

A review of cardiac and non-cardiac causes of troponin elevation and clinical relevance part i: cardiac causes

Abstract

Cardiac troponin elevation is found in numerous clinical conditions. The relevance of Cardiac troponin elevation in many patients tends to point towards poorer prognosis with few exceptions such as physical exercise and pericarditis. In the year 2007, a consensus statement from the Joint European Society of Cardiology and The American College of Cardiology committees redefined myocardial infarction (MI) as an elevation of cardiac troponin T (cTnT) or I (cTnI) in conjunction with clinical evidence of myocardial ischemia. Since then, cardiac troponins have been the pivotal marker for acute MI; still, the presence of a positive troponin occurs in several other conditions. It is even more challenging to determine the real significance of cardiac troponin elevation in this era of high sensitive assays which can detect mild increases in troponin levels. A thorough history and physical examination is indispensable to appropriately diagnose the cause of elevated troponin, especially if it is a mild elevation. This manuscript reviews the cardiac and non-cardiac clinical conditions in which cardiac troponin levels are an important factor in patient care.

Keywords: cardiac troponins, myocardial infarction, pericarditis, myocarditis, cardiac infiltrative disease, takotsubo

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Introduction

Cardiac troponin T (cTnT) and troponin I (cTnI) are cardiac regulatory proteins that control the calcium mediated interaction between actin and myosin.¹ The troponin complex consists of three subunits: troponin C, troponin I, and troponin T. This complex is located on the myofibrillar thin (actin) filament of striated (skeletal and cardiac) muscle. The cardiac isoforms troponin T and I are only expressed in cardiac muscle.¹

In the year 2007 a consensus statement from the Joint European Society of Cardiology and The American College of Cardiology committees redefined myocardial infarction (MI) as an elevation of cTnT or cTnI in conjunction with clinical evidence of myocardial ischemia.² They recommended high-sensitivity cardiac troponin assays to rule out MI using a 3-hour pathway based on the 99th percentile of the normal reference range.² Cardiac troponins are detected in the serum by the use of monoclonal antibodies to epitopes of cTnI and cTnT. These antibodies are highly specific for cardiac troponin but do not react with skeletal muscle troponins.^{3,4} Troponin assays are quite sensitive and can detect <1 g of myocardial necrosis; therefore, the diagnosis of myocardial infarction requires that cTn must be above the 99th percentile upper reference limit for the specific assay being used.⁵ Some studies have reported that the 99th percentile reference limit differs between men and women when measured with high-sensitivity assays for cardiac troponin.⁶

An elevation of cTn indicates the presence of, but not the underlying reason for, myocardial injury. Elevated troponins have been noted in several clinical conditions in addition to acute myocardial infarction (AMI). These conditions include pulmonary embolism, sepsis, heart failure, myocarditis, myocardial contusion, critical illness, cardio-toxic chemo, defibrillator shocks, atrial fibrillation, and end stage renal disease. Elevated cTnT and cTnI almost always imply a poor prognosis regardless of the mechanism by which troponins were released from cardiac myocytes into circulation. Ottani et al. found

that the odds ratio for death and MI was 3.44-fold at 30 days in the cTnT-positive group compared to patients with unstable angina who did not have elevated troponins.⁷

The aim of this article is to highlight different conditions in which elevated troponins have been commonly noted, and to discuss the suggested mechanisms for elevated troponins in these patients. It is still unclear how to manage troponin elevation in clinical conditions other than AMI, but it is important to note the differential diagnosis for elevated troponins and the clinical significance of troponin elevation in each setting. Troponin elevation reflects acute or chronic myocardial damage but is not exclusive for ACS, thus causing some problems with interpretation of results. Differentiating elevated troponins due to non-coronary diseases is challenging; however, this differentiation is paramount in order to provide timely and appropriate treatment. This is a two-part article - the first section addresses elevated troponins due to cardiac pathology and the second section addresses non-cardiac etiologies.

Acute coronary syndrome

Elevated cardiac troponins are a necessary factor in diagnosing AMI. In 2007, The Joint European Society of Cardiology (ESC), the American College of Cardiology Foundation (ACCF), American Heart Association (AHA) and the World Heart Federation (WHF), redefined spontaneous MI diagnosis to include myocardial ischemic symptoms in addition to a troponin elevation above the 99th percentile, with a variation coefficient of <10%, in an apparently healthy adult population.⁸ This definition led to clinicians diagnosing MI in a patient population with the entire spectrum of acute coronary syndrome (ACS), and subsequently the prevalence increased by 25 percent. The World Health Organization requires two of the three following criteria to make the diagnosis of AMI: chest pain suggestive of cardiac disease, an electrocardiogram (EKG) with characteristic changes consistent with myocardial ischemia, and elevated cardiac enzymes in a pattern consistent with AMI.⁹ In addition, supportive

data including EKG, echocardiogram, or clinical picture should assist with guiding the diagnosis.¹⁰ The American Heart Association/American College of Cardiology guidelines for the diagnosis of non-ST elevation myocardial infarction (NSTEMI) recommends obtaining a 2nd troponin 6 hours after the first to confirm the diagnosis as the rise and fall of troponin levels are an important component in confirming the diagnosis.¹⁰ The term ACS includes unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI). The pathophysiology underlying ACS is atherosclerotic plaque rupture which leads to myocardial ischemia, and, if prolonged, infarction can occur. The three components of ACS can further be distinguished based on troponin elevations and electrocardiogram (EKG) changes. Cardiac enzymes are elevated in NSTEMI, but not UA. ST elevations on EKG are seen in STEMI, but not in NSTEMIs.¹¹

The pathophysiology of the troponin elevation that occurs during myocardial infarction stems from the fact that cardiac troponins are regulatory proteins that ensure the proper contraction of cardiomyocytes. They control the calcium mediated interaction of actin and myosin. The troponin complex consists of three components: troponin T, troponin I and troponin C. Troponin C is not used in clinical assays because it is found in both smooth and skeletal muscle, and is not detected by the current assay used for detecting cTnI and cTnT.^{9,12} When myocardial injury occurs, troponin is rapidly released from its loose attachments to myofibrils.¹⁰ The treatment for patients experiencing myocardial infarction is reperfusion via thrombolytic therapy or percutaneous coronary intervention. The ESC, ACCF, AHA, and WHF defined five different clinical classes of MI as shown in Table 1.

