

Elevated Troponin: A Comprehensive Review

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ABSTRACT

Troponin is a complex protein that plays an important role in regulating muscle contraction especially in the heart. It consists of three subunits known as troponin C troponin I and troponin T. When there is damage to a tissue or to the heart troponin is released into the bloodstream making it a valuable biomarker for detecting tissue/cardiac related issues. In recent years, new methods for the early detection of coronary heart diseases have become developed. Acute myocardial infarction (AMI) has been recognized as a clinical condition resulting from atherosclerosis of the coronary arteries. Early diagnosis, facilitated by measurement of elevated troponin levels is a beneficial detection tool to prevent various problems such as coronary heart diseases most notably AMI. Due to high sensitivity of troponin assays, we have notable capabilities to detect minor injuries with greater accuracy. Troponin is a crucial biomarker for diagnosing acute cardiac conditions, yet its elevation in diverse non-cardiac diseases presents a diagnostic challenge. Understanding the significance of recognizing alternative causes of troponin elevation is paramount. It not only prevents misdiagnosis but also ensures accurate identification and timely intervention in cardiac diseases, underscoring the importance of a comprehensive approach to troponin interpretation. This article reviews troponin levels and challenges the conditions that contribute to elevated troponin concentration in the blood. By examining the influencing factors more closely, we gain a deeper understanding of the complex nature of elevated troponin and its diagnostic implications.

Keywords: Acute Myocardial Infarction (AMI), Acute Coronary Syndrome (ACS), Kidney Diseases, Pulmonary Disease, Sepsis, Troponin Elevation.

INTRODUCTION

Troponin protein or the troponin complex protein is a complex of three regulatory proteins including troponin C, troponin I, and troponin T that are main cause of muscle contraction in skeletal and cardiac muscle. The troponin complex protein does not exist in smooth muscle [1-3]. Laboratory measurements of cardiac-specific troponins I and T are widely used as diagnostic and prognostic indicators in the control of myocardial infarction and acute coronary syndrome. Blood troponin levels may be used as a diagnostic biomarker for stroke or other ongoing heart

Vol No: 07, Issue: 02

Received Date: November 17, 2023

Published Date: December 08, 2023

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Citation: Neyestanaki MHK, et al. (2023). Elevated Troponin: A Comprehensive Review. Mathews J Cardiol. 7(2):31.

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damages, although the sensitivity of this test is low [4-6]. Normally, blood troponin levels are so low that only the most sensitive types of laboratory tests are able to determine it. But if the heart muscle is damaged, its blood level increases significantly with the entry of a large amount of troponin into the bloodstream [4,7-9]. Troponin measurement can confirm damage to the heart muscle from a heart attack. The more damage to the heart muscle, the more troponin is released into the blood. Therefore, accurate determination of blood troponin levels will provide a more reliable estimate of heart damage. Sometimes troponin levels higher than normal, may be caused by other conditions that can eventually lead to heart muscle damage [7-10]. Two types of troponins, troponin I and troponin T, may be measured to diagnose heart damage. Common tests can measure either type. Other names used for different types of troponin include cardiac troponin I (cTnI), cardiac troponin T (cTnT), cardiac troponin (cTn), cardiac-specific troponin I (csTnI), and cardiac-specific troponin T (csTnT) [1-4,7,11]. For many years, myocardial infarction has been recognized as a clinical condition resulting from atherosclerosis of the coronary arteries. In recent decades, particularly with advancements

in diagnostic tools utilizing state-of-the-art technology, new methods for the early detection of acute myocardial infarction (AMI) have become available to physicians. Early diagnosis, facilitated by these tools, has contributed to a reduction in mortality and fewer complications associated with this condition. Cardiac troponins, proteins present in myofibrils, comprise troponin C (cTnC), troponin I (cTnI), and troponin T (cTnT) [1-3].

This article offers an exploration of levels of troponin. It dives into factors and conditions that contribute to an increase in its concentration within the blood. By examining causes spanning from events, to external influences we gain a deeper understanding of the complex nature of troponin elevation and its diagnostic implications.

CARDIAC TROPONINS

As illustrated in Figure 1, cardiac troponin is a protein complex consisting of cTnC, cTnI, and cTnT, which, aided by calcium ions, regulates muscle contraction in skeletal and cardiac muscles, while it is absent in smooth muscles. Cardiac troponin serves as a biomarker assessed in myocardial damage and myocardial infarction investigations [1-3].

