[6] COPD exacerbations can lead to detectable troponins in the bloodstream. Studies have shown that patients with higher levels of cardiac troponins during a COPD exacerbation have a higher rate of mortality within 3 years.[10] Since patients with COPD exacerbations have similar symptoms to those who have ACS, such as chest pain and dyspnea as well as possibly ECG changes, it is, therefore, essential that these be differentiated, as the management strategy is different for each.

Troponin leaks due to neurogenic causes

Other causes of myocardial injury with the presence of detectable troponin in the bloodstream of note are neurogenic in nature. A stroke or any type of brain hemorrhage compromises the body's neurologic system to regulate normal autonomic function.[11,12] The heart rate and the cardiac conduction system are primarily regulated by the autonomic system; thus, changes in brain function affect cardiac function, leading to dysfunctional rates or rhythms.[12] These effects may lead to myocardial injury, causing detectable cardiac troponin levels. While a syncopal episode can be due to a brain injury or a direct cardiac injury, both however, can lead to troponin leak and need to be differentiated with further diagnostic testing.

Chronic elevation of troponins

In patients with chronic renal failure, cardiac troponin, specifically troponin T, is elevated at baseline and directly correlates with the severity of renal disease. The exact cause of this chronic elevation is not entirely understood.[13] Some explanations include a subclinical myocardial injury, an inflammatory response in renal failure, or a chronic volume overload. Chronic renal insufficiency may possibly cause microinfarcts in the myocardium, leading to low levels of troponin leaks.[14,15] Moreover, troponin T is considered to be elevated due to poor renal clearance in chronic renal insufficiency.[16] A few studies have shown that the baseline level of cardiac troponin in renal failure may be used to determine prognosis of disease progression and mortality.[17,18] Thus, when presented with an elevated troponin in a patient with renal failure, it is helpful to obtain serial troponin levels when a concern for ACS is raised. It is important to follow the trends of troponin to determine whether elevated troponin levels are in line with a chronically elevated

baseline, or whether such an elevation is caused by an insult or mechanism, such as ACS, where a typical rise and fall of the troponin in the bloodstream will be seen.

Sepsis and the ICU setting

Septic shock leads to systemic inflammation, which causes changes in the myocyte membrane permeability and may lead to a leak of cardiac troponin markers into the bloodstream.[19] Systemic inflammation and metabolic processes by itself may cause right and left ventricular dysfunction, which may lead to further myocyte injury.[20] This process is, however, reversible with resolution of sepsis. Thus, management includes maintaining systemic pressure and organ perfusion until sepsis resolves.[21]

Other conditions causing troponin elevations

Transient hypotension and limited ventricular reserve, as in cases of decompensated heart failure, lead to strain on the diseased myocardial cells and can result in troponin elevation.[22,23] As myocardial cells are already in a diseased state secondary to a chronic decrease in blood supply, they may have greater difficulty in maintaining the integrity of the cell membrane.

GUIDELINES FOR DIAGNOSING ACS

Troponin elevation is truly a marker for myocardial injury but not necessarily for diagnosing an episode of ACS or an acute MI. Guidelines on diagnosing an acute MI need to be followed and considered in all cases where there is a troponin rise and clinical evidence suggesting ACS.

In 2000, the European Society of Cardiology and American College of Cardiology published a consensus statement on the diagnosis of MI.[24] These criteria include a typical rise and gradual fall in troponin levels or a rapid rise and fall in creatinine kinase-muscle brain biomarkers with at least 1 of the following:

- Ischemic symptoms
- Development of pathologic Q waves on ECG
- ST segment changes on ECG
- Imaging evidence of new loss of myocardium or new wall motion abnormality

In 2007, the Joint Task Force of the European Society of Cardiology, the American College of Cardiology Foundation, the American Heart Association, and the World Health Organization again revised the criteria for an acute MI. In this update, an acute MI is defined as the death of cardiac myocytes secondary to ischemia.[1] Since cardiac troponin levels are sensitive enough to detect even minute injury to the myocardial tissue, the criteria for ACS and of MI take into account the amount of myocardial cell loss, circumstances leading up to the infarction, and the timing of observing the infarction leading to a differential classification.[24] The most up-to-date classification system for the causes of MI is described by Thygesen and colleagues in their article "Universal Definition of Myocardial Infarction," in the journal *Circulation* in 2007.[3]

Hence, a purist may classify cases of myocardial injury that occur from decreased supply of oxygen and nutrients to the cells, or increased demand from the cells itself, as type 2 MI. Thus, many of the non-ACS causes of troponin leak can be classified under a type 2 MI, whereas true ACS would be a type 1 MI. This classification system is now standardized and provides a better classification for MI than the previous traditional classification of STEMI vs NSTEMI. The underlying etiology of these type 2 infarctions needs to be treated, as some of these troponin leaks are due to increased demand or changes in cell permeability. Not treating the underlying conditions may lead to misdiagnosis and failure to treat the patient.

Patients with underlying chronic conditions (eg, CHF, COPD, and HTN) are prone to frequent troponin leaks with a slight rise in BP, heart rate, or blood volume. Such patients must be evaluated clinically and treated for their underlying conditions as well as CAD, if present. Troponin biomarkers are thus a sensitive marker for myocardial strain and damage and need to be used to rule *out* any myocardial damage, not ACS. Due to its high sensitivity, cardiac troponin levels are now used more as a test to rule out ACS than to rule it in.

CONCLUSION

Although it is important not to miss an ACS, it is equally important for physicians and other health care providers to determine the underlying cause of troponin elevation. It may not be related to ACS but to a condition that is causing myocardial strain, loss of cell integrity, and cell death. Proper clinical investigations through good history taking, physical examination, and diagnostic testing will assist in determining a reason for an isolated elevation of troponins in the bloodstream.

This review has highlighted some common scenarios that need to be considered when troponins are elevated. Diagnosing the underlying cause of troponin elevation helps in patients' treatments, affects quality of life, and avoids pitfalls and additional medical care costs. Troponin elevation is thus not an automatic diagnosis of ACS but an injury to cardiac cell from many causes, including ACS. By broadening our knowledge on conditions that cause elevated troponins and considering the different mechanisms by which cardiac troponin el-

evations can occur, we will improve the care of patients when confronted with elevated troponin.

Author disclosures

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