

Troponin I in the intensive care unit setting: from the heart to the heart

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Abstract When measured in the plasma, cardiac troponins T (cTnT) and I (cTnI) are considered to be highly specific markers of myocardial cell damage; however, research has demonstrated that troponin elevation may be associated with causes other than coronary artery disease. In the intensive care unit (ICU) setting, increased cTnI levels are quite common findings and when documented, even on admission, intensivists should bear in mind that this laboratory finding holds a prognostic role independent of the reason for ICU admission. The mechanism(s) (such as demand ischemia, myocardial strain, etc.) and not simply the cause (i.e., renal failure) of the increment in serum cTnI should be investigated to better tailor the therapeutic regimen in the single patient. In this review, we therefore consider the nonthrombotic causes of troponin elevation in the critical setting.

Keywords Troponin · Critically ill · Intensive care unit · Trauma · Sepsis

Introduction

Damage of myocardial cells results in the release of cardiac troponin I (cTnI) and T (cTnT) into circulation. These cardiac troponins differ from troponins present in the skeletal muscles and in physiological conditions they are not detectable in the blood. Thus, when measured in the plasma, cTnT and cTnI are considered to be highly specific markers of myocardial cell damage.

The European Society of Cardiology/American College of Cardiology (ESC/ACC) Committee Consensus document states that there is “no discernible threshold below which an elevated value of cardiac troponin would be harmless” and that “any amount of myocardial damage...implies an impaired clinical outcome for the patients” [1–3].

However, several lines of evidence [1–4] indicate that the myocardial necrosis signified by troponin elevation may not necessarily be due to atherosclerotic coronary artery disease.

Among patients with a high pretest probability or clinical suspicion of thrombotic coronary artery disease, the diagnostic and prognostic values of troponin are clear. In fact, it is known that mortality at 30 days is significantly higher in patients with chest pain and elevated troponin levels at presentation than in patients with no biomarkers detected [5]. Furthermore, the risk for subsequent death appears to be related to the degree of troponin elevation. There is a statistically significant increase in mortality with increasing levels of troponin, and the relative risk for death is 7.8 in the highest troponin levels [6].

Troponin testing is now also being used as a screening tool among patients with a low pretest probability of thrombotic coronary artery disease. Given the high sensitivity of cardiac troponin for detecting even minimal

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myocardial-cell necrosis, these markers may become “positive” even in the absence of thrombotic acute coronary syndromes. In fact, during the past few years, emerging data have been published showing that elevated troponin levels are present not only in patients with acute coronary syndromes but also in those with myocarditis, percutaneous cardiac interventions, infiltrative disease of the myocardium (e.g., amyloidosis and sarcoidosis), cardiac trauma, tachycardia, congestive heart failure and perioperative cardiac complications. Noncardiac disease with reported elevated cardiac troponin levels includes sepsis or septic shock, renal failure, pulmonary embolism, hypothyroidism, transient ischemic attack, stroke and subarachnoid bleeding [7–9].

Among patients in ICU who have an elevation in troponin level but do not have an acute thrombotic coronary syndrome, the etiology and prognostic value of this finding have not been well defined. This review will focus on investigating the clinical and prognostic significances of troponin elevation in critically ill patients in the intensive care unit (ICU) setting.

Biochemistry

The troponins form complexes with actin and tropomyosin on the thin filament of the contractile apparatus in striated muscle. The troponin complex consists of three subunits such as troponin C, troponin T and troponin I. The troponin C binds calcium and regulates activation of the thin filaments during contraction. Troponin T binds the troponin complex to tropomyosin. Troponin I is inhibitory and prevents contractions in the absence of calcium and troponin C.

Troponin I (TnI) has three specific isoforms such as fast skeletal, slow skeletal and cardiac muscle [10]. TnI becomes the sole troponin I expressed in myocardial cells after postnatal development, prior to which slow skeletal troponin I predominates [10]. TnI is not expressed in the skeletal muscle and that is why it is considered to be a highly specific marker of cardiac injury, together with TnT [11].

Troponin T has also three specific isoforms such as fast skeletal, low skeletal and cardiac muscle. Troponin C has two isoforms. The fast isoform is found in skeletal muscle whereas the slow isoform is found in both skeletal and cardiac muscles. The lack of cardiac specificity has meant that no assay has been developed to test for this protein.

