



Professional article

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Snezana Ciric Zdravkovic

Clinic of Cardiovascular Disease
Clinical Center Nis**CARDIAC TROPONIN RELEASE
UNRELATED TO ACUTE
CORONARY SYNDROME**

SUMMARY

Cardiac troponin T and troponin I are the most specific and sensitive laboratory markers of myocardial cell injury. Accordingly, the definition of acute myocardial infarctions was based on elevations of cardiac troponins in blood in the setting of ischemia. Acute coronary syndrome without ST elevation have attributed troponin measurements a central role in the diagnostic work-up and therapeutic decision making. The test results should be available within 30 to 60 minutes, because elevated troponins are helpful in identifying the patients who benefit most from early invasive strategies, anticoagulant therapy with glycoprotein IIb/IIIa antagonists used, and in low molecular weight heparin (LMWH) therapy. Troponin elevations are mostly, but not necessarily always, related to ischemic cell injury in acute coronary syndrome. An elevation of cTn indicates the presence of, but not the underlying reasons for, myocardial injury. Abnormal values have been described in various conditions not related to acute coronary disease, like myocarditis, pulmonary embolism, acute heart failure, septic shock, and as a result of cardiotoxic drugs as well as after therapeutic procedures, such as coronary angioplasty, electrophysiological ablations, or electrical cardioversions. In intensive care unit, pulmonary embolism and perimyocarditis represent the most important differential diagnosis associated with elevated troponin levels. In acute pulmonary embolism, troponins probably rise because of acute right heart overload. The release is of shorter duration than in unstable angina, and the peak level is linked to the outcome. In histologically confirmed myocarditis, troponins are regularly elevated but also rise in about half of the patients with only clinically suspected myocarditis.

Key words: acute coronary syndrome, troponins T and I, non-coronary troponin elevation

INTRODUCTION

Heart troponins are used as specific markers for acute coronary syndrome (ACS) diagnosis. The decision for including cardiac troponins (cTn) in diagnostic pathway was made because of the high sensitivity of cTn for detection of even small percentage of cells affected with myocardial necrosis. An elevation of cTn indicates the presence

of, but not the underlying reason for, myocardial injury. Hence, besides acute myocardial infarction (AIM), there are hundreds of potential diseases with troponin release, including acute pulmonary embolism, heart failure, myocarditis, and end stage renal disease. But regardless of what the release mechanism into the blood from cardiac myocytes is, elevated cTnT and cTnI almost always imply a poor prognosis (1).

The cardiac isoforms troponin T and I are only expressed in cardiac muscle. Hence, cardiac troponin cTnT and cTnI are more specific than creatinine kinase (CK) values for myocardial injury and, because of their high sensitivity, they may even be elevated when CK-MB concentrations are not. cTn are found as structural (bound) proteins and as a small free pool that exists in the cytosol, which is about 6-8% for cTnT and 3.5% for cTnI. In some diseases, and supposedly in the case of pulmonary embolism or after endurance physical exercise, a transient leakage of the cytosolic pool of cTn, although never proven, cannot be excluded. Following myocardial damage, cTn egress rapidly from the myocyte and will appear in blood after 2-4 hours and persist long enough (up to 10-21 days) for convenient diagnosis. Furthermore, making ideal biomarkers should be imperative in the future. This did expand the diagnostic capacity to detect micro-myocardial infarction, which was not evident by CK-MB measurements. cTn do not only allow for more sensitive diagnosis of AMI but also the most important predictor of acute thrombotic risk (1,2). (Figure 1).

