

Troponin elevation in conditions other than acute coronary syndromes

Asli Tanindi
Mustafa Cemri

Gazi University Faculty of Medicine,
Department of Cardiology, Ankara,
Turkey

Abstract: Acute coronary syndromes comprise a large spectrum of clinical conditions ranging from unstable angina pectoris to acute ST-elevation myocardial infarction. Chest pain is usually the major symptom of atherosclerotic heart disease; however, it may be challenging to diagnose correctly, especially in the emergency department, because of the ambiguous way that pain is characterized by some patients. Cardiac troponins are sensitive and specific biomarkers used in the diagnosis of myocardial infarction that are released into the bloodstream when cardiac myocytes are damaged by acute ischemia or any other mechanism. They are the cornerstone for the diagnosis, risk assessment, prognosis, and determination of antithrombotic and revascularization strategies. However, troponin elevation indicates the presence, not the mechanism, of myocardial injury. There are many clinical conditions other than myocardial infarction that cause troponin elevation; thus, the physician should be aware of the wide spectrum of disease states that may result in troponin elevation and have a clear understanding of the related pathophysiology to effectively make a differential diagnosis. This review focuses on causes of troponin elevation other than acute coronary syndromes.

Keywords: cardiac troponin, troponin elevation without acute coronary syndrome, differential diagnosis

Introduction

Acute coronary syndromes constitute a large spectrum of clinical conditions ranging from unstable angina pectoris to acute ST-elevation myocardial infarction. Chest pain is usually the major symptom of atherosclerotic heart disease; however, it may be challenging to diagnose correctly, especially in the emergency department, because of the ambiguous way that some patients characterize their pain. Cardiac serum markers, especially cardiac troponins (cTns), are the cornerstone of the diagnosis, risk assessment, prognosis, and determination of antithrombotic and revascularization strategies. Physicians should be aware of the wide spectrum of disease states that may result in elevation of cTns and have a clear understanding of the related pathophysiology to effectively make a differential diagnosis. This review focuses on causes of troponin elevation other than acute coronary syndromes. Pubmed Central and Cochrane Library were browsed for related topics.

Cardiac troponins consist of three proteins known as cTnC, cTnI, and cTnT¹ that interact with tropomyosin to form the troponin-tropomyosin complex. This complex forms the skeleton of the striated muscle and has a regulatory function in the excitation-contraction coupling of the heart. If heart muscle cells are damaged by acute ischemia or any other mechanism, these proteins are released into the bloodstream.

Correspondence: Asli Tanindi
Gazi University Hospital, Department
of Cardiology, 06500, Besevler, Ankara,
Turkey
Tel +90 312 202 5629
Fax +90 312 212 9012
Email aslitanindi@gmail.com

The European Society of Cardiology/American College of Cardiology Joint Committee has redefined myocardial infarction (MI) to be an elevation of serum cTn above the 99th percentile of the healthy reference population in the presence of ischemic signs and symptoms.² In addition, a rising and/or falling troponin pattern is an important component of the universal definition of MI. The major limitation of the standard cTn assays is their low sensitivity in the first few hours after MI at the time of the first presentation in the patient due to a delayed increase in the circulating levels of cTns. The diagnosis may take 6–12 hours of monitoring and serial blood sampling, which delays diagnosis and probably increases morbidity and mortality.³ To overcome this issue, highly sensitive cTn assays have been developed that can detect cTn levels well below the 99th percentile of the normal reference population.⁴ However, increased sensitivity comes at the cost of decreased specificity. Although the availability of highly sensitive assays allows for the earlier detection of MI, the number of patients with detectable cTn values in the emergency department or other in-hospital settings increases substantially as a result, which challenges the clinician to make a differential diagnosis. With these new assays in particular, nonischemic causes of troponin elevation should be kept in mind since troponin elevation indicates the presence, not the mechanism, of myocardial injury.

Noncardiac causes of troponin elevation

Chronic renal failure

Acute coronary syndromes are frequently observed in renal failure; however, the use of troponin for diagnosis is inconvenient since cTn levels may be elevated in the absence of an acute ischemic event.^{5–7} Mortality remains high in end-stage renal disease despite dialysis therapy; approximately 50% of these deaths are due to cardiac causes.^{8–10} Electrocardiography (ECG) may not be reliable in most of these patients because intraventricular conduction defects and left ventricular hypertrophy are very common. Troponins are commonly used as prognostic indicators in end-stage renal disease although troponins and creatinine kinase-myocardial band (CKMB) may show false positivity in this group as mentioned elsewhere.¹¹ In acute myocardial injury, slightly elevated troponin levels may be detected but creatinine kinase (CK) and CKMB levels remain in the reference range. This finding is due to the unbound fraction of troponins in the cytoplasm of the cardiac myocytes, which is approximately 6% of cTnT and 3% of cTnI.¹² Although it

remains to be proven, it is thought that the unbound fraction increases in renal failure.