The release of cardiac troponin from myocyte into the blood can be due to *reversible* or *irreversible* cell damage (Table 1). For example, it is believed that myocardial depressive factors (released in the setting of sepsis and other inflammatory states) cause degradation of free

Table 1 Mechanisms of release of cardiac troponins

Irreversible damage
Acute myocardial infarction
Cardiac contusion
Reversible damage
Angina
Sepsis
Myocarditis

troponin in situ to lower molecular-weight fragments [12]. With increased membrane permeability, those smaller troponin fragments could be released into the systemic circulation. In this setting, myocyte damage may not be permanent, and, thus, cell necrosis does not occur. This notion is also supported by the clinical observation that myocardial depression during sepsis is a fully reversible process in most surviving patients [13]. In the daily ICU practice, the distinction between reversible and irreversible cell damages [myocardial necrosis and myocardial infarction (MI)] is not straightforward. Even according to the redefined definition [14], the diagnosis of MI remains clinical: detection of elevated values of cardiac biomarkers above the 99th percentile of normal together with one of the following: ischemic symptoms, ECG changes indicative of new ischemia, development of pathological Q waves or imaging evidence of new loss of viable myocardium. In the ICU setting, endotracheal intubation, coma and use of sedatives and narcotics all limit the ability of critical patients to report symptoms associated with ischemia. This is the reason why the diagnosis of MI in critically ill patients is not simple since accepted criteria are not always applicable to these patients.

Troponin assays are not only more sensitive but also more specific than CK-MB assays [15]. Expression of CK-MB is not unique to the heart, since CK-MB is found in skeletal muscle and the gastrointestinal tract as well as in the uterus of pregnant women. The specificity of CK-MB can be enhanced by the calculation of the CK-MB/CK ratio. However, the use of this ratio markedly reduces sensitivity in patients with concurrent cardiac and skeletal muscle injury.

Nonthrombotic mechanisms of troponin elevation in ICU setting (Table 2)

Demand ischemia

The concept of “demand ischemia” without significant artery disease refers to a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting stenosis. Myocardial oxygen demand frequently increases in the setting of sepsis or septic shock and the systemic

Table 2 Nonthrombotic mechanisms of troponin elevation in ICU setting

Demand ischemia: a mismatch between myocardial oxygen demand and supply in the absence of flow-limiting stenosis (i.e., systemic inflammatory response, hypotension, tachyarrhythmias)
Myocardial ischemia in the absence of fixed obstructive coronary disease: an imbalance of the autonomic nervous system and increased catecholamine effect on the myocardial cells (i.e., vasospastic angina, acute stroke or intracranial hemorrhage and subarachnoid hemorrhage)
Direct myocardial damage: cell injury by traumatic or inflammatory process (i.e., pericarditis and myocarditis)
Myocardial strain: volume and pressure overload of both ventricles (i.e., congestive heart failure, pulmonary embolism)

inflammatory response [16–18], hypotension or hypovolemia [19] and atrial fibrillation or other tachyarrhythmias [20].

Myocardial ischemia in the absence of fixed obstructive coronary artery disease

In the absence of acute coronary syndromes with thrombus formation and total vessel occlusion or distal embolization, myocardial ischemia can be caused by *vasospasm* (Prinzmetal angina) [21]. Elevated cardiac troponin levels along with ischemic changes on the electrocardiogram are frequently observed in the setting of acute stroke or intracranial hemorrhage. Up to 27% of patients with acute stroke symptoms [22] and 20% of patients with a diagnosis of subarachnoid hemorrhage [23] were found to have increased troponin levels. The most possible explanation of troponin elevation and myocardial damage in this setting is an imbalance of the autonomic nervous system and increased catecholamine effect on the myocardial cells, rather than pre-existing coronary artery disease [24].

Direct myocardial damage

Troponin elevation can occur in the presence of structural heart disease. The mechanisms of troponin release in these circumstances include cell injury by traumatic or inflammatory process.