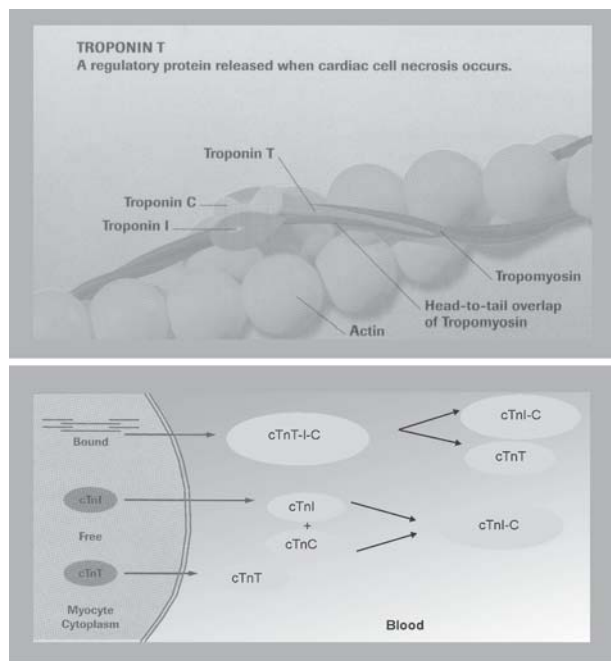


Figure 1. Schematic representation of the cardiac myofibrillar thin filament. Cardiac troponins exist in a structural (bound) form and in free cytosolic pool. Cardiac troponins are released from myocytes as complexes or as free proteins as indicated on the right.

Several angiographic and angioscopic studies have demonstrated that the presence and magnitude of intracoronary thrombus is directly related to the concentration of cTn. Therefore, cTn is regarded as a surrogate marker for activated plaque

and intracoronary thrombus. As an indirect finding, numerous randomised trials have found that patients with a positive troponin have a good result from a more intense antithrombin or antiplatelet treatment and also from an early invasive strategy (3).

Recent studies report significant number of critically ill patients without ACS, whose troponins are positive, especially in sepsis, pulmonary embolism, pericarditis/myocarditis, heart failure, renal end stage disease, stroke etc. Data shows that troponin elevation can be used as a new mortality risk factor for intensive care patients without coronary artery disease. Troponins in intensive care patients give additional prognostic information (4).

The aim of the study was to review the current knowledge about non-coronary troponin elevation, their diagnostic and prognostic significance in severe heart diseases. The author thinks that this review rounds up the knowledge of troponin use as a whole.

If clinical conditions suggest that ischaemic mechanism of troponin elevation is not probable, other causes of heart injury must be considered. Potential list can include subendocardial injury because of the wall stress elevation which appears in the patients with congestive heart failure or hypertension with hypertrophy of left ventricle or alternatively in response to tachycardia and haemodynamic compromises (patients in shock) or because of right ventricle injury in patients with pulmonary embolism. Bio-markers can be increased secondarily because of direct trauma as a result of myocardial toxins such as adriamycin or in response to endogenous substances released in critically ill patients (patients with septic shock). Mechanical injury (such as ablation), discharge of implantable cardioverter defibrillator, and conversion, all cause heart injury. Even small transitory abnormalities can cause small degrees of myocardial injury that can be self-renewing. For example, troponin elevation can appear in cardiotropical virus infection with just a small percent of patients that progress in manifested myocarditis or heart failure. Recent investigations suggest that myocarditis is much more frequent than it was previously suspected. It can be diagnosed when sensitive technique like immunohistochemistry for identification of abnormal lymphocyte pools in combination with troponin elevation is used. When the cause of troponin elevation is identified, therapy must be directed towards it (4,5).

Detectable heart injury biomarker elevation is indicative of myocardial injury, but elevation is not a synonym of ischaemic injury mechanism. In fact, troponin elevation is neither now nor has been in the past the synonym of myocardial infarction. The term myocardial infarction must be used when there are

proofs for heart injury, like troponin detection in clinical circumstances consistently with myocardial ischaemia. Clinician must determine whether the troponin elevation is induced by mechanism of ischaemic nature. It is probable that the clinician can determine when the present ischaemic milieu is based on history of coronary heart diseases or presence of risk factors, clinical presentation and ECG. However, if it is unclear whether further ischaemic etiology (for example patients with less typical symptoms, lesser risk factors, unclear changes in ECG) additional information may be necessary to determine the troponin elevation mechanism. The doctor must not make infarction diagnosis only because of the presence of elevated troponin values (2).