Some animal experiments have shown that trauma and stress induce the cTnT isoform in skeletal muscle. It is speculated that chronic skeletal muscle damage and inflammation in dialysis patients induce cTnT in a similar way.^{13–15}

Heart failure is also a common comorbidity in renal failure, in which troponins increase without any evidence of ischemia or infarct.¹⁶

Decreased clearance is another proposed explanation for troponin elevation in renal failure;¹⁷ however, troponins are large macromolecules like CK, CKMB, and albumin that are cleared by the reticuloendothelial system. Recent studies suggest that cardiac troponins are fragmented into immunoactive particles of 8–25 kDa in length that are quite sensitive to immunoassays.¹⁸ Although these fragments are small enough to be cleared by healthy kidneys, renal impairment leads to clearance decrease. The healthy human heart is always prone to microloss of cardiac myocytes but, when renal failure is involved, clearance of troponin fragments due to routine myocyte loss is impaired.

In renal failure, cTnT elevation is seen more frequently than cTnI. cTnI is less stable in the blood and is more prone to chemical changes in addition to higher rates of clearance during dialysis; as a result, it is thought to have an advantage over cTnT in patients with renal impairment.¹⁹

Advanced heart failure

Patients with acute heart failure/acute pulmonary edema constitute an important proportion of emergency department admissions. Troponin levels may rise without overt ischemia in heart failure.^{20,21} This phenomenon was first reported by Missov and Calzolari.²² In another study by the same group, it was concluded that myocyte injury in the chronically damaged myocardium results in damage of the contractile proteins, which consequently causes protein leakage to the circulation.²³ Sato et al have reported dismal prognoses in patients with nonischemic heart failure with the highest percentile of admission cTnT levels, although they were treated with optimal medical therapy.²¹ This was associated with the ongoing subclinical myocardial damage within the subgroup with the highest admission cTnT levels. Troponin positivity was reported to be 10.4% and 92% using standard and highly sensitive cTnT assays, respectively, in 4053 chronic heart failure patients enrolled in the Valsartan Heart Failure Trial (Val-HeFT).²⁴ Many studies have reported that troponin can be used as predictor of mortality, especially when ultrasensitive assays are used.^{25,26}

Cerebrovascular accidents

Subarachnoid hemorrhage (SAH)

The cardiac effects of intracardiac bleeding were first defined in 1903 by Cushing as alterations in blood pressure and cardiac rhythm disturbances.²⁷ Electrocardiographic manifestations were first mentioned by Byer in 1947.²⁸ Several studies since then have shown the effects of hypothalamic stimulation on ECG and the cardiac rhythm in addition to the fact that myocardial injury was not mandatory for manifested electrocardiographic changes.²⁹ Earlier, it was believed that atherosclerotic coronary artery disease or coronary vasospasm was the basis of cardiac injury in subarachnoid bleeding, but this was not shown angiographically. Myocardial ischemia secondary to tachycardia and/or hypertension was the other proposed mechanism.

Today, the most widely accepted theory is the “catecholamine hypothesis.”³⁰ Several autopsy studies have revealed petechial subarachnoid bleeding sites and histologically dense eosinophilic transverse bands in the myocardium. This phenomenon is termed “contraction band necrosis” and is detected in both patients with electrocardiographic changes and those with completely normal ECGs. Similar lesions are also detectable in patients with pheochromocytoma or in animal experiments using stellate ganglion stimulation or catecholamine infusion.³¹ An increase in plasma catecholamines of up to 30× is possible, but it is uncertain whether myocardial necrosis is related to the plasma catecholamine increase or to the catecholamine surge that is locally stimulated by cardiac nerves. It is possible that acute brain injury results in a massive release of norepinephrine from the myocardial sympathetic nerve terminals to the myocardial interstitium, which may subsequently lead to myocyte necrosis and contractile dysfunction in addition to sympathetic nerve terminal damage.

The latest studies have reported the rate of cardiac injury markers as being 20%–40% in the presence of subarachnoid bleeding.^{30,32} Approximately 10% of these patients have reversible segmental wall motion abnormalities that fit the distribution pattern of the myocardial sympathetic nerve terminals rather than the pattern of coronary artery disease. The most severe form of myocardial injury involving elevated myocardial injury markers is “neurogenic cardiogenic shock”^{33,34} accompanied by pulmonary edema.