Inflammatory disorders leading to troponin elevation include acute pericarditis [25], myocarditis [26] and an immune response after heart transplantation. In fact, chronically elevated troponin levels after cardiac transplantation may be associated with a poorer prognosis [27].

Myocardial strain

Volume and pressure overload of both the right and left ventricles, as in congestive heart failure, can lead to the

release of cardiac troponin in the absence of myocardial ischemia, because of excessive wall tension or “myocardial strain” (defined as the percentage change of a structure from its initial length with the application of stress) [28].

Noncardiac causes of elevated cardiac troponins

Renal diseases

Both TnI and TnT are found to be elevated in patients with end-stage renal disease (ESRD) in the absence of active cardiac disease. Therefore, a higher troponin threshold was proposed for the diagnosis of myocardial ischemia in patients with chronic renal insufficiency [29]. The concentration of the cardiac troponins [30] can vary over time, with up to a 50% variation being noted over a year [31]. The prevalence of increased troponin values of patients with chronic renal failure in the absence of clinically suspected ischemia may be as high as 53% [32]. This may be the result of small areas of clinically silent myocardial necrosis, but other causes, such as increased left ventricular mass and impaired renal troponin excretion have also been proposed. Recent evidence demonstrated that troponin T is fragmented into molecules small enough to be renally excreted [33].

Irrespective of the cause, an elevated concentration identifies patients with renal disease at greater risk of all-cause mortality and a negative troponin remains a good prognostic predictor in both the acute and chronic setting of renal disease.

Sepsis or septic shock

Elevated troponin levels either cTnI or cTnT have been reported among critically ill patients suffering from sepsis or septic shock [18]. Of the 20 septic patients treated in an ICU, 85% were noted to have elevated troponin level. Majority (59%) had no evidence of significant coronary artery disease [18]. Similarly, Guest et al. found that elevated cardiac troponin level is a common finding among critically ill patients and is associated with a significant increase in mortality [16]. Recently, Ammann et al. [17] reported that 55% of included critical ill patients (total number 58 patients; 88% suffered from sepsis, septic shock or systemic inflammatory response syndrome) without evidence of acute coronary syndromes were cTnT- or cTnI-positive, or both (cTnT > 0.1 or cTnT > 0.1 µg/l). In addition, the left ventricular ejection fraction was significantly lower among troponin positive patients. Flow-limiting coronary artery disease could only be demonstrated among 38% of troponin-positive patients indicating that elevated troponin levels are due to causes other than

coronary syndromes. Thus, troponin elevation among patients with sepsis and systemic inflammatory response syndrome with or without shock in the ICU is common and largely affects patients without significant coronary artery disease. Troponin elevation is associated with a worse prognosis, but whether any cardiovascular intervention could improve outcomes among these patients is unclear. Although a causal relationship has yet to be established, inflammatory mediators in conjunction with a myocardial oxygen demand supply mismatch may be possible explanations for this phenomenon.

Pulmonary embolism

Patients with acute pulmonary embolism are likely to have elevated cardiac troponin levels [34, 35]. Mehta et al. [36] reported that among 38 patients with pulmonary embolism [exclusion criteria were history of coronary artery disease, chronic renal failure, evidence of ongoing infection or inflammatory disease, or a history of moderate or severe chronic obstructive pulmonary disease (COPD)], 47% had elevated cTnI levels (cTnI > 0.4 µg/l) [36]. Significant clinical signs in the cTnI-positive group were right ventricular dilatation/hypokinesia, higher right ventricular systolic pressure and lower mean systemic blood pressure.

Chronic obstructive pulmonary disease

Baillard et al. [37] included 71 ICU patients hospitalized for severe exacerbation of COPD, in whom pulmonary embolism could not be completely excluded. Eighteen of these patients showed elevated cTnI levels (cTnI > 0.5 µg/l). There were no significant differences with respect to a history of coronary artery disease and cardiovascular risk factors between cTnI-positive and cTnI-negative patients.