Cardiac troponin and percutaneous coronary intervention (PCI) or open heart surgery

Percutaneous coronary intervention

In addition to spontaneous AMI, current guidelines have also labeled postprocedural elevations of troponins after PCI or coronary artery by-pass surgery as AMI. Minor elevations of cTn are frequently observed after elective PCI and are always found after open heart surgery. While there is no doubt as to the cardiac origin of troponins in these settings, neither the exact pathological mechanism nor the prognostic impact of these minor elevations are currently determined (6).

An elevation of cTn has been reported in 24-40% of patients after successful PCI in stable and unstable coronary artery disease. Possible reasons for the appearance of cTn include side branch occlusion, coronary dissection, devices causing transient ischaemia, and microembolisms. Regardless of exact mechanism, contrast-enhanced magnetic resonance imaging has beyond doubt demonstrated that postprocedural increases in cTn are related to myocardial necrosis. In direct comparison, cTn were more sensitive for detection of minor injury and hence were detectable more frequently than CK-MB after elective PCI. Threefold elevation of cTn after successful elective PCI was predictive for future cardiac events, especially for early repeated vascularisation (6)

Open heart surgery

Cardiac troponins are always increased in small amounts and for an average time of five days following open heart surgery, even when no coronary artery bypass is effective. These troponin elevations do not necessarily reflect perioperative MI, but are

more often attributable to myocardial cell injury resulting from incomplete cardioprotection, reperfusion injury, and direct surgical trauma. Therefore, it is difficult to distinguish perioperative MI from „normal“ elevations of cTn, especially as no accepted cut-offs have yet been defined. Recent trials have established a significant association between elevated postoperative troponin values and increased mortality and morbidity (6).

Cardiac troponin release unrelated to ACS

Sepsis/ septic shock

Among patients treated in intensive care units for sepsis or systemic inflammatory response syndrome (SIRS), elevated cTn have been detected in 36% (cTn \geq 0.1 ng/ml) to 85% (cTnI 0.1 ng/ml) of cases (7). Significant coronary artery disease has been ruled out, indicating that other mechanisms underlie these troponin elevations. One reason for the release of cTn from damaged myocardial cells might be an oxygen supply-demand mismatch of myocardium. As a consequence of fever and tachycardia, oxygen demand of the myocardium is increased. Simultaneously, oxygen supply of the myocardium is reduced due to systemic hypoxaemia from respiratory failure, microcirculatory dysfunction, hypotension and sometimes anaemia. In addition, local and circulating inflammatory markers including tumor necrosis factor, interleukin 6 and reactive oxygen species, as well as bacterial endo-toxins, may lead to direct myocardial injury by cytotoxic effects. Elevated cTn values provide prognostic information and the extent of cTn elevation seems to correlate with the severity of the disease process. Values of cTn were strongly associated with left ventricular (LV) dysfunction and correlated significantly with the degree of hypotension. Patients with cTnT values \geq 0.2 /L had an increased mortality rate (83% v 38%, $p=0.02$) compared to the group with values below this value (4).

Pulmonary embolism

In acute pulmonary embolism (PE), elevated cTn are found in up to 50% of cases, elevated cTnI values (0.4 ng/ml) were seen in 47%. (8) It is believed that cTn are released from injured right ventricular myocardial cells due to the acute dilatation of the right ventricle as the consequence of the abrupt increase in pulmonary artery pressure. Other possible reasons include reduced coronary perfusion, hypoxaemia from perfusion-ventilation mismatch, systemic hypoperfusion, or a

combination of these factors. Studies investigating the release kinetics of cTnT in patients with PE showed that the peak cTnT was lower and persisted for a shorter time compared to cTnT values in AMI. Hence, in contrast to ACS, where cTn are released only after irreversible myocardial damage, in patients with PE, the brief appearance of amounts of cTn suggests that troponin elevation may be caused by the efflux of the free cytosolic pool of cTnT due to transient membrane leakage (9).