Table 1 Joint ESC, ACCF, AHA and WHF task force clinical classification of MI.⁸

Type 1	Spontaneous myocardial infarction (MI) related to ischemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2	Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension
Type 3	Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a	Myocardial infarction associated with PCI
Type 4b	Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5	Myocardial infarction associated with CABG

Demand ischemia

Also known as type 2 MI, demand ischemia occurs when there is an imbalance between myocardial oxygen demand and cardiac blood supply.^{2,13} This disparity causes lack of sufficient oxygen delivery to the myocytes leading to injury and necrosis and subsequent troponin release. Examples of type 2 infarction include coronary artery spasm or embolism, arrhythmias, severe anemia, and extreme high or low blood pressures. The mechanism for troponin release is ischemic in nature, despite it not being true ACS, or type 1 MI (due to plaque rupture). It tends to occur in patients with known CAD.^{2,14} Many practitioners confuse this type of MI with non-ischemic myocardial injury and necrosis which can be caused by various mechanisms. Examples of these non-ischemic etiologies include cytokine release,

catecholamines, and severe electrolyte imbalance which occur in the setting of other cardiac stressors such as tachycardia, hypotension, and renal failure.² Of course, patients may be at risk for developing more than one type of MI, making identifying the exact mechanism in any specific patient very difficult. For example, there is a general concern for type 1 MI in peri-operative patients with known CAD; however, type 2 MIs are just as commonly noted on autopsy.¹⁴ In the early post-operative period, the imbalance between oxygen supply and demand predominates, likely due to peri-procedural hypotension and platelet activation. Plaque rupture type 1 MIs occur randomly anytime post-operatively. Causes of both type 2 MI and non-ischemic necrosis will be discussed in other sections in this article.

Congestive heart failure

The value of troponin measurement in patients presenting with acute heart failure exacerbation has been controversial in the past; however, the evidence of its prognostic benefit has been demonstrated by numerous studies and is now common knowledge.¹⁵⁻³⁹ In acute exacerbation, an elevated troponin has been shown to be associated with increased inpatient mortality, and the association holds true when looking at the troponin as a continuous variable; the higher the troponin, the higher the mortality, regardless of whether or not the heart failure is due to ischemia.^{40,41} For patients following up in outpatient with chronic heart failure, a troponin level can also be helpful to identify patients at higher risk for adverse events. Van Boven et al.⁴² showed that troponin elevation in patients with chronic heart failure, either preserved or reduced ejection fraction, is associated with NYHA class, making it a more objective way to monitor patients at risk for adverse outcomes.⁴² Another study noted that a troponin level checked one month after an admission for acute systolic heart failure, rather than troponin during the admission, was predictive of 12-month mortality, mainly due to an association with CAD.²² The trend holds for even longer outpatient follow up; Thawabi et al.⁴³ showed that troponin elevation is an independent predictor of mortality in patients with preserved ejection fraction up to 2 years later.⁴³ With new highly sensitive assays available, it was uncertain if the troponin would retain prognostic value at the lower positive range, but studies have shown that it continues to be important indicator of adverse outcomes.^{18,28,29,38} Studies have developed different risk stratification models that may become helpful in clinical practice.^{16,25,33,36,42} Overall, monitoring troponin levels in patients with systolic or diastolic heart failure may alert clinicians to patients who might benefit from more aggressive monitoring and treatment.

While some patients will have elevated troponin due to subendocardial ischemia, oxygen supply and demand mismatch or a type 2 MI, others will develop myocyte necrosis due to non-ischemic causes. One possible mechanism for this injury includes adrenergic stimulation via various sources including renin, angiotensin, endothelin, or aldosterone. Abnormal calcium metabolism, inflammatory cytokines, and nitric oxide have also been implicated in myocardial damage as well as both mechanical and oxidative stress.⁴⁰

Aortic dissection

Acute aortic dissection has an incidence of 2.6-3.6 cases per 100,000/year.⁴⁴ Aortic and coronary dissections are associated with micro infarctions which can lead to troponin elevations. The mechanism for troponin release in coronary artery dissection is myocardial hypoxia from impaired blood flow and oxygen delivery, leading to cardiac tissue injury.⁹ Aortic dissections may have alternative etiologies to explain the troponin elevation. Vrsalovic et al.⁴⁵ postulated that elevated troponins in acute aortic dissection (AAD)

may be due to demand ischemia from decreased blood pressure and aortic regurgitation, or intimal flap covering coronary ostia.⁴⁵ There are few studies that have identified the prognostic role of elevated troponins in the setting of AAD. Bonnefy et al.⁴⁶ studied a group of 28 patients with type A aortic dissection with an elevated troponin and found that an elevated troponin may be an indicator of increased hemodynamic stress, but in multivariate analysis, it did not increase overall mortality.^{46,47} Vrsalovic et al.⁴⁵ completed a systemic review and meta-analysis of 4 studies to evaluate the role of elevated cardiac troponins in AAD. The study found that an elevation in the cardiac troponin at the time of admission was associated with an increased risk of in-hospital mortality. Elevated troponins in a patient presenting with an AAD may be at higher risk for poorer outcomes, but further studies need to be completed to determine the true prognostic role for troponin elevation in this setting.⁴⁵

