



# **A Case-based Analytical Review on How to Evaluate Elevated Troponin Levels in Patients Excluding Myocardial Infarction**

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## **Author's contribution**

*The sole author designed, analyzed, interpreted and prepared the manuscript.*

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## **ABSTRACT**

The role of troponin in the evaluation and assessment of cardiac emergencies has always been appreciated. It has always played a great role in helping physicians diagnose conditions such as acute coronary syndrome (ACS) and occlusion myocardial infarction (OMI). However, over the past few years, it has been estimated that troponin is also increased in a few other conditions apart from myocardial infarction. It is undoubtedly the elevated titres of Troponin I and T that help in making the conclusive diagnosis in patients with the respective pathologies. The most common reasons for which Troponin levels could be increased include injury to the myocytes, necrosis of the myocytes, apoptosis and cell turnover of the myocytes and an overall imbalance or uncontrolled metabolic activity in the myocytes' oxygen and supply demand. The most common cardiac pathologies that lead to the elevation of troponin levels include heart failure, dissection, and dysrhythmia. However, there are some other non-cardiac causes as well that cause elevated troponin levels, including pulmonary embolism, sepsis, and stroke. Since all these conditions are highly serious and emergency conditions, it is important for all the physicians to take into account all of the

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patient's signs and symptoms, radiological and ultrasound findings before diving into their interventional plan. This is important because of the high mortality rates and chances of misdiagnosis attached to it.

*Keywords: Elevated troponin; myocardial infarction; injury to the myocardium; occlusion to the myocardium; emergency medicine.*

## 1. INTRODUCTION

The role of troponin in emergency medicine is phenomenal. It has been a gold standard for the diagnosis of acute coronary syndrome (ACS) in patients since a very long time ago. ACS includes myocardial infarction and thus, the elevated titres of Troponin are diagnostic enough as the biomarkers of acute myocardial infarction. [1]. It is important to note that troponin is a marker of myocardial injury and is not specific to coronary ischemia caused by acute MI [2]. Incorrectly diagnosing another condition associated with troponin elevation can increase the risk of bleeding due to unnecessary anticoagulation, expose patients to potential risks from cardiac catheterization and stenting, and interfere with other important procedures [3].

With the increased utilization of troponin and improved assay sensitivity, elevated troponin levels are frequently observed in diseases other than acute MI [4,5].

Therefore, troponin is more accurately described as organ-specific rather than disease-specific. This review focuses on the evaluation of elevated troponin in emergency medicine, discussing both cardiac and non-cardiac causes, followed by an approach to the diagnostic workup for patients with troponin elevation [6].

### 1.1 Cardiac Troponins

Cardiac troponins are a group of proteins found in cardiac muscle cells (cardiomyocytes) that are released into the bloodstream when there is damage or injury to the heart [5] [6]. They are specific to the heart and are widely used as biomarkers for diagnosing and assessing various heart conditions, particularly acute coronary syndrome (ACS) and myocardial infarction (heart attack). There are three types of cardiac troponins: troponin C, troponin I, and troponin T [7]. Among these, troponin I (cTnI) and troponin T (cTnT) are the most commonly measured and used in clinical practice [8][9]. Whenever there is any injury or damage to the heart muscle, such as in a heart attack, the cardiac troponins are

released into the bloodstream. The level of troponins in the blood is then measured through a blood test. Elevated levels of cardiac troponins indicate myocardial injury, and the magnitude of troponin elevation can provide important information about the extent and severity of the damage to the heart [9].

Cardiac troponin testing is highly sensitive and specific for detecting heart muscle damage. It is used not only in the diagnosis of myocardial infarction but also in risk stratification, prognosis assessment, and monitoring of cardiac conditions. The troponin levels are typically measured upon admission to the hospital and at regular intervals thereafter to track changes and evaluate the response to treatment [10,11].