Troponin I and critical illnesses

Noble et al. [38] observed that increased serum cTnI concentration occurs frequently in the ICU (in their series 70.6%, 77/109 patients), suggesting that there is a high prevalence of cardiac injury in these patients. Guest et al. [16] showed that the incidence of cardiac injury as defined by an elevated level of cTnI was unexpectedly high among medical ICU patients and was associated with increased patients morbidity and mortality. Kollef et al. [39] evaluated, in a cohort of 260 adult patients admitted to a medical ICU, the relative importance of recognized cardiac dysfunction and unrecognized cardiac injury to hospital mortality. Fifty-five (21.2%) patients had clinical evidence of cardiac dysfunction, among whom 22 (40%) had an elevated level of cardiac troponin I. A total of 41 patients (15.8%) had evidence of acute myocardial injury on the

basis of elevated levels of cardiac troponin I. Multiple logistic-regression analysis controlling for potential confounding variables demonstrated that the presence of clinically recognized cardiac dysfunction was independently associated with hospital mortality. However, having an elevated blood level of cTnI was found not to be an independent determinant of hospital mortality. The authors conclude that, among critically ill patients, recognized cardiac dysfunction is an independent determinant of hospital mortality. The identification of unrecognized cardiac injury, using serial measurements of cardiac troponin I, did not independently contribute to the prediction of hospital mortality.

Drug-abuse and troponin

Currently, cocaine use is responsible for more emergency department visits than any other illicit drugs [40]. Because most cocaine users are young, they are at a lower risk for coronary artery atherosclerotic disease. An estimated 25 million people between the ages of 26 and 34 years have used cocaine at least once, 20% were women and 30% men. Habitual users of cocaine are estimated to number 1.5 million. ECG findings can be misleading in the diagnosis because the early repolarization syndrome, a normal variant, is a frequent finding. The measurement of cardiac troponin levels is the most reliable diagnostic test. Kontos et al. [41] evaluated the utility of troponin I in patients with cocaine-associated chest pain. These authors observed that most patients with cTnI elevations meet CK-MB criteria for MI, as well as have a high incidence of underlying significant disease. They concluded that in their population troponin I appeared to have an equivalent diagnostic accuracy compared with CK-MB for diagnosing necrosis in patients with cocaine-associated chest pain and suspected MI. MI after cocaine is multifactorial since it involves several mechanisms which are still under debate. Some authors [42–43] suggest that cocaine-induced myocardial ischemia is to be related to coronary vasospasms. Others [44–46] point to coronary thrombosis since cocaine activates platelets, increases platelet aggregability and potentiates thromboxane formation promoting thrombus formation. This is a controversial area and so far the role of spasm or thrombosis or other factors remain uncertain [47, 48].

Rhabdomyolysis

Punukollu et al. [49] examined the etiology and clinical significance of elevated cTnI in 91 consecutive patients with rhabdomyolysis. Patients were divided into two groups namely, cTnI-positive with serum cTnI > 0.6 ng/ml ($n = 19$) and cTnI-negative with serum cTnI < 0.6 ng/ml ($n = 72$). Prevalence of cardiovascular risk factors was

equal in both groups. Illicit substance use was more common in the cTnI-positive group (31% vs. 14%, $P = 0.04$). Interestingly, none of the cTnI-positive patients had segmental wall motion abnormalities at transthoracic echocardiography (TTE). The duration of hospitalization was longer in the cTnI-positive group but there was no significant difference in mortality. The authors concluded that in rhabdomyolysis, serum cTnI may be elevated unrelated to the degree of muscle damage, renal failure and cardiovascular risk factors, and is likely related to the etiology of rhabdomyolysis, as is evidenced by significantly higher serum cTnI with illicit substance use, hypotension, and sepsis. In patients with rhabdomyolysis, elevated serum cTnI is associated with a higher morbidity.

Troponin I and trauma

The frequency and prognostic influence of cardiac injury in patients with blunt chest trauma are controversial. Myocardial contusion is reported to be present in as few as 0% of patients and as many as 63% with blunt chest trauma depending on the criteria used for establishing the diagnosis [50]. Chest pain, dyspnea and nonspecific electrocardiographic changes are frequently present in patients with chest trauma, even in the absence of cardiac injuries [51].