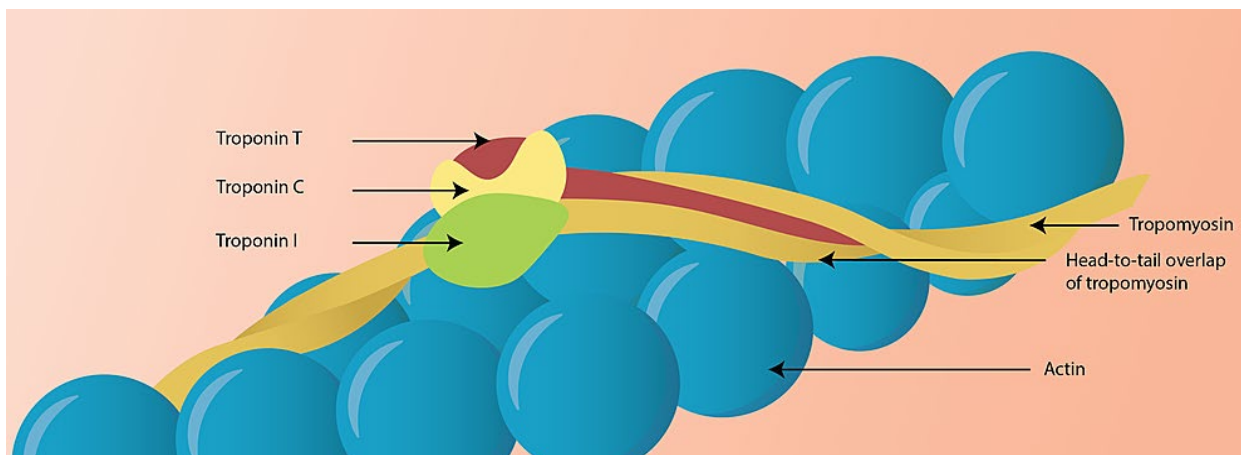


Figure 1. Different protein complex of cardiac troponin [3].

Troponin is a protein that plays a role, in regulating muscle contraction especially in the heart. It consists of three subunits known as troponin C troponin I and troponin T. These subunits are responsible for facilitating the process by which muscle fibers contract and relax through the regulation of calcium. When there is damage or injury to the heart troponin is released into the bloodstream making it a valuable biomarker for detecting cardiac related issues [2-4].

The measurement of troponin levels, troponin (cTn) has become instrumental in diagnosing various heart conditions most notably acute myocardial infarction (AMI). With

advancements in high sensitivity troponin assays we have improved capabilities to detect minor cardiac injuries with greater accuracy [7,11].

ACUTE CORONARY SYNDROME (ACS) RELATED FACTORS

Acute Myocardial Infarction (AMI)

Acute myocardial infarction, characterized by myocardial cell death resulting from prolonged myocardial ischemia, is identified through elevated cardiac troponin (cTn) levels. These troponins serve as highly sensitive and specific markers for myocardial injury, allowing detection of even

minor damages with advanced high-sensitivity troponin methods. Notably, while elevated cTn levels indicate cardiac injury, they do not specify the cause of the injury [4].

After Percutaneous Coronary Intervention

Following successful percutaneous coronary intervention (PCI) in both stable and unstable coronary artery disease, 24–40% of patients exhibit an elevation in cTn levels. Potential causes for increased cTn post-PCI include side branch occlusion, coronary dissection, transient ischemia induced by bulky devices, and microembolisms. Regardless of the precise mechanism, contrast-enhanced magnetic resonance imaging has unequivocally demonstrated the association between postprocedural cTn increases and myocardial necrosis [11].

Open Heart Surgery

In the context of open heart surgery, cardiac troponins consistently experience a slight increase for an average duration of five days, even in the absence of coronary artery bypass. This elevation in troponin levels post-surgery suggests myocardial involvement, highlighting the sensitivity of troponins as indicators of cardiac impact in this setting [7].

FACTORS UNRELATED TO ACS

Sepsis/Septic Shock and Systemic Inflammatory Response Syndrome

In intensive care unit patients treated for sepsis or systemic inflammatory response syndrome (SIRS), elevated cardiac troponin (cTn) has been observed in a range of 36% (cTnT > 0.1 ng/ml) to 85% (cTnI > 0.1 ng/ml). The variability in prevalence is attributed to diverse underlying causes of sepsis, variations in troponin assays, and differences in applied cut-off values. In most instances, the absence of significant coronary artery disease suggests alternative mechanisms for these troponin elevations [12].

Pulmonary Disease

Troponin elevations are documented in various pulmonary diseases often correlated with notable right heart strain. In acute pulmonary embolism (PE), elevated cTn is detected in up to 50% of cases. Depending on the cut-off used (0.1 ng/ml vs. 0.01 ng/ml), cTnT rates of 32% and 50% have been reported, respectively. Recently, cardiac troponins have emerged as crucial prognostic tools for risk stratification in patients with PE [8].