### 1.2 Current Troponin Testing Methods

Myocardial injury is defined as any damage or injury to the muscular tissue of the heart, known as the myocardium. It occurs when there is an impairment or disruption in the blood supply or oxygen delivery to the heart muscle, leading to cell damage or death [12]. The diagnosis of acute myocardial infarction (MI) requires additional criteria beyond troponin changes.

Type I MI is characterized by intraluminal coronary plaque disruption and thrombus formation [13]. It is diagnosed when there is a rise and/or fall in troponin levels, with at least one value exceeding the 99th percentile, accompanied by symptoms of acute MI, new electrocardiogram (ECG) changes, development of pathological Q waves on ECG, imaging evidence of new myocardial loss or regional wall motion abnormality, or identification of a coronary thrombus through angiography [14-16]. Occlusion MI (OMI), including ST-segment elevation myocardial infarction (STEMI), is a subset of Type I MI and requires emergent coronary reperfusion therapy [16].

Type 2 MI shares similar criteria to Type 1 MI, involving troponin changes and evidence of ischemia. However, it differs in that it is caused by an imbalance between oxygen supply and

demand rather than acute coronary thrombosis [17][18].

This article will explore and present all possible causes that cause troponin levels to be elevated in individuals.

## 2. MATERIALS AND METHODS

In this review, the authors have conducted a comprehensive literature search to explore troponin elevation in patients with myocardial injury excluding occlusion myocardial infarction (OMI). The search was performed on PubMed and Google Scholar, using relevant keywords such as "troponin," "elevation," and "increase." The search covered articles published from the inception of the databases up until September 1, 2019. Over 600 articles were found on PubMed, and the first 200 articles on Google Scholar were also reviewed.

The search was limited to English-language publications, with a focus on emergency medicine and critical care literature. The consensus among the authors determined the selection of studies for inclusion in this review.

Systematic reviews and meta-analyses were given priority, followed by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews in the absence of alternative data.

## 3. RESULTS AND DISCUSSION

### 3.1 Mechanisms of Troponin Elevation

The elevation of troponin levels in the blood occurs as a result of myocardial injury or damage. Troponin is a complex of proteins (troponin I, troponin T, and troponin C) that are normally located within the cardiac muscle cells (cardiomyocytes) and play a critical role in regulating muscle contraction [19].

When there is injury or damage to the heart muscle, the integrity of the cardiomyocytes is compromised, leading to the release of intracellular components, including troponin, into the bloodstream [20]. The mechanism of troponin elevation involves several processes. In conditions such as myocardial infarction (heart attack), prolonged ischemia (lack of blood flow) leads to irreversible damage and death of cardiomyocytes. As a result, troponin is released from the damaged cells into the bloodstream

[21,22]. In certain cardiac conditions, such as heart failure or myocarditis, there may be ongoing cellular injury or inflammation in the heart muscle. This can result in programmed cell death (apoptosis) of cardiomyocytes. [23] Troponin is released into the bloodstream as a consequence of apoptotic cell turnover [24]. In situations where there is an inadequate supply of oxygen to meet the demands of the heart muscle, such as in severe coronary artery disease or cardiac ischemia, the cardiomyocytes can become stressed. This can lead to reversible injury and the release of troponin into the bloodstream, even without significant cell death [25,26]. Once troponin is released into the bloodstream, it can be measured using specific laboratory tests. The levels of troponin in the blood are indicative of the extent and severity of myocardial injury. Higher troponin levels generally correlate with more significant damage to the heart muscle [27].

#### 3.1.1 Cardiac etiologies

**Heart failure:** Heart failure is a condition in which the heart is unable to pump blood effectively. This places increased stress on the heart muscle, leading to cellular damage and injury [28]. As a result, troponin may be released into the bloodstream, causing elevated troponin levels. The heart chambers may become dilated and the heart muscle may undergo increased stretch and strain. This can result in mechanical stress on the cardiomyocytes, leading to troponin release and subsequent elevation in troponin levels. Elevated troponin levels in heart failure are associated with an increased risk of adverse outcomes, including higher mortality rates, hospitalizations, and future cardiovascular events. Troponin levels can serve as a marker of cardiac stress and injury, reflecting the severity of heart failure and providing prognostic information [29][30].