Arrhythmias

Tachyarrhythmias such as atrial fibrillation and atrial flutter can cause elevated troponins in the absence of significant coronary artery disease or microcirculatory dysfunction. Atrial fibrillation is the most common tachyarrhythmia, effecting about 25% of subjects aged 40 years and older.⁴⁷ The elevation in troponin occurs because of a mismatch between oxygen demand and supply. The escalated heart rate increases myocardial oxygen demand while decreasing myocardial oxygen supply by shortening diastolic time.⁹ The shortened diastolic phase reduces the time for myocardial perfusion, a majority of which occurs during diastole. Bakshi et al.¹² noted that tachycardia was the cause of elevated troponins in 28% of patients without coronary artery disease as determined by lack of obstructive disease on left heart catheterization.^{12,49} Alghamy et al.⁵⁰ investigated the predictive value of elevated cTnI for severe coronary artery disease (sCAD) in patients presenting with atrial fibrillation (afib). They conducted a retrospective case-control study and found that troponin elevation above the 99th percentile cut-off did not predict sCAD; however, elevated cTnI was a strong indicator of sCAD especially if it exceeded 2.1 micrograms per liter.⁵⁰ Tachyarrhythmias should be considered a possible etiology of elevated troponins in patients presenting with elevated cardiac troponins who do not have ischemic risk factors or a clinical picture consistent with AMI. Though a numerical cut off has not been established, peak troponin levels may indicate the presence of sCAD.

Cardiac ablation

Electrical damage causes stunning of the cardiac muscle.⁹ Radiofrequency (RF) catheter ablations are used for the interventional treatment of afib, atrial flutter, and ventricular tachycardias (VT). RF ablation causes cardiac tissue damage by introducing thermal energy to the tissue with an ablation catheter. An increase in cardiac markers occurs due to cardiac necrosis that happens during the procedure.⁵¹ The cardiac troponin levels for both groups were comparable to those of ST-elevation myocardial infarction (STEMI) patients.⁵² Reichlin et al.⁵² aimed to assess the kinetics of cardiac troponin release following ventricular and atrial ablation. The study included 19 patients undergoing VT ablation and 24 undergoing first time ablation for paroxysmal afib. The study revealed that troponin levels rose faster in patients undergoing VT ablation when compared to afib ablation, but similar levels were observed after 24 hours. The troponin levels correlated with the total RF time for afib, but not VT ablations. The article postulates reasons for faster rise in troponin after VT ablation could be due to the following: the ventricular wall is thicker than the atrial wall thus lesions are likely to cause greater myocardial injury, the ventricle receives a greater blood supply than the atria

(95% compared to 5%), and VT is introduced, even if only briefly, in patients undergoing VT ablation. Also, pathophysiological differences in lesion formation in the atria and ventricles may contribute to these troponin observations.⁵² Clinically, it is important for clinicians to note that elevations in troponins are expected after cardiac ablation. Ablation-related injury must be considered when using troponins to evaluate post-procedural chest pain.

Cardiac contusion

Blunt cardiac injury (BCI) is a rare but serious finding in blunt thoracic trauma. The incidence of myocardial contusion in patients with chest trauma ranges between 3%-56%.⁵³ Troponin elevations can occur in response to blunt trauma by causing direct myocardial injury. There are no definitive diagnostic criteria available which makes diagnosis of BCI difficult.^{54,55} The diagnosis is typically made if abnormal electrocardiogram, abnormal echocardiogram, and/or elevated troponin levels are present in a patient who presents with blunt thoracic trauma. A retrospective cohort study by Joseph et al attempted to assess the predictors of mortality in BCI patients. It found that when comparing survivors and non-survivors, the non-survivors were more likely to have an elevated cTnI and higher mean level of troponin. That same study stated that a troponin level of greater than 0.2 was significantly more common in the non-survivor group and was found to be a predictor of mortality.⁵⁵ Velmahos et al.⁵⁶ studied 333 patients with thoracic trauma and noted the negative predictive value of cardiac troponins was 21% and the positive predictive value was 94%. This same study concluded that normal electrocardiogram and normal cTnI on admission and 8 hours later can rule out significant BCI.^{54,56} A prospective study by Bertinchant aimed to determine if cardiac troponins would improve the ability to detect myocardial contusion in stable patients with blunt chest trauma in comparison to conventional markers. It was conducted over 18 months and included 26 patients diagnosed with myocardial contusion. It found that cTnI and cTnT improved specificity in diagnosing myocardial contusion.⁵⁷ Rajan et al.⁵⁸ found that higher troponin I levels were associated with severe arrhythmias and damage to the myocardium. He studied 63 individuals diagnosed with myocardial contusion. The patients were analyzed as two groups: symptomatic and non-symptomatic patients. The level of troponins in the symptomatic group remained elevated longer than those with no abnor. In this same study, LV dysfunction inversely correlated with TnI levels.⁵⁸ Though diagnostic criteria for BCI remains elusive, troponin I does have a prognostic role when assessing the severity of myocardial contusion.