Heart Failure

Troponin elevations are often linked to advanced heart failure and an unfavorable prognosis. In heart failure (HF), elevated cardiac troponin (cTn) is associated with reduced left ventricular ejection fraction, reflecting the severity of heart failure and predicting prognosis. The deterioration of heart failure, whether ischemic or non-ischemic, stems from progressive myocyte loss due to necrosis and apoptosis. Contributing factors such as the activation of the renin-angiotensin-aldosterone and sympathetic nervous systems, along with inflammatory mediators, may further contribute to myocardial injury [10].

Strenuous Exercise

Regular physical activity is known to enhance cardiovascular health and extend lifespan. However, exercise can trigger a transient increase in cardiac troponin (cTn) levels, which may surpass the upper reference limit for a significant portion of the population. The debate over whether exercise-induced cTn elevations represent a physiological or pathological response and their clinical significance has persisted for decades. To date, exercise-induced cTn elevations have been considered the sole benign form of cTn elevation. Nevertheless, recent investigations have revealed intriguing findings that shed fresh light on the underlying mechanisms and clinical implications of exercise-induced cTn elevations. Following intense ultra-endurance exercise, studies have documented the appearance of cTnT or cTnI. However, the mechanisms behind these elevations and their prognostic significance remain unclear. Exercise, particularly in young individuals, can lead to increased membrane permeability through various mechanisms, including dehydration, hemoconcentration, and altered acid-base balance, resulting in elevated non-pathological troponin levels [13].

Acute Pericarditis/Myocarditis

In patients presenting to the emergency room with acute chest pain and elevated troponins, acute pericarditis/myocarditis is commonly diagnosed alongside acute myocardial infarction and acute pulmonary embolism. Although troponins are not inherently present in the pericardium, cTnI has been reported to be elevated in 32–49% of pericarditis cases due to the involvement of the epicardium in the inflammatory process. In acute myocarditis, elevated cTnI concentrations have been observed in 34% of patients [14].

Cardiotoxic Chemotherapy

The majority of chemotherapeutic agents, including anthracyclines, alkylating agents, anti-metabolites, or

anti-microtubules, may have cardiotoxic side effects. Adverse cardiac events associated with chemotherapy include ischemia (anti-metabolites, alkylating agents), endomyocardial fibrosis and cardiomyopathy (alkylating agents, e.g., anthracyclines), pericarditis (alkylating agents, e.g., cyclophosphamide), and various arrhythmias (anti-microtubules, e.g., paclitaxel) [5].

External Current Cardioversion or Defibrillator Shocks

Following radiofrequency catheter ablation, over 90% of patients experience an elevation of cardiac troponin (cTn), attributed to direct traumatic myocardial injury. However, these elevations lack prognostic significance. External current cardioversion (ECV) for atrial fibrillation or flutter results in either no elevation or only small increases in cTnI [15].

Cardiac Infiltrative Disorders

In systemic amyloidosis, the degree of cardiac involvement is closely tied to clinical outcomes. Extracellular amyloid deposition is believed to compress myocytes, leading to the subsequent release of cardiac troponin [16].

Post-Heart Transplantation

Since the early 1990s, it has been recognized that cardiac troponin (cTn) can be elevated in nearly all heart transplant recipients for up to three months following successful transplantation. Subsequent investigations revealed a connection between cTn levels and allograft rejection in the years that followed [17].

Direct Myocardial Injury

Among patients with end-stage kidney disease, persistent elevation of cTn is frequently observed. In the context of severe blunt chest trauma, cardiac contusion occurs in 3–56% of cases. Given that cardiac contusion may lead to lethal arrhythmias and heart failure, prompt diagnosis holds significant clinical importance [9].

Chronic Kidney Disease and End Stage Renal Disease

In advanced renal failure, cardiac troponin (cTn) concentrations exhibit higher peaks and remain detectable for extended periods. Patients with end-stage renal disease (ESRD) already have elevated troponin values before an acute cardiac event, necessitating repeated early measurements to identify a significant rise indicative of acute ischemia. The widely held belief that reduced renal clearance of cTn contributes to elevated values in ESRD patients is complemented by the potential influence of concomitant diseases associated with cTn release, such as

severe heart failure and left ventricular hypertrophy leading to subendocardial ischemia [18].

Coronavirus Disease 2019 (COVID-19)

Elevated troponin levels are commonly observed in patients with or suspected of having COVID-19 infection. Troponin testing is a routine practice in hospitalized COVID-19 patients due to its potential prognostic value and as a baseline for comparison in those who develop manifestations of possible myocardial injury, such as heart failure or arrhythmia. Some experts also advocate troponin testing in selected outpatients with an uncertain level of risk. Notably, troponin levels are most prevalent and elevated in patients with more severe manifestations of COVID-19 [19].