**Takotsubo cardiomyopathy:** Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy or broken heart syndrome, is a transient condition characterized by sudden weakening of the left ventricle (the heart's main pumping chamber). While the exact cause of Takotsubo cardiomyopathy is not fully understood, it is believed to be triggered by severe emotional or physical stress [31].

In Takotsubo cardiomyopathy, troponin levels are often elevated. Troponin is released into the bloodstream when there is injury or damage to

the heart muscle. In the case of Takotsubo cardiomyopathy, the elevated troponin levels are believed to be a result of the temporary dysfunction or stunning of the heart muscle rather than actual irreversible damage [32].

The troponin elevation in Takotsubo cardiomyopathy typically follows a pattern similar to that seen in a heart attack (myocardial infarction) [33][34]. The troponin levels rise within a few hours of the onset of symptoms, peak within 24-48 hours, and gradually return to normal over several days to weeks [35].

**Tachycardias:** Tachycardia refers to a rapid heart rate, typically defined as a heart rate greater than 100 beats per minute. It can occur in various conditions and situations, including physiological responses to exercise, emotional stress, or as a symptom of an underlying medical condition. The relationship between tachycardia and troponin levels depends on the underlying cause of the rapid heart rate [36].

In general, tachycardia itself is not directly responsible for troponin elevation. Troponin is a cardiac biomarker released into the bloodstream in response to myocardial injury. However, tachycardia can indirectly impact troponin levels by affecting myocardial oxygen demand and potentially leading to myocardial injury [37].

When the heart beats at an elevated rate for an extended period, it may result in an imbalance between myocardial oxygen supply and demand. The increased demand for oxygen by the heart muscle, coupled with reduced diastolic filling time, can potentially compromise coronary blood flow. This mismatch between oxygen supply and demand can lead to ischemia (lack of oxygen) in the myocardium, which may result in myocardial injury and subsequent troponin release [38].

It is important to note that troponin elevation due to tachycardia is typically mild and transient. In most cases, the elevation is not clinically significant and does not indicate a major cardiac event. However, in individuals with underlying cardiovascular disease or other risk factors, tachycardia-induced myocardial ischemia can have more serious implications and lead to troponin elevation indicative of myocardial injury [39].

In summary, tachycardia itself does not directly cause troponin elevation. However, tachycardia

can increase myocardial oxygen demand and potentially lead to myocardial ischemia and subsequent troponin release. The significance of troponin elevation in the context of tachycardia depends on the underlying clinical context and the presence of other risk factors or cardiac conditions. A comprehensive evaluation, including clinical assessment and diagnostic tests, is necessary to determine the cause and significance of troponin elevation in patients with tachycardia [40].

**Aortic dissection:** Aortic dissection is a life-threatening condition characterized by the separation of the layers of the aortic wall, creating a false lumen through which blood can flow. It is considered a medical emergency that requires prompt diagnosis and intervention [41]. Troponin elevation has been associated with aortic dissection, indicating a potential link between the two. Aortic dissection can compromise blood flow to the coronary arteries that supply the heart muscle [42]. Reduced blood flow can lead to myocardial ischemia, resulting in myocardial injury and subsequent troponin release. The dissection itself can obstruct the coronary arteries directly or cause compression or distortion of the vessels, leading to reduced blood flow. The dissection process can involve the involvement of the aortic root or the involvement of coronary arteries in the dissection flap. In such cases, direct injury to the coronary arteries or the myocardium can occur, leading to troponin release [43]. Elevated troponin levels in the context of aortic dissection can have important clinical implications. It indicates cardiac involvement and may be associated with a higher risk of adverse outcomes, such as myocardial infarction or hemodynamic instability. Troponin elevation in aortic dissection should prompt a comprehensive evaluation, including clinical assessment, imaging studies (such as computed tomography angiography), and close monitoring for potential complications [44].