Cardiac infiltrative disorders

Infiltrative cardiomyopathies are characterized by the deposition of abnormal substances in the myocardium, causing the ventricular walls to become progressively rigid, thereby impeding ventricular filling. Some infiltrative cardiac diseases increase ventricular wall thickness, while others cause chamber enlargement with secondary wall thinning. Increased wall thickness, small ventricular volume, and occasional dynamic left ventricular outflow obstruction can outwardly appear similar to conditions with true myocyte hypertrophy. Likewise, infiltrative disease that presents with a dilated left ventricle with global or regional wall motion abnormalities and aneurysm formation such as sarcoidosis may mimic ischemic cardiomyopathy.⁵⁹ Cardiac amyloidosis is characterized by heart failure with reduced or normal ejection fraction (EF), ventricular hypertrophy, and atrial enlargement. It occurs when beta amyloid deposits within the heart leads to cardiomyocyte separation, cellular toxicity, apoptosis, and tissue stiffness.²⁸ The diagnosis is typically made with cardiac MRI, but right ventricular biopsy that demonstrates positive Congo

Red staining is the gold standard.^{60,61} Cardiac amyloidosis is a primarily restrictive cardiomyopathy that is characterized by diastolic dysfunction that progresses to biventricular systolic heart failure and can be associated arrhythmias.^{61,62} Angina may develop due to small vessel involvement in the heart.³⁰ The mechanism for elevated troponin levels associated with infiltrative disorders is unclear but may be due to myocyte compression injury from extracellular deposition of the amyloid plaque.¹² A case study by Dispenzieri et al.⁶³ determined that troponins were better predictors of survival in patients with cardiac amyloidosis than EKG and symptoms. The median survival was 6-8 months in patients with detectable troponin levels compared with 22 months for those with an undetectable level.³¹ This finding suggests that elevated troponin levels may be a poor prognostic indicator in patients with cardiac amyloidosis.⁶³

Cardiac sarcoidosis is a granulomatous disease which affects the basal septum, atrioventricular node, atrioventricular (His) bundle, focal regions in the ventricular free walls, and the papillary muscles. These lesions lead to wall thickening (>13 mm) due to granulomatous expansion and wall thinning (<7 mm) due to fibrosis. Aneurysms may develop, especially if the patient has been treated with corticosteroids. Kandolin et al.⁶⁴ performed a retrospective multicenter study to determine the usefulness of cTn in monitoring disease response to steroids in patients with CS. They measured the levels of troponin at the initial diagnosis of cardiac sarcoid and remeasured the levels 4 weeks after steroid treatment, they found that troponin levels decreased after treatment. Though additional data is needed this study suggest that monitoring troponin may be helpful in determining disease activity in patients on immunosuppressive agents?⁶⁴ Hs-cTnT is considered to be a reliable parameter for evaluating the activity of cardiac sarcoidosis. It has a sensitivity of 87.5% and specificity of 75.0%, positive predictive value (PPV) of 87.5% and negative predictive value (NPV) of 75.0%. Furthermore, hs-cTnT levels decreased after steroid therapy in some patients.⁶⁵

Anderson Fabry disease is caused by an X linked inherited deficiency of lysosomal alpha galactosidase. The absence of this enzyme causes excessive accumulation of globotriaosylceramide.^{66,67} Myocardial deposits of globotriaosylceramide causes myocyte hypertrophy, scarring and deterioration of left ventricular function, these factors, in combination with the proliferation of smooth muscle endothelial cells, cause increased coronary vascular resistance and increased oxygen demand.⁶⁶ Seydelmann and colleagues found that cTn levels correlated with the amount of replacement fibrosis in patients with Anderson Fabry disease.⁶⁷

Defibrillator shocks

Troponin elevation occurs in the majority of patients after inappropriate ICD discharges secondary to lead fracture. This indicates that ICD shocks can cause myocardial injury. A large proportion of patients with multiple ICD shocks have cTnI elevation, and these patients have a higher risk of death or hospitalization due to heart failure.⁶⁸ Some studies have shown that up to 62% of patients have elevated troponins 12 hours after a shock. Miranda et al.⁶⁸ revealed that patients with cTnI elevation after multiple ICD shocks had higher risk of death or heart failure hospitalization (hazard ratio, 7.0; 95% confidence interval, 1.2-16.0; P =.03) compared with patients without elevation of this biomarker.⁶⁸ Blandea et al.⁶⁹ in a prospective observational study of 174 patients (mean (SD) age 68 (12) years, 32 women) who received spontaneous (n=66) or induced (n=108) ICD discharges found that elevation of cTnT after ICD discharge, even when it occurs after device testing, is a risk factor for mortality that is independent of other clinical factors that predict survival in

such patients.⁶⁹ The shocks may be an epiphenomenon or marker of underlying disease progression; however, it cannot be excluded that shocks cause direct myocardial damage. Implantation of ICD leads has been associated with release of troponin, but there is no clear evidence that ICD shocks alone cause myocardial injury. In fact, Guy et al.⁷⁰ studied 32 patients who underwent a total of 34 procedures and found that implantable cardioverter defibrillator implantation and testing is associated with release of cardiac troponin and is correlated to the number of ventricular lead deployments during the procedure. Secondly, they also noted that implantable cardioverter defibrillator testing conducted as a stand-alone procedure does not result in the release of cardiac troponin.⁷⁰

Heart transplant

Evidence is starting to suggest that heart transplant patients, similar to heart failure patients, may benefit from troponin monitoring for prognostic reasons as well. Studies have shown that transplant patients with elevated troponin on follow-up have higher risk of mortality and other cardiac events.^{71,72} In addition to transplant rejection and vasculopathy, infection, and myocarditis, patients can also develop CAD causing demand ischemia or a type 1 (plaque rupture) MI.⁷¹ These patients were also more likely to have prior CAD, increased left ventricular mass, elevated body mass index, poorer renal function, and heart failure post-transplant.⁷² The mechanism for the increased myocyte injury and necrosis, similar to heart failure, can be type 2 demand ischemia or non-ischemic. Careful attention to the patient's symptoms and objective findings such as blood that includes a troponin is an important aspect to post-transplant care.