Blunt cardiac injury (BCI) is an elusive term over which the trauma community has agonized for decades. The real challenge becomes to identify patients with a high likelihood to develop cardiac complications and restrict advanced investigations and monitoring only to them [52–53]. These patients are deemed to have clinically significant BCI (SigBCI). Ideally, patients at risk for SigBCI would be immediately admitted to a highly monitored ward, whereas patients at no risk would be discharged early in the absence of other injuries. This distinction should be made early and by simple methods without taxing hospital resources inappropriately. In recent years, the availability of measuring serum levels of troponin I, a myocardial-specific enzyme, seemed to shed a light on early diagnosis of SigBCI in trauma patients.

Unfortunately, existing scientific evidence is still controversial on this topic, since the results from published studies cannot be compared as criteria for patient inclusion vary, definition of cardiac blunt injury differs, methods for BCI detection are variable and a metaanalysis is lacking.

Discrepancy between available clinical studies may arise from the following main factors:

- (a) different, not homogeneous, definition(s) of cardiac injury, ranging from ECG alterations, to elevated concentrations of TnI (with or without a serum threshold, which varies from study to study) and,

finally to wall motion alterations detectable at echocardiography [transthoracic and/or transesophageal echocardiography (TTE/TOE)];

- (b) different characteristics of the studied populations; stable trauma patients, unstable trauma patients or patients with severe trauma;
- (c) different methodologies employed to study enrolled patients; in some studies, patients were evaluated by means of TnI levels and ECG, in others by comparing TnI levels and echocardiography finding, depending on availability of tests (in particular TTE and/or TOE). This phenomenon makes difficult to compare results from different studies.

On the other hand, trauma patients frequently show increased levels of TnI. Since elevation of TnI holds a prognostic role in this setting, intensivists should make an attempt to elucidate its pathophysiological mechanisms in the single patient, besides and beyond BCI. In this way, they could perform a correct stratification of risk in these patients and tailor a therapeutical strategy.

In the following, existing data are briefly summarized.

In patients with blunt chest trauma the first reports documented [54–55] that measurement of TnI accurately detected cardiac injury in patients with blunt chest trauma. Afterward, other papers emphasized the importance of *timing* of TnI measurements. In fact, Collins et al. [56] reported that normal troponin levels 4–6 h post-injury effectively exclude the diagnosis of cardiac contusion. Similarly, Velmahos et al. [57] concluded that the combination of normal ECG and TnI on admission and 8 h later is able to rule out the diagnosis of SigBCI. Their results were somewhat comparable with those by Salim et al. [58] who similarly concluded that only patients with abnormal ECG and TnI needed close monitoring for at least 24 h.

On the other hand, Edouard et al. [59] distinguished three groups of patients according to the time course of troponin I, three groups of patients were defined a priori: very transient (≤ 12 h) and limited release (troponin I < 2 $\mu\text{g/l}$), transient (≤ 36 h) and significant release (troponin I ≥ 2 $\mu\text{g/l}$), and sustained (> 36 h) and significant release (troponin I > 2 $\mu\text{g/l}$). Unfortunately, according to these authors, although a sustained and significant release of troponin I was frequently associated with chest trauma, a significant myocardial contusion may occur without troponin I release and, moreover, troponin I release does not have a prognostic value in trauma patients.

Besides, Mori et al. [60] introduced the concept of a “serum troponin threshold” for diagnosing of SigBCI in trauma patients. In fact, they observed that abnormal titers of TnI suggesting myocardial injury were detectable in more than half of the patients but myocardial contusion could be detected by TOE only for TnI levels > 1 ng/ml; cTnI ranging

between 0.4 and 1 ng/ml might be indicative of myocardial microlesions, not detectable by echocardiography.

More recently, Rajan et al. [61], considered both *timing* and *serum threshold* of troponin release. The authors concluded that the levels of cTnI below 1.05 $\mu\text{g/l}$ in asymptomatic patients at admission and within the first 6 h after admission rule out myocardial injury, whereas positive cTn levels above 1.05 $\mu\text{g/l}$ mandate further cardiologic workup for the detection and management of myocardial injury.

Finally, the prognostic role of cTnI was investigated by Bertinchant et al. [62] in hemodynamically stable patients with suspected myocardial contusion after blunt chest trauma. The authors documented a poor relationship between cardiac troponin increase and both early and late clinically outcomes.