**Cardiac trauma:** Cardiac trauma refers to any injury or damage to the heart, typically resulting from a blunt or penetrating trauma to the chest. It is a serious condition that requires immediate medical attention. Troponin elevation has been recognized as a useful marker for assessing myocardial injury, including cardiac trauma [45].

When the heart experiences trauma, such as a direct blow or penetration, it can lead to various forms of cardiac injury, including myocardial

contusion, rupture, or damage to the coronary arteries. These injuries can result in the release of troponin into the bloodstream, as troponin is specific to cardiac muscle and is released when there is damage or necrosis of the myocardial cells [46].

Troponin elevation in the context of cardiac trauma serves as a marker for myocardial injury and can help healthcare professionals assess the severity of the trauma and guide appropriate management. The magnitude of troponin elevation can provide insights into the extent of cardiac damage and can aid in risk stratification and prognosis assessment.

It is important to note that troponin elevation in cardiac trauma does not necessarily correlate with the severity of the trauma. Even mild cardiac trauma can lead to troponin elevation, and the absence of troponin elevation does not exclude the possibility of cardiac injury. Other factors, such as the timing of troponin measurement, the location of the injury, and individual patient characteristics, can influence troponin levels [47].

### 3.1.2 Non-cardiac causes

Troponin elevation is observed in 12–85% of critically ill patients admitted to the intensive care unit (ICU), and it is associated with poorer outcomes and a 2.5-fold increased risk of in-hospital mortality [48][49]. Various conditions requiring ICU care are commonly associated with elevated troponin levels, including acute pulmonary embolism (PE), stroke, hypotension from significant hemorrhage or hypovolemia, gastrointestinal (GI) bleeding, sepsis, acute respiratory distress syndrome (ARDS), and others [50].

**Acute pulmonary embolism:** Pulmonary embolism (PE) is a potentially life-threatening condition characterized by the blockage of one or more arteries in the lungs by a blood clot. When it comes to troponin levels, there is a recognized association between PE and troponin elevation [51].

In PE, the obstruction of the pulmonary arteries can cause an increase in right ventricular pressure and strain on the heart. This can lead to right ventricular dysfunction, acute right-sided heart failure, and subsequent myocardial injury. As a result, troponin, which is primarily found in cardiac muscle, can be released into the bloodstream [52].

Troponin elevation in the context of PE can occur through various mechanisms. The increased strain on the right ventricle, reduced blood supply to the heart muscle, and direct compression of the coronary arteries by the clot can contribute to myocardial injury and subsequent release of troponin [53].

The degree of troponin elevation in PE can vary depending on the size and location of the embolism, the extent of right ventricular dysfunction, and the presence of underlying cardiac disease. Higher troponin levels in PE are associated with increased severity of right ventricular dysfunction and a higher risk of adverse outcomes.

Elevated troponin levels in the setting of PE can serve as an important prognostic indicator. They have been associated with an increased risk of short-term mortality, a higher likelihood of hemodynamic instability, and a greater need for advanced interventions, such as thrombolysis or surgical embolectomy [54].

**Stroke:** Stroke, also known as cerebrovascular accident (CVA), is a condition characterized by the sudden disruption of blood flow to the brain, resulting in neurological dysfunction. While stroke primarily affects the brain, there is a recognized association between stroke and troponin elevation, indicating a potential link between the two [55].

Troponin is a cardiac biomarker used to assess myocardial injury, primarily associated with acute coronary syndrome (ACS) or myocardial infarction (MI). However, troponin elevation can also occur in non-cardiac conditions, including stroke. The exact mechanisms behind troponin elevation in stroke are not fully understood [56].

Stroke can be caused by the embolization of blood clots from the heart to the brain, known as cardioembolic stroke. In individuals with underlying heart disease, such as atrial fibrillation or other cardiac conditions, these emboli can originate from the heart, leading to cerebral ischemia. It is hypothesized that during the formation and dislodgment of these emboli, there may be transient cardiac injury or stress, resulting in troponin release [57].