Open heart surgery

As noted in other sections in this article, elevated troponin levels frequently portend poor prognosis for patients, and cardiac surgery is no different. In the post-operative period following on-pump cardiac surgery (valve replacement or repair, coronary artery bypass graft, or both), the trend in troponin from first to second post-operative day is an important indicator of 12-month mortality from any cause.⁷³ Presumably, trending beyond the first day mitigates the procedure-related myocyte injury and indicates necrosis related to outside factors that contribute to the higher mortality. Paparella et al.⁷⁴ notes different troponin cutoff values to separate higher and lower risk patients depending on what type of valvular procedure the patient completed. The cutoffs are beneficial in risk stratification as different surgeries themselves cause different levels of myocyte injury.⁷⁴ A meta-analysis noted elevated troponin levels short- and mid-term mortality as well as the 12-month mortality noted above; however, the exact timing of troponin testing has yet to be confirmed.⁷⁵

Pericarditis/myocarditis

Myocarditis is an example of non-ischemic myocyte necrosis and injury. It is on the same spectrum of disease as pericarditis, but since the pericardium is electrically neutral and does not contain myocytes (or subsequently troponin), pericarditis alone, without any myocardial involvement, will not lead to elevated troponin levels. As they are related, they can be caused by the same infectious or noninfectious etiologies including multiple viruses, tuberculosis, inflammatory bowel disease, and connective tissue diseases.⁷⁶ In many patients, a diagnosis cannot be found and the etiology is determined to be idiopathic.

Typically, pericarditis and myocarditis are both diagnosed based on history, physical exam, EKG, and echocardiogram. Classically, patients will present with pleuritic chest pain that worsens when

the patient is supine, EKG with PR depressions and diffuse ST elevation, a pericardial rub, and new pleural effusion. Patients with EKG abnormalities are more likely to have higher troponin levels than normal EKG counterparts.⁷⁷ This finding suggests an association between the myocyte damage causing both troponin release and electrical abnormalities. Interestingly, myopericarditis and elevated troponin is more likely to be found in male patients than females.^{76,78} The reason for this male predominance is unclear, but is likely related to hormonal differences considering there is an increase in myocarditis in females of post-menopausal age when estrogen levels are low.

Unlike other etiologies of troponin elevation, an elevated troponin level and myocardial involvement in pericarditis does not portend a worse prognosis. In fact, not only was troponin elevation not associated with increased complications, but patients with elevated troponin levels were less likely to have recurrent pericarditis.⁷⁶

Post-percutaneous coronary intervention

Percutaneous coronary intervention (PCI) is becoming increasingly common with 954,000 procedures completed in 2010.⁷⁹ Whether the PCI is successful or not, there will be blood flow limitation downstream from the balloon used during the procedure. There will also be plaque debris that embolizes distally and interrupts the microcirculation. A post-procedure troponin elevation above the 99th percentile, assuming a normal pre-procedural value, is considered indicative of myonecrosis. A troponin level above 3 times the 99th percentile is considered PCI-related myocardial infarction, or a type 4a MI. A type 4b MI is due to stent thrombosis and is diagnosed by angiography or autopsy rather than troponin value.¹³

In addition to diagnostic assistance, troponin measurements in the setting of PCI can assist clinicians with prognosis. Any level of troponin elevation is associated with increased 12-month mortality, and levels higher than 5-times the normal limit is associated with the highest mortality.⁸⁰ This dose-response relationship is also found in troponin measurements in the setting of heart failure and is consistent with the idea that larger myocardial damage causes increased complications and death.

Takotsubo

Takotsubo cardiomyopathy (TCM) is a transient cardiac syndrome that involves left ventricular apical akinesis and mimics ACS. It is also known as “stress induced cardiomyopathy” because the symptoms are triggered by a significant emotional or physical stressor.⁸¹ TCM occurs in approximately 1% to 2% of patients presenting with positive troponin levels and suspected ACS or STEMI.⁸² The etiology is unclear, but possible mechanisms include multi-vessel coronary artery spasm, impaired cardiac microvascular function, impaired myocardial fatty acid metabolism, ACS with reperfusion injury, and endogenous catecholamine-induced myocardial stunning with microinfarction.⁸³⁻⁸⁵ Cardiac markers, specifically cTnI and cTnT, are elevated in 90% of patients with TCM, even though the elevation is in lesser magnitude than is seen in STEMI. In patients with TCM, the mean cTnT level at the time of admission has been found to be 0.49 ng/mL (normal, <0.01ng/mL), and the mean cTnI level has been reported as 4.2 ng/mL (normal, <0.04ng/mL); during hospitalization, mean peak values for cTnT and cTnI have been demonstrated to be 0.64 and 8.6 ng/mL, respectively. In the International Takotsubo Registry study, serum cardiac troponin levels are elevated in most patients with TCM, with a reported median initial troponin 7.7 times the upper limit of normal.⁸⁶

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Conflict of Interest

None.