In a population of patients with blunt chest trauma (consecutively admitted to our ICU from January 1 to December 31, 2004), we evaluated whether cardiac troponin on admission could offer the possibility of stratification of severity and risk of adverse outcome. We also assessed the possible relation(s) between TnI levels and ECG changes and with abnormalities at TTE/TOE in these patients. Three subgroups of patients were considered: (1) with TnI < 0.1 ng/ml; (2) with TnI between 0.1 and 1 ng/ml; and (3) with TnI > 1 ng/ml. The reasons for trauma were motor vehicle accident in 43 (69%), accidental fall in 11 (18 %) and other in 8 (13%). The length of stay was 13 ± 12 days and intra ICU mortality 19.4% (12/62). At ECG, a complete RRBB was detected in 8 (13%) patients, an incomplete RRBB in 7 (11%), PR interval was 0.12 ± 0.39 ms and QT interval was 406 ± 6 ms. At TTE/TOE pericardial effusion was observed in 16 points (26%), wall motion abnormalities in 5 (8%) and cardiac hematoma in 1 (2%). We observed that (a) high levels of TnI at admission are associated with a high intra ICU mortality, thus indicating a prognostic role for TnI; (b) TnI levels are not related with ST elevation, mostly associated with myocardial injury; (c) increased levels of TnI was detected in the 64% of patients without wall motion abnormalities at TTE/TOE.

On the basis of our results and of our experience, we elaborated a flowchart (Fig. 1) we use on our daily practice in our ICU. In the presence of increased TnI levels, we perform an echocardiogram. The choice of TTE versus TOE depends not only on the acoustic window but also mainly on the clinical impending problem, since, in our opinion, echocardiography is to be considered in the ICU setting a tool to solve a clinical problem. For example, to evaluate a hemodynamically unstable patient, TOE is preferred even if the transthoracic acoustic window is acceptable [63]. If the echocardiogram is normal, only troponin levels will be monitored afterward. On the other hand, if echocardiographic abnormalities are detected, the

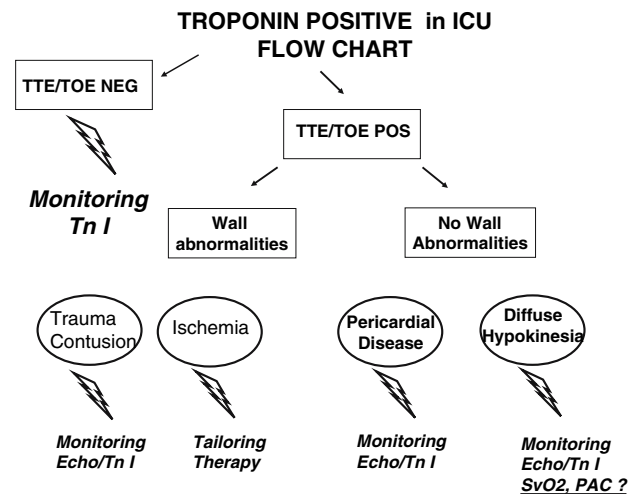


Fig. 1 Proposed flow-chart for the assesment of trauma patients with positive troponin

patients will be monitored by means of both TnI levels and serial echocardiograms. We are performing further studies (still on going) to assess the feasibility as well as costs of this proposed flowchart.

Conclusion

In the ICU setting, increased troponin I levels are quite a common finding. In our opinion, in the presence of a patients with higher TnI concentrations, even on admission, intensivists should bear in mind that this laboratory finding holds a prognostic role independent of the reason for ICU admission (sepsis, trauma, acute respiratory failure, shock, etc.). Second, the mechanism(s) (such as demand ischemia, myocardial strain, etc.) and not simply the cause (i.e., renal failure) of the increment in serum TnI should investigated to better tailor the therapeutical regimen in the single patient. In this context, also diagnostic tests (such as echocardiogram, CT scan) could help to rule out or identify possible causes for higher TnI levels (i.e., myocardial wall motion abnormalities and bleeding).

However, available data on this topic are so far heterogeneous and, somewhat, controversial. Further studies are needed to assess the relationship between therapy based on TnI levels and whether measuring TnI levels in the critically ill could help in monitoring the efficacy of therapy.

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