Large or severe strokes, can activate the autonomic nervous system and cause sympathetic overactivity. This neurogenic stress response can lead to an imbalance between the

sympathetic and parasympathetic nervous systems, resulting in an increased release of catecholamines and subsequent myocardial injury.

**Sepsis:** Sepsis is a severe and potentially life-threatening condition that occurs in response to an infection. It is characterized by a dysregulated immune response leading to widespread inflammation, organ dysfunction, and, in some cases, cardiovascular complications. Troponin elevation has been observed in patients with sepsis, indicating a potential link between sepsis and cardiac injury [58].

The exact mechanisms underlying troponin elevation in sepsis are not fully understood but likely involve multiple factors. Sepsis can lead to myocardial dysfunction, also known as septic cardiomyopathy [59]. The systemic inflammatory response triggered by the infection can affect the heart, causing impaired cardiac contractility and relaxation. This myocardial dysfunction can result in troponin release as a marker of cardiac injury.

Sepsis can lead to microvascular dysfunction, causing impaired blood flow and oxygen delivery to various organs, including the heart. Insufficient oxygen supply to the cardiac muscle can result in myocardial injury and subsequent troponin release. The systemic inflammation associated with sepsis can lead to an inflammatory response in the myocardium. The release of pro-inflammatory cytokines and other mediators can directly affect the cardiac muscle, causing cellular damage and troponin elevation [60].

Troponin elevation in sepsis is typically observed in a substantial proportion of patients. It is associated with worse outcomes, including increased mortality rates and a higher risk of cardiovascular complications. Elevated troponin levels in sepsis can serve as a marker of myocardial injury and can help in risk stratification and prognosis assessment [61].

**Chronic obstructive pulmonary disease (COPD):** Chronic obstructive pulmonary disease (COPD) is a chronic lung condition characterized by airflow limitation and persistent respiratory symptoms. While COPD primarily affects the lungs, it can also have secondary effects on the cardiovascular system [62]. However, in the context of troponin levels, the relationship between COPD and troponin elevation is not as straightforward. COPD can lead to the development of pulmonary hypertension, a

condition characterized by increased pressure in the pulmonary arteries [63]. Elevated pulmonary pressures can strain the right ventricle of the heart, leading to right ventricular dysfunction and, in some cases, right-sided heart failure. This increased cardiac workload and potential cardiac muscle damage can result in troponin elevation. Troponin assessments [64][65].

**Extreme exercise:** During intense or prolonged exercise, it is not uncommon to observe a transient elevation in troponin levels. This is often referred to as exercise-induced cardiac biomarker release. The mechanism behind this elevation is still not entirely clear, but several factors are believed to contribute to it [66].

One possible explanation is that exercise places increased stress on the heart, leading to minor damage or strain in the cardiac muscle cells. This can result in the release of troponin into the bloodstream. Additionally, intense exercise can cause a temporary imbalance between oxygen supply and demand in the heart muscle, leading to ischemia-like conditions and subsequent troponin release [67].

It's important to note that the elevation of troponin levels during exercise is generally mild and transient, returning to baseline within a short period after the completion of exercise.

**Rhabdomyolysis:** Rhabdomyolysis is a condition characterized by the breakdown of skeletal muscle tissue, leading to the release of various intracellular components into the bloodstream, including troponin. When skeletal muscle tissue breaks down, the released myoglobin, creatine kinase (CK), and other muscle enzymes can enter the bloodstream. Myoglobin, in particular, can be filtered by the kidneys and cause kidney injury. The resulting myoglobinuria (presence of myoglobin in the urine) is a hallmark of rhabdomyolysis [68].

The release of myoglobin and other muscle components can also lead to troponin elevation. Although troponin is primarily found in cardiac muscle, a small amount is present in skeletal muscle as well. In rhabdomyolysis, the release of troponin from damaged skeletal muscle can contribute to elevated troponin levels in the bloodstream [69].