Recently, cTn have emerged as important prognostic tools for risk stratification of patients with PE. Giannitsis et al. (9) showed that troponin-positive patients (≥ 0.1 ng/ml) were at increased risk of a complicated in-hospital course including death, prolonged hypotension, cardiogenic shock, and need for resuscitation. Elevated admission cTnT values correlate significantly with severity of PE. Conversely, normal troponin values are associated with a good outcome. Especially in patients with moderate PE, defined by haemodynamic stability and right ventricular dysfunction, elevated cTn may help in guiding therapeutic management. It has been shown that patients with right ventricular dysfunction determined by echocardiography are at increased risk of adverse clinical outcome. This risk is 10-fold higher in the presence of elevated cTn (> 0.04 ng/ml), justifying a more aggressive treatment approach such as thrombolysis or embolectomy (8,9,10).

Acute and chronic heart failure

Elevated cTn in heart failure (HF) are associated with decreased left ventricular ejection fraction and correlate with severity of heart failure and prognosis. The aggravation of HF, ischaemic or non-ischaemic, results from progressive myocyte loss caused by necrosis and apoptosis. Additional factors, including the activation of renin-angiotensin-aldosterone and sympathetic nervous systems as well as inflammatory mediators, may contribute to myocardial injury. Lost myocytes are replaced by fibrotic tissue leading to progressive cardiac dysfunction. cTn elevations in patients with HF reflect myocardial injury. In the setting of decompensated heart failure (HF), the release of cTn is thought to be caused by excessive myocardial wall tension from acute volume and pressure overload. In addition, increased wall strain leads to subendocardial ischaemia. In patients with chronic stable HF, elevated cTnI values were found in 15-23% of cases (> 0.1 ng/ml). For cTnT, values above 0.1 ng/ml were reported in 10-15% of cases. There was no difference between the ischaemic and non-ischaemic group. Of the patients admitted to hospital

because of acute HF, 52-55% had elevated cTnT value (11). The presence of cTn in HF predicts a poorer short and long-term outcome. Patients with increased troponin values have significantly lower ejection fractions, higher clinical grading of HF (NYHA functional class) and greater mortality. Moreover, serial measurements of cTn could provide additional prognostic information. A decrease of cTn is associated with an improvement of left ventricular function, while persistent elevation of rising troponin values were observed in patients who eventually died (11,12,13).

Strenuous exercise

Several studies have reported the appearance of cTnT or cTnI after strenuous ultraendurance exercise. Interestingly, following prolonged endurance exercise, only transient elevations of small amounts of cTn that decreased or normalized within 24 hours after the race have been detected. These changes in plasma concentrations are very different from those found in MI. This led to the assumption that elevated cTn could result from a transient release of the cytoplasmic pool of cTnT and cTnI and not from continuous release of structurally bound troponin after myocardial necrosis (1,2).

Acute pericarditis/myocarditis

In addition to AMI and acute pulmonary embolism, acute pericarditis/myocarditis is commonly diagnosed in patients with elevated troponins presenting to the emergency room with acute chest pain. Although troponins are not present in the pericardium, cTnI was reported to be elevated in 32-49% of pericarditis cases, as a consequence of the involvement of the epicardium in the inflammatory process. In patients with acute myocarditis, cTnI concentrations have been found to be increased in 34% of the patients (14).

Usually in patients with suspected pericarditis, coronary angiography is performed to rule out MI. In the absence of significant coronary disease, endomyocardial biopsies (EMB) are taken to establish the diagnosis. However, in only 10-25% of patients with clinically suspected myocarditis EMB have shown the typical myocarditis and lymphocytic infiltrates. Elevated cTnT values are seemingly more sensitive than EMB and may confirm the clinical suspicion of myocarditis even in the absence of histological signs of myocarditis (15).

Cardiotoxic chemotherapy

Most chemotherapeutic agents, including anthracyclines, alkylating agents, anti-metabolites or anti-microtubules, can have cardiotoxic side effects. Observed adverse cardiac events following chemotherapy are ischaemia (anti-metabolites, alkylating agents), endomyocardial fibrosis and cardiomyopathy (alkylating agents - for example, anthracyclines), pericarditis (alkylating agents - e.g, cyclophosphamide), and different types of arrhythmias (anti-microtubules-for example, paclitaxel). Routinely, cardiac toxicity is detected by echocardiography, ECG, or endomyocardial biopsies. Recent data suggests that biochemical markers such as troponins and natriuretic peptides could be useful in identifying patients at risk for myocardial damage and in monitoring the development of cardiac damage (1,5).