Among patients with aneurysmal SAH, the subgroup with higher Hunt–Hess scores, which are used to grade the bleeding severity, had higher troponin I levels.³⁵

In another study, it was reported that functional recovery of the aneurysmal SAH patients with higher troponin levels was poor, and the sequela rates were higher.³⁶ The authors conclude here that cTn also plays a role in predicting SAH prognosis.

Ischemic cerebrovascular accident

Studies investigating troponin release in the course of ischemic cerebrovascular disease have reported contradictory results in contrast to studies on cerebral hemorrhage. Troponin levels were found to be increased and had prognostic significance in some studies^{37,38} but not others.^{39,40} As a result, troponin cannot be reliably used as a prognostic indicator for ischemic cerebrovascular disease. The proposed mechanisms regarding troponin release in the early phase of ischemic cerebrovascular disease include secondary cardioembolic cerebral ischemia related to primary myocardial damage, secondary central nervous system activation to primary cerebral ischemia, and cerebral disease-related heart failure.

Acute pulmonary embolism

Acute massive or submassive pulmonary embolism is associated with elevated serum cTn levels.⁴¹ Rates of troponin positivity have been reported as 16%–47% in several studies, and troponin has been proposed as a risk determinant that may help in the decision of performing thrombolysis or embolectomy.^{42–44}

Massive pulmonary embolism may cause cardiogenic shock and acute right ventricular dilatation. The sudden increase in oxygen demand of the right ventricle, increase in right ventricle intramural pressure, decrease in cardiac output, and release of endothelial mediators such as thromboxane, serotonin, and endothelin contribute to right ventricular ischemia and damage.^{45,46}

Chronic obstructive pulmonary disease (COPD)

Cardiovascular risk factors and cardiac comorbidity are frequent in patients with COPD. Troponin elevation was found to be an independent predictor of the need for noninvasive mechanical ventilation and mortality in patients who were admitted with acute exacerbation of COPD.^{47–49} The amount of energy and oxygen needed for respiration is increased in the acute exacerbation period; in addition, the left ventricular afterload is increased in relation with more negative intrathoracic pressure. Worsened pulmonary hypertension, hypoxia, and hypercapnia also contribute to myocardial damage during the acute exacerbation period.

Acute noncardiac critical illness

The term “critically ill patient” refers to individuals who are hospitalized in intensive care units, patients who are typically elderly with multiple comorbid illnesses.⁵⁰ However, some fragile older patients, who live alone or in nursing homes and are referred to emergency departments and subsequently hospitalized, may also be included in this category.

Studies of intensive-care-unit patients report that troponin is elevated in patients with increased myocardial demand due to multiple comorbid conditions, positive end expiration therapy, the need for inotropic support, or high body temperature; these patients typically have higher morbidity and mortality rates.^{51,52} Hypotension, anemia, and microocclusion impair oxygenation. Increased myocardial oxygen demand, increased wall tension, hypertension, tachycardia, pulmonary embolism, or the presence of myocardial toxins in sepsis can cause minor myocardial damage. Troponin can be temporally elevated in some situations, a finding that is related to increased membrane permeability.⁵³ The myocardial depressing factors released in sepsis and other inflammatory conditions cause troponin to be fragmented into low molecular weight particles in situ. These fragments are secreted into the circulation in the presence of increased membrane permeability. Since there is no necrosis, the myocyte damage is not permanent. Myocardial depression is completely reversible in patients who recover from sepsis.

Strenuous exercise

Competitive endurance sports have been suggested to be associated with elevations in cardiac biomarkers, especially cTns. Different human studies in the literature have reported a wide range of rates for troponin elevation, up to as much as 78%.⁵⁴ Use of different generation assays with different cutoffs is the probable cause of this wide range of results. The pathophysiology and probable clinical impact of cTn elevation have been addressed in many studies, but a consensus does not exist. Middleton et al suggested that the increased myocardial demand related to endurance exercise could physiologically increase the turnover of cardiac troponins.⁵⁵ Another proposal was that stress induces free radical overload, which causes a transient increase in membrane permeability and leads to troponin leakage from the cytosol.⁵⁶ A recent rat study supported this hypothesis in that it was shown that the temporal change in serum cTn was matched by an increase in the concentration of myocardial malondialdehyde, a marker of free radical-related lipid peroxidation.⁵⁷ Exercise-induced dehydration, hemoconcentration, and