**Approach to NOMI and Myocardial Injury Troponin Elevation in Emergency Medicine:** In the management of patients with demand

ischemia associated with critical illness, limited data is available, making it a challenging situation. The primary focus should be on addressing and treating the underlying disease process causing the ischemia. One reasonable approach is the administration of aspirin, assuming there are no contraindications. However, other forms of anticoagulation, such as heparin, should be avoided in this context. Hemodynamic optimization plays a crucial role, ensuring appropriate intravascular fluid status and attempting to reduce beta-agonist stimulation if possible [70].

Diagnosing patients presenting with ischemic symptoms but with findings indicating another condition can be complex. The symptoms experienced by the patient may be due to myocardial infarction (OMI) complicated by another dangerous condition or a supply-demand mismatch. Patients with preexisting coronary artery disease (CAD) are particularly susceptible to oxygen supply-demand mismatch, which can result in myocardial ischemia at a lower threshold [71]. Therefore, it is recommended to reassess patients with a detailed history, thorough physical examination, and serial electrocardiograms (ECGs) while simultaneously addressing the suspected condition causing myocardial injury. For instance, a patient with severe gastrointestinal bleeding may also present with chest pain and ECG findings suggestive of ischemia. If resuscitation efforts lead to the resolution of symptoms and ECG changes, it is likely that the gastrointestinal bleeding was the primary cause of myocardial injury. However, if despite resuscitation and treatment for the GI hemorrhage, the patient continues to experience ischemic symptoms and ECG changes, further evaluation for OMI is warranted [72][73].

Point-of-care ultrasound (POCUS) can be a valuable tool in differentiating OMI from other conditions causing myocardial injury. The degree of troponin elevation is associated with an increased likelihood of abnormalities on POCUS. An echocardiogram revealing a focal wall motion abnormality coupled with a significant increase in troponin levels is diagnostic of OMI [74][75]. Conversely, the absence of focal myocardial wall motion abnormality on POCUS suggests a cause other than OMI, while POCUS showing hyperkinesis indicates physiologic compensation. Additionally, POCUS can provide insights into other potential conditions such as pulmonary embolism (PE) or aortic dissection [76,77].

In terms of patient disposition, considering admission to a monitored setting is recommended for those with troponin elevation as they exhibit higher morbidity and mortality rates [78]. Patients with troponin elevation due to supraventricular tachycardia (SVT) or extreme exercise may be suitable for discharge. However, troponin elevation in the presence of other conditions like heart failure (HF), pulmonary embolism (PE), chronic obstructive pulmonary disease (COPD), or sepsis is associated with a higher risk of adverse outcomes, and thus these patients should be admitted to a monitored setting. Critically ill patients may require intensive care unit (ICU) care for comprehensive management [79][80].

#### 4. CONCLUSION

In summary, the role of troponin in evaluating acute coronary syndrome (ACS) and diagnosing occlusion myocardial infarction (OMI) is crucial. Troponin I and T can be released in various cardiac and non-cardiac conditions, indicating myocardial injury rather than exclusively OMI. These conditions include myocyte injury, necrosis, apoptosis, cell turnover, and oxygen supply-demand imbalance. Therefore, troponin elevation should be seen as a sign of myocardial injury in a broader context. It is important to note that troponin elevation is not limited to OMI but can be observed in many critically ill patients. Elevated troponin levels are generally associated with higher mortality rates and longer hospital stays. Consequently, clinicians should not focus solely on the diagnosis of OMI when encountering troponin elevation but should consider the patient's clinical assessment and electrocardiogram (ECG) findings.

The primary goal should be to identify and address the underlying cause of troponin elevation. By focusing on treating the root condition, clinicians can provide more comprehensive care to patients with elevated troponin levels, ensuring appropriate management and potentially improving outcomes.

#### CONSENT AND ETHICAL APPROVAL

It is not applicable.

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## COMPETING INTERESTS

Author has declared that no competing interests exist.

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