Tachycardia

Tachycardia alone has been identified as a potential cause of troponin elevations, as evidenced in small case series. In one series involving 21 patients with elevated cTnI levels and normal coronary angiograms, tachycardia was determined to explain the troponin elevation in six patients [20].

Left Ventricular Hypertrophy

Elevations in cardiac troponin (cTn) have been observed in the context of left ventricular hypertrophy (LVH). In a series of 74 consecutive patients undergoing routine echocardiography without clinical evidence of active myocardial ischemia, 7 of 25 patients in the tertile with the greatest LV mass had elevated cTnI. In contrast, one patient in the intermediate range and none in the lowest tertile exhibited elevated troponin levels [21].

Coronary Vasospasm

Myocardial ischemia resulting from coronary vasospasm, such as Prinzmetal angina, can lead to troponin elevations. This was demonstrated in a series of 93 patients with suspected myocardial ischemia, where coronary angiography revealed no hemodynamically significant lesions [22].

Acute Stroke

In the context of acute stroke or intracranial hemorrhage, both elevated cardiac troponin (cTn) levels and ischemic electrocardiographic changes have been reported. In one series involving 149 patients with acute stroke symptoms, 27% exhibited elevated serum cTnI. Additionally, elevations in cTnI have been observed in two case series of patients with subarachnoid hemorrhage [23].

Atrial Fibrillation

Elevated concentrations of cardiac troponin (cTn),

particularly when measured with high-sensitivity (hs) assays, have been documented in patients with atrial fibrillation, even in the absence of clinically overt heart failure or demand myocardial ischemia [24].

Burns

Severe thermal injury is linked to cardiac contractile dysfunction and elevated cardiac troponin. Elevation of cardiac troponin (cTn) is demonstrated in patients with thermal injuries exceeding 25 percent of total body surface area. The increase in cTn appears to be correlated with the extent of burns rather than the patient's age, pre-existing medical conditions, or the administration of resuscitation fluid [25].

Kawasaki Disease

The association between elevated cardiac troponin (cTn) and myocarditis among patients with Kawasaki disease (KD) is not entirely clear. Some suggest a significant increase in cTn among children with Kawasaki disease, indicating acute myocarditis and myocardial cell injury in the early stages of the disease [26].

False-Positive

By definition, 1% of healthy volunteers with minor elevation of cTnT must be labeled as false positives. Causes of false positives include rhabdomyolysis in first and second-generation troponin assays, heterophilic antibodies, rheumatoid factor, fibrin clots, microparticles, and analyzer or analyte malfunction [6].

CONCLUSION

New challenges were posed by the prevalence coronary heart diseases for physicians and people around the world. Many conditions cause elevated blood troponin such as acute coronary syndrome related factors and unrelated acute coronary syndrome factors. Troponin is a protein that released into the bloodstream when there is damage to the body tissue/organs. So troponin is making it a valuable biomarker for detecting tissue/organ related issues. Early diagnosis, facilitated by measurement of troponin levels is a beneficial detection tool to prevent various diseases. With advancements in high sensitivity troponin assays we have improved capabilities to detect minor injuries with greater accuracy. Diagnostic tool as troponin assay has contributed to a reduction in mortality and fewer complications associated with coronary related or unrelated factors.

Understanding the diverse causes of elevated troponin levels extends beyond cardiac diagnoses, playing a crucial role in comprehensive patient care. Troponin elevation, traditionally associated with myocardial infarction, serves as a sensitive indicator for various physiological disruptions. Recognizing these diverse causes enables healthcare professionals to differentiate cardiac issues from other conditions, providing a more nuanced understanding of a patient's overall health. As troponin assays evolve in prognostic assessment and treatment monitoring, a comprehensive grasp of troponin elevation enhances their clinical utility for personalized patient care. Furthermore, physicians must consider a broad range of clinical conditions and patient histories, along with ECG criteria and symptoms, to diagnose acute myocardial infarction accurately. Elevated troponin levels, while indicative, lack diagnostic precision in non-cardiac conditions. The pathophysiology of increased cardiac troponins remains unclear. Therefore, a comprehensive evaluation beyond troponin elevation is essential for an accurate diagnosis of a heart attack.

ACKNOWLEDGEMENTS

N/A.

COMPETING INTERESTS

The authors declare that there is no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

N/A.

CONSENT FOR PUBLICATION

N/A.

AVAILABILITY OF DATA AND MATERIAL

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

FUNDING

This article did not have any funding resources.

AUTHORS' CONTRIBUTIONS

The main idea of the article was from Dr. Mohammad Hassan Kalantar and literature search and data analyses were performed by all the authors. Dr. Majid Kalantar drafted and critically revised the work.

SOURCE(S) OF SUPPORT

There was no funding source endorsing this articles preparation process.

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