altered acid–base balance were also reported to be associated with this increased membrane permeability.⁵⁸ Hickman et al suggested that transient ischemia induced the development of blebs on the cytoplasmic membrane, leading to cTn release.⁵⁹ Whatever the mechanism, the kinetics of the asymptomatic cTn release after intense exercise with an early peak and quick normalization is quite different from the elevation pattern observed in acute coronary syndromes.⁶⁰ Exercise duration, exercise intensity, and running distance were the suggested risk factors for cTn elevation,^{61,62} however, it was shown that running even a short distance could result in significant cTn release in untrained individuals.⁶³ Troponin elevation was not found to be associated with any functional impairment using either echocardiography or cardiac magnetic resonance imaging.^{64–66} In light of the current knowledge, there seems to be no prognostic implication of troponin elevation.

Direct myocardial trauma

Direct cardiac trauma may cause troponin elevation due to the impairment of cardiac myocyte integrity. Velhamos et al enrolled 333 patients with direct myocardial contusions to examine the predictive value of troponin levels.⁶⁷ Serial evaluation of ECG and troponin measurements and selective echocardiographic examination revealed that the combined use of ECG and cTnT had a negative predictive value of 100% for blunt cardiac trauma, whereas cTnI alone had a negative predictive value of 94%.

Cardiac causes of troponin elevation other than acute coronary syndromes

Acute pericarditis

Although troponins are not found in the pericardium, they may be elevated because of the involvement of the epicardium in the inflammatory process.^{68,69} In addition, some myocardial damage may take place, and the pattern of troponin release in acute pericarditis mimics that of acute coronary syndromes. One should also keep in mind that these two conditions may coexist, meaning that troponins cannot be used for the differential diagnosis of acute coronary syndrome and acute pericarditis.⁷⁰ In contrast to acute coronary syndromes, troponin positivity was not associated with poor prognosis.

Acute inflammatory myocarditis

Acute myocarditis may mimic MI since chest pain, segmental wall motion abnormalities, and myocardial necrosis proven

by troponin elevation exist in both conditions.^{71,72} Smith et al reported the rate of troponin positivity as being 34% in a study population with biopsy-proven myocarditis.⁷³ It has also been found that troponin is more sensitive than CKMB and correlates well with the symptoms of heart failure at 1 month after acute myocarditis. How long the troponins remain elevated depends on the inflammation severity.

Tachycardia

Supraventricular or ventricular tachycardia, atrial fibrillation with high ventricular response, or any other tachycardia may cause troponin elevation by increasing the myocardial oxygen demand without epicardial coronary stenosis. Temporal myocyte damage due to hemodynamic compromise is the mechanism responsible for this phenomenon.^{74,75}

Elective cardioversion, using direct current shocks of up to 1370 V, was not associated with significant troponin increase.⁷⁶ However, multiple shocks for ventricular fibrillation during cardiopulmonary resuscitation raise serum troponin levels, which makes non-ST-elevation myocardial infarction diagnoses difficult.⁷⁷

False-positive troponin elevation

Troponin measurements are rarely prone to false-positive elevation in the absence of cardiac or noncardiac reasons. Fibrin in the specimens or endogenous antibodies interfering with the immunoassays are the most frequent causes.⁷⁸ Endogenous antibodies include rheumatoid factor or heterophilic antibodies, which develop against animal immunoglobulins. Frequent contact with animals, injection of animal antibodies for some imaging and treatment procedures, immunotherapies, vaccinations, and blood transfusions may cause the production of interfering antibodies in the circulation.⁷⁹ To prevent interference, use of ultracentrifugation is proposed, which has been reported to satisfactorily decrease the rate of false-positive results.⁷⁸ Other strategies include dilution, use of heterophilic blocking tubes, use of immunoglobulin-inhibiting reagents, or precipitation with polyethylene glycol.⁷⁹ Modern immunoassays have been developed through the addition of nonspecific blocking antibodies to prevent interference; regardless, there may still be patients whose conditions exceed the blocking capacity of these immunoassays.⁸⁰

Conclusion

Although cardiac troponins have been accepted as the gold standard in the diagnosis and risk stratification of acute coronary syndromes, misinterpretation of detectable troponin

levels in the emergency department or other in-hospital settings may lead to confusion in terms of diagnosis and choice of suitable therapy options. Physicians should be aware of the nonischemic causes of troponin positivity as well as their pathophysiology and clinical impact in an effort to prevent unnecessary invasive and noninvasive treatments and coronary care unit admissions.

Disclosure

The authors report no conflicts of interest in this work.

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