References

1. Sharma S, Jackson PG, Makan. Cardiac troponins. In: *J Clin Pathol* 2004;57:1025–1026.
2. Alpert JS, Thygesen KA, White HD, et al. Diagnostic and therapeutic implications of type 2 myocardial infarction: review and commentary. *Am J Med* 2014;127(2):105–108.
3. Shave R, Dawson E, Whyte G, et al. The cardiac specificity of the third-generation cTnT assay after exercise-induced muscle damage. *Med Sci Sports Exerc*. 2002;34(4):651–654.
4. Collinson PO, Boa FG, Gaze DC. Measurement of cardiac troponins. *Ann Clin Biochem*. 2001;38(Pt5):423–449.
5. Alpert, J S TK, Antman E. In.
6. Apple FS, Collinson PO. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem*. 2012;58(1):54–61.
7. Ottani F, Galvani M, Nicolini FA, et al. Elevated cardiac troponin levels predict the risk of adverse outcome in patients with acute coronary syndromes. *Am Heart J*. 2000;140(6):917–927.
8. Kristian Thygesen, Joseph S. Alpert, Allan S. et al. Third universal definition of myocardial infarction. *J Am Coll Cardiol*. 2012;60(16):1581–1598.
9. Mahajan N, Mehta Y, Rose M, et al. Elevated troponin level is not synonymous with myocardial infarction. *Int J Cardiol*. 2006;111(3):442–449.
10. Vasile VC, Jaffe AS. High-Sensitivity Cardiac Troponin for the Diagnosis of Patients with Acute Coronary Syndromes. *Curr Cardiol Rep*. 2017;19(10):1–92.
11. Park KC, Gaze DC, Collinson PO, et al. Cardiac troponins: from myocardial infarction to chronic disease. *Cardiovasc Res*. 2017;113(14):1708–1718.
12. Jeremias A, Gibson CM. Narrative review: alternative causes for elevated cardiac troponin levels when acute coronary syndromes are excluded. *Ann Intern Med*. 2005;142(9):786–791.
13. Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *Eur Heart J*. 2007;28(20):2525–38.
14. Biccard BM, Rodseth RN. The pathophysiology of peri-operative myocardial infarction. *Anaesthesia*. 2016;65(7):733–741.
15. Del Carlo CH, Pereira-Barretto AC, Cassaro-Strunz C, et al. Serial measure of cardiac troponin T levels for prediction of clinical events in decompensated heart failure. *J Card Fail*. 2004;10(1):43–48.
16. Demissei BG, Cotter G, Prescott MF, et al. A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial. *Eur J Heart Fail*. 2017;19(8):1001–1010.
17. Felker GM, Hasselblad V, Tang WH, et al. Troponin I in acute decompensated heart failure: insights from the ASCEND-HF study. *Eur J Heart Fail*. 2012;14(11):1257–1264.
18. Felker GM, Mentz RJ, Teerlink JR, et al. Serial high sensitivity cardiac troponin T measurement in acute heart failure: insights from the RELAX-AHF study. *Eur J Heart Fail*. 2015;17(12):1262–1270.
19. Fonarow GC, Horwich TB. Combining natriuretic peptides and necrosis markers in determining prognosis in heart failure. *Rev Cardiovasc Med*. 2003;4 (Suppl4):S20–28.
20. Gattis WA, O'Connor CM, Hasselblad V, et al. Usefulness of an elevated troponin-I in predicting clinical events in patients admitted with acute heart failure and acute coronary syndrome (from the RITZ-4 trial). *Am J Cardiol*. 2004;93(11):1436–1437.

