Interpretation of Cardiac and Non-Cardiac Causes of Elevated Troponin T Levels in Non-Acute Coronary Syndrome Patients in the Emergency Department

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Abstract
The definition of myocardial infarction was updated in 2000 to include an elevation of cardiac troponin T or I (cTnT or cTnI) alongside clinical evidence of myocardial infarction. The redefinition was jointly done by the American College of Cardiology Committee and the European Society of Cardiology. Since then, cardiac troponin T and I have assumed the position as the primary biochemical markers for diagnosing myocardial infarction. The high sensitivity of cardiac troponin for myocardial necrosis influenced the decision to include cardiac troponins (cTn) in the diagnostic pathway. An elevated cTn level indicates the presence of myocardial injury. However, it does not give the underlying reason for the damage. Apart from acute myocardial infarction (AMI), a range of potential diseases feature troponin release, including heart failure, acute pulmonary embolism, end-stage renal disease, and myocarditis. However, regardless of the mechanism that triggers the release from cardiac myocytes, elevated cTnI and cTnT typically implies a poor prognosis. This review attempts to explain both the cardiac and non-cardiac causes of increased cTnT in emergency department patients.

Introduction And Background
Cardiac troponin T (cTnT), cardiac troponin I isoforms (cTnI), and cardiac troponin C (cTnC) are typically expressed in the cardiac muscle tissues (Figure 1).

**FIGURE 1: Morphology of the troponin complex in cardiac muscle**

Troponin is a three-unit complex of troponin T, I, and C (T for ‘tropomyosin-binding,’ I for ‘inhibitory,’ and C for ‘calcium-binding’). Troponin I (TnI) and T (TnT) have cardiac-specific isoforms and are used for assessing the cardiac injury.

It is important to note that they are the most sensitive and most specific indicators for acute myocardial infarction (AMI) diagnosis [1-4]. Not many studies have reported the cTnT and cTnI expression outside the myocardium, especially in the skeletal muscle [5-7]. However, these studies all have contradictory results.
A study by Giannitis and colleagues resulted in difficulties and wrong differential diagnosis. Coronary pain, resulting in hypotension and left ventricular (LV)-dysfunction (78% vs. 9% in cTnI-negative patients; p < 0.001). There was a significant correlation between the values of cTnI with APACHE II score and the degree of hypotension.
Acute Pericarditis

levels could be triggered by an underlying subclinical heart disease unmasked by strength training. Acute coronary heart disease in athletes who were presumed to be healthy. As such, the elevation of cTn results and extensive cardiac examinations have shown significant distortion of the heart structure and cTnT and not from the constant release of troponin after myocardial necrosis. Conversely, autopsy (MI). This birthed the assumption that an increase in cTn level could result from a transient release of cTnI detected transient increases of small amounts of cTn normalized or decreased within 24 hours after the activity was exercise results from several studies have reported the appearance of cTnI and cTnT after strenuous ultra-endurance event eventually died. Prognostic information. A decrease in cTn concentration is associated with improved left ventricular heart failure, and higher mortality. Patients whose troponin values are on the high side have lower ejection fractions, high clinical grading of heart failure, and necrosis. Other factors, such as the activation of the renin-angiotensin-aldosterone system and the sympathetic nervous system and inflammatory mediators, may also trigger an injury to the myocardium. Myocytes lost are replaced by fibrotic tissue resulting in progressive cardiac dysfunction. Elevation of cTn in heart failure patients indicates myocardial injury. In decompensated heart failure, cTn release is believed to be caused by excessive tension from the myocardium wall due to acute volume and pressure overload. Also, increased strain on the myocardial wall results in subendocardial ischemia. In patients with chronic stable heart failure, high cTn values occurred in 15-23% of cases (> 0.1 ng/ml). In the case of cTnT, values exceeding 0.1 ng/ml have been reported in at least 10-15% of cases [33]. No difference was found between the ischemic and non-ischemic groups [33]. Over 52-55% of the acute HF patients admitted to the facility had increased cTnT values. When cTn occurs in HF, it indicates a poor short and long-term outcome. Patients whose troponin values are on the high side have lower ejection fractions, high clinical grading of heart failure, and higher mortality [54]. It is also important to note that serial cTn measurements can provide prognostic information. A decrease in cTn concentration is associated with improved left ventricular function. On the other hand, persistently increased troponin values were readily expressed in patients who eventually died.