21. Goto T, Takase H, Toriyama T, et al. Circulating concentrations of cardiac proteins indicate the severity of congestive heart failure. *Heart*. 2003;89(11):1303–1307.
22. Greene SJ, Butler J, Fonarow GC, et al. Pre-discharge and early post-discharge troponin elevation among patients hospitalized for heart failure with reduced ejection fraction: findings from the ASTRONAUT trial. *Eur J Heart Fail*. 2017.
23. Horwich TB, Patel J, MacLellan WR. Cardiac troponin I is associated with impaired hemodynamics, progressive left ventricular dysfunction, and increased mortality rates in advanced heart failure. *Circulation*. 2003;108(7):833–838.
24. Hudson MP, O'Connor CM, Gattis WA, et al. Implications of elevated cardiac troponin T in ambulatory patients with heart failure: a prospective analysis. *Am Heart J*. 2004;147(3):546–552.
25. Ishii J, Nomura M, Nakamura Y, et al. Risk stratification using a combination of cardiac troponin T and brain natriuretic peptide in patients hospitalized for worsening chronic heart failure. *Am J Cardiol*. 2002;89(6):691–695.
26. Januzzi JL Jr, Filippatos G, Nieminen M, et al. Troponin elevation in patients with heart failure: on behalf of the third Universal Definition of Myocardial Infarction Global Task Force: Heart Failure Section. *Eur Heart J*. 2012;33(18):2265–2271.
27. Kuwabara Y, Sato Y, Miyamoto T, et al. Persistently increased serum concentrations of cardiac troponin in patients with acutely decompensated heart failure are predictive of adverse outcomes. *Circ J*. 2007;71(7):1047–1051.
28. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. *Circulation*. 2007;116(11):1242–1249.
29. Masson S, Anand I, Favero C, et al. Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: data from 2 large randomized clinical trials. *Circulation*. 2012;125(2):280–288.
30. Miller WL, Hartman KA, Burritt MF, et al. Profiles of serial changes in cardiac troponin T concentrations and outcome in ambulatory patients with chronic heart failure. *J Am Coll Cardiol*. 2009;54(18):1715–1721.
31. Connor O CM, Fiuzat M, Lombardi C, et al. Impact of serial troponin release on outcomes in patients with acute heart failure: analysis from the PROTECT pilot study. *Circ Heart Fail*. 2011;4(6):724–732.
32. Parenti N, Bartolacci S, Carle F, et al. Cardiac troponin I as prognostic marker in heart failure patients discharged from emergency department. *Intern Emerg Med*. 2008;3(1):43–47.
33. Pascual-Figal DA, Manzano-Fernández S, Boronat M, et al. Soluble ST2, high-sensitivity troponin T- and N-terminal pro-B-type natriuretic peptide: complementary role for risk stratification in acutely decompensated heart failure. *Eur J Heart Fail*. 2011;13(7):718–725.
34. Perna ER, Macin SM, Canella JP, et al. Ongoing myocardial injury in stable severe heart failure: value of cardiac troponin T monitoring for high-risk patient identification. *Circulation*. 2004;110(16):2376–2382.
35. La Vecchia L, Mezzana G, Zanolla L, et al. Cardiac troponin I as diagnostic and prognostic marker in severe heart failure. *J Heart Lung Transplant*. 2000;19(7):644–652.
36. Waxman DA, Hecht S, Schappert J, et al. A model for troponin I as a quantitative predictor of in-hospital mortality. *J Am Coll Cardiol*. 2006;48(9):1755–1762.
37. Xue C, Yu H, Li R, et al. Clinical significance of serum cardiac troponin T in patients with congestive heart failure. *Chin Med J (Engl)*. 2003;116(3):469–471.
38. Xue Y, Clopton P, Peacock WF, et al. Serial changes in high-sensitive troponin I predict outcome in patients with decompensated heart failure. *Eur J Heart Fail*. 2001;13(1):37–42.
39. You JJ, Austin PC, Alter DA, et al. Relation between cardiac troponin I and mortality in acute decompensated heart failure. *Am Heart J*. 2007;153(4):462–470.
40. Peacock WF, De Marco T, Fonarow GC, et al. Cardiac troponin and outcome in acute heart failure. *N Engl J Med*. 2008;358(20):2117–2126.
41. Kociol RD, Pang PS, Gheorghiadu M, et al. Troponin elevation in heart failure prevalence, mechanisms, and clinical implications. *J Am Coll Cardiol*. 2010;56(14):1071–1078.
42. van Boven N, Akkerhuis KM, Anroedh SS, et al. In search of an efficient strategy to monitor disease status of chronic heart failure outpatients: added value of blood biomarkers to clinical assessment. *Neth Heart J*. 2017;25(11):634–642.
43. Thawabi M, Hawatmeh A, Studyvin S, et al. Cardiac troponin and outcome in decompensated heart failure with preserved ejection fraction. *Cardiovasc Diagn Ther*. 2017;7(4):359–366.
44. Zhang R, Chen S, Zhang H, et al. Biomarkers Investigation for In-Hospital Death in Patients With Stanford Type A Acute Aortic Dissection. *Int Heart J*. 2016;57(5):622–626.
45. Vrsalovic M. Prognostic effect of cardiac troponin elevation in acute aortic dissection: A meta-analysis. *Int J Cardiol*. 2016;214: 277–278.
46. Bonnefoy E, Godon P, Kirkorian G, et al. Significance of serum troponin I elevation in patients with acute aortic dissection of the ascending aorta. *Acta Cardiol*. 2005;60(2):165–170.
47. Pourafkari L, Tajlil A, Ghaffari S, et al. Electrocardiography changes in acute aortic dissection—association with troponin leak, coronary anatomy, and prognosis. *Am J Emerg Med*. 2016;34(8):1431–1436.
48. McCarthy CP, Yousuf O2, Alonso A3, et al. High-Sensitivity Troponin as a Biomarker in Heart Rhythm Disease. *Am J Cardiol*. 2017;119(9):1407–1413.
49. Bakshi TK, Choo MK, Edwards CC, et al. Causes of elevated troponin I with a normal coronary angiogram. *Intern Med J*. 2002;32(11):520–525.
50. Alghamry A, Hanna J, Pelecanos A, et al. Predictors of significant coronary artery disease in atrial fibrillation: Are cardiac troponins a useful measure. *Int J Cardiol*. 2016;223:744–749.
51. Saygi S, Drca N, Insulander P, et al. Myocardial injury during radiofrequency and cryoablation of typical atrial flutter. *J Interv Card Electrophysiol*. 2016;46(2):177–181.
52. Reichlin T, Lockwood SJ, Conrad MJ, et al. Early release of high-sensitive cardiac troponin during complex catheter ablation for ventricular tachycardia and atrial fibrillation. *J Interv Card Electrophysiol*. 2016;47(1):69–74.
53. Gautam PL, Luthra N, Kaur M, et al. Evaluation of Myocardial Injury using Standard Diagnostic Tools and Tissue Doppler Imaging in Blunt Trauma Chest. *J Clin Diagn Res*. 2017;11(6):OC33–OC36.
54. Bellister SA, Dennis BM, Guillaumondegui . Blunt and Penetrating Cardiac Trauma. *Surg Clin North Am*. 2017;97(5):1065–1076.
55. Joseph B, Jokar TO, Khalil M, et al. Identifying the broken heart: predictors of mortality and morbidity in suspected blunt cardiac injury. *Am J Surg*. 2016;211(6):982–988.
56. Velmahos GC, Karaiskakis M, Salim A, et al. Normal electrocardiography and serum troponin I levels preclude the presence of clinically significant blunt cardiac injury. *J Trauma*. 2003;54(1):45–50; discussion 50–51.
57. Bertinchant JP, Polge A, Mohty D, et al. Evaluation of incidence, clinical significance, and prognostic value of circulating cardiac troponin I and T elevation in hemodynamically stable patients with suspected myocardial contusion after blunt chest trauma. *J Trauma*. 2000;48(5):924–931.
58. Rajan GP, Zellweger R. Cardiac troponin I as a predictor of arrhythmia and ventricular dysfunction in trauma patients with myocardial contusion. *J Trauma*. 2004;57(4):801–808; discussion 808.

59. Seward JB, Casaclang Verzos G. Infiltrative cardiovascular diseases: cardiomyopathies that looks alike. *J Am Coll Cardiol*. 2010;55(17):1769–1779.
60. Izumiya Y, Takashio S, Oda S, et al. Recent advances in diagnosis and treatment of cardiac amyloidosis. *J Cardiol*. 2017;71(2):135–143.
61. Sharma N, Howlett J. Current state of cardiac amyloidosis. *Curr Opin Cardiol*. 2013;28(2):242–248.
62. Muchtar E, Blauwet LA, Gertz MA. Restrictive Cardiomyopathy: Genetics, Pathogenesis, Clinical Manifestations, Diagnosis, and Therapy. *Circ Res*. 2017;121(7):819–837.
63. Dispenzieri A, Kyle RA, Gertz MA, et al. Survival in patients with primary systemic amyloidosis and raised serum cardiac troponins. *Lancet*. 2003;361(9371):1787–1789.
64. Kandolin R, Lehtonen J, Airaksinen J, et al. Usefulness of Cardiac Troponins as Markers of Early Treatment Response in Cardiac Sarcoidosis. *Am J Cardiol*. 2015;116(6):960–964.
65. Baba Y, Kubo T, Kitaoka H, et al. Usefulness of high-sensitive cardiac troponin T for evaluating the activity of cardiac sarcoidosis. *Int Heart J*. 2012;53(5):287–292.
66. Rimoldi O, Maranta F. Microvascular dysfunction in infiltrative cardiomyopathies. *J Nucl Cardiol*. 2017.
67. Seydelmann N, Liu D, Kramer J, et al. High-Sensitivity Troponin: A Clinical Blood Biomarker for Staging Cardiomyopathy in Fabry Disease. *J Am Heart Assoc*. 2016;5(6):e002839.
68. Miranda CH, Schmidt A, Pazin Filho A. Prognostic evaluation of the troponin I elevation after multiple spontaneous shocks of the implantable cardioverter/defibrillator. *Am J Emerg Med*. 2014;32(9):1085–1088.
69. Blendea D, Blendea M, Banker J, et al. Troponin T elevation after implanted defibrillator discharge predicts survival. *Heart*. 2009;95(14):1153–1158.
70. Furniss G, Shi B, Jimenez A, et al. Cardiac troponin levels following implantable cardioverter defibrillation implantation and testing. *Europace*. 2015;17(2):262–266.
71. Erbel C, Taskin R, Doesch A, et al. High-sensitive Troponin T measurements early after heart transplantation predict short- and long-term survival. *Transpl Int*. 2013;26(3):267–272.
72. Ambrosi P, Kreitmann B, Fromonot J, et al. Plasma ultrasensitive cardiac troponin during long-term follow-up of heart transplant recipients. *J Card Fail*. 2015;21(2):103–107.
73. Mauermann E, Bolliger D, Fassel J, et al. Association of Troponin Trends and Cardiac Morbidity and Mortality After On-Pump Cardiac Surgery. *Ann Thorac Surg*. 2017;104(4):1289–1297.
74. Paparella D, Guida P, Caparrotti S, et al. Myocardial damage influences short- and mid-term survival after valve surgery: a prospective multicenter study. *J Thorac Cardiovasc Surg*. 2014;148(5):2373–2379. e2371.
75. Lurati Buse GA, Koller MT, Grapow M, et al. The prognostic value of troponin release after adult cardiac surgery – a meta-analysis. *Eur J Cardiothorac Surg*. 2010;37(2):399–406.
76. Imazio M, Brucato A, Barbieri A, et al. Good prognosis for pericarditis with and without myocardial involvement: results from a multicenter, prospective cohort study. *Circulation*. 2013;128(1):42–49.
77. Saricam E, Saglam Y. potentially missed acute pericarditis: atypical pericarditis. *Am J Emerg Med*. 2016;34(12):2451–2453.
78. Laufer Perl M, Havakuk O, Shacham Y, et al. Sex-based differences in prevalence and clinical presentation among pericarditis and myopericarditis patients. *Am J Emerg Med*. 2017;35(2):201–205.
79. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart Disease and Stroke Statistics–2016 Update: A Report From the American Heart Association. *Circulation*. 2016;133(4):e38–e360.
80. Ferreira RM, De Souza ESNA, Salis LHA, et al. Troponin I elevation and all-cause mortality after elective percutaneous coronary interventions. *Cardiovasc Revasc Med*. 2017;18(4):255–260.
81. Boland TA, Lee VH, Bleck TP. Stress-induced cardiomyopathy. *Crit Care Med*. 2015;43(3):686–693.
82. Prasad A, Dangas G, Srinivasan M, et al. Incidence and angiographic characteristics of patients with apical ballooning syndrome (takotsubo/stress cardiomyopathy) in the HORIZONS-AMI trial: an analysis from a multicenter, international study of ST-elevation myocardial infarction. *Catheter Cardiovasc Interv*. 2014;83(3):343–348.
83. Afonso L, Bachour K, Awad K, et al. Takotsubo cardiomyopathy: pathogenetic insights and myocardial perfusion kinetics using myocardial contrast echocardiography. *Eur J Echocardiogr*. 2008;9(6):849–854.
84. Khallafi H, Chacko V, Varveralis N, et al. “Broken heart syndrome”: catecholamine surge or aborted myocardial infarction? *J Invasive Cardiol*. 2008;20(1):E9–E13.
85. Lindsay J, Paixao A, Chao T, et al. Pathogenesis of the Takotsubo syndrome: a unifying hypothesis. *Am J Cardiol*. 2010;106(9):1360–1363.
86. Templin C, Ghadri JR, Diekmann J, et al. Clinical Features and Outcomes of Takotsubo (Stress) Cardiomyopathy. *N Engl J Med*. 2015;373(10):929–938.