Strenuous Exercise

Results from several studies have reported the appearance of cTnI and cTnT after strenuous ultra-endurance exercise [35]. But then, we do not have a complete understanding of elevated cardiac troponin mechanisms, nor do we have a sense of its prognostic significance. However, after prolonged strength training, only transient increases of small amounts of cTn normalized or decreased within 24 hours after the activity was detected [35]. In addition, the plasma changes differ significantly from those found in myocardial infarction (MI). This birthed the assumption that an increase in cTn level could result from a transient release of cTnI and cTnT and not from the constant release of troponin after myocardial necrosis. Conversely, autopsy results and extensive cardiac examinations have shown significant distortion of the heart structure and acute coronary heart disease in athletes who were presumed to be healthy. As such, the elevation of cTn levels could be triggered by an underlying subclinical heart disease unmasked by strength training.

Acute Pericarditis

Acute pericarditis/myocarditis is typically diagnosed in patients in the emergency department presenting with acute chest pain. While troponins may not be present in the pericardium, it was reported that cTnI was
elevated in 32-49% of pericarditis cases due to the involvement of the epicardium in the process of inflammation. In patients presenting with acute myocarditis, cTnI concentrations are seen to increase in no less than 34% of patients [36].

Coronary angiography is usually performed in patients who have pericarditis. The aim is to rule out myocardial infarction. In the absence of coronary disease, endomyocardial biopsies (EMB) are done to establish an accurate diagnosis. However, EMB shows lymphocytic and myocytolysis infiltrates in only 10 - 25% of patients with myocarditis. Increased cTnT values have a higher sensitivity than EMB and may have the capacity to confirm the clinical diagnosis of myocarditis [36].

**Chronic Renal Failure**

Looking at modern concepts, one may consider cardiac troponins to be products of normal myocardial metabolism [37], and there’s a lack of troponin-negative patients. These concepts were birthed due to the establishment of the most recent immunoassays for the detection of cardiac troponin [38, 39]. For example, cardiac troponin molecules can be detected in all healthy patients using ultrasensitive test systems. The concentration of the molecules is usually below the threshold level. On the other hand, if one exceeds this threshold, the concentrations of troponin will be considered abnormal, and clinicians should review the possible causes of elevation.

Because of the presence of cardiac troponins in healthy patients, researchers are now compelled to consider what causes their release from cardiomyocytes under normal circumstances [37]. It is also worth mentioning that the mechanism by which troponin molecules are eliminated from the general circulation is a major factor that may affect the concentration of troponin in the serum. Currently, troponins are eliminated from the blood serum through the following methods:

- In reticuloendothelial system cells (intracellular cleavage by certain proteases)
- In the serum (extracellular cleavage by proteolytic enzymes). It has been established that thrombin (an enzyme of the hemostasis system) causes the troponin T molecule to cleave into two fragments.
- Glomerular filtration

Glomerular filtration, without a doubt, is the most discussed and possibly the primary mechanism by which cardiac troponin is eliminated with regards to clinical significance. Some researchers have reported that the involvement of the kidneys in the elimination of cardiac troponin is highly doubtful and controversial, owing to the fact that cardiac troponin molecules were not detected in the urine of the majority of the patients [40]. Regardless, high concentrations of cardiac troponin in renal patients without any symptoms of cardiovascular disease have been seen several times in clinical practice [36]. These findings are an indication that the renal system is involved in the elimination of serum troponin.

**Conclusions**

Based on this review, it can be concluded that several factors can contribute to the elevation of cardiac troponin concentration. The pathological conditions (chronic renal failure, pulmonary embolism, sepsis, and inflammatory myocardial disease) and the physiological conditions (strength training) are very common causes of high cardiac troponin concentration. It is also important to note that modern sensitive techniques for the determination of cardiac troponin detect troponin molecules at a higher frequency and in a larger number of individuals at the same time. It is worth mentioning that, for the sake of increasing a key criterion of lab diagnostics, the developers gave up another key criterion for diagnostics (specificity of immunoassays). Clinicians should consider this circumstance when interpreting laboratory results of patients admitted with possible acute myocardial infarction. Otherwise, the chances of misdiagnosis in the blood serum after these are numerous and differ from the mechanism of increased cardiac troponins in acute MI. Taking note of the mechanisms of high-sensitivity cardiac troponin concentration elevation will improve the differential diagnosis of acute myocardial infarction from the conditions listed above and also introduce additional diagnostic techniques. For instance, one can determine high-sensitivity troponins in serum after pharmacological or physical exercise, thus troponins can serve as markers of latent ischemic disease.

**Additional Information**

**Disclosures**

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.
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