High frequency ablation/ external current cardioversion/ defibrillator shocks

Following radiofrequency catheter ablation, an elevation of cTn has been reported in more than 90% of patients and is related to direct traumatic myocardial injuries, but this elevation has no prognostic significance. External current cardioversion (ECV) of atrial fibrillation or flutter caused no or only small increases of cTnI and no increases of cTnT, especially when biphasic modus was used. Repetitive defibrillator shocks because of ventricular tachycardia or fibrillation or mechanical cardiac resuscitation are known to release cTn (1,16).

Cardiac infiltrative disorders

In systemic amyloidosis, the extent of cardiac involvement is tightly linked to the clinical outcome. It showed that the median survival of patients with detectable cTnI and cTnT was significantly reduced. It is believed that extracellular amyloid deposition causes compression of myocytes with subsequent release of cTn. In many patients, the diagnosis of cardiac involvement is made incidentally by a positive troponin result in the absence of signs or symptoms of ACS. Routine measurement of cardiac troponin could allow earlier detection of prognostically adverse cardiac involvement (1,5).

Post-heart transplantation

Since the early 1990s, it has been known that cTn can be elevated in nearly all heart transplant recipients for up to 3 months after successful transplantation. In the following years, cTn were found to be related to allograft rejection. It is found that cTnT values increase in parallel with severity of graft rejection. In the group with severe rejection, nearly all patients have elevated cTnT values; if cTnT was negative, significant rejection could be excluded with probability of 96.2%. Troponin was elevated in all patients during the first month following the transplantation. However, the aforementioned study including persistent elevation of cTnI values during the follow-up period of 12 months points to increased risk of subsequent development of coronary artery disease and graft failure. Cardiac troponins can provide additional information, especially if they are negative (15).

Myocardial contusion

In the setting of the severe blunt chest trauma, cardiac contusion occurs in 3-56% of cases. Because cardiac contusion may cause a lethal arrhythmias and heart failure, diagnosis is of great importance. Cardiac troponins have been reported to be elevated in 14-45% of patients with cardiac contusion. Their high negative predictive value helps in precluding cardiac injury after severe chest trauma in conjunction with standard echocardiography (15).

Renal failure/end stage renal disease

In symptomatic patients with suspected ACS, elevation of cTn is associated with adverse outcomes regardless of the degree of renal insufficiency. In patients with advanced renal failure, cTn concentrations develop higher peaks and troponin remains detectable for longer period. Given that patients with end stage renal disease (ESRD) already have elevated troponin values before the acute cardiac event, repeated early measurements are needed to detect a pronounced rise indicating an acute ischaemia (1).

Only sparse information exists for peritoneal dialysis patients. Both cTnT and cTnI are commonly increased in asymptomatic patients with ESRD, even when there is no suspected myocardial ischaemia. Using third generation assay for cTnT, up to 53% (10% coefficient variation, > 0.03 ng/ml) of haemodialysis patients had elevated cTnT values, while elevation of cTnI was less frequently observed (up to 19%). This finding led to the assumption that cTnI would be a more specific marker for myocardial

ischaemia in patients with ESRD than cTnT (1,5,15). This is not true, however, and there are some possible explanations for the different prevalence of the two troponins. First, as mentioned above, the cytosolic unbound fraction of CtnI is half of that of cTnT (approximately 3.5% v 7%). Secondly, the cTnI molecule is more positively loaded than cTnT and has a higher affinity for the negative loaded dialysis membrane. Thirdly, the cTnI protein is more unstable than cTnT and might therefore undergo fragmentation, oxidation, and phosphorylation which might influence epitope binding. Finally, reduced renal clearance of cTn in ESRD patients was widely believed to contribute to elevated cTn values. In addition, increased cTn values can be caused by concomitant diseases known to be associated with

cTn release such as severe HF, left ventricular hypertrophy leading to a subendocardial ischaemia or renal anaemia with consecutive oxygen supply-demand mismatch (1).

CONCLUSION

Troponin elevations are mostly, but not always, related to ischaemic cell injury in acute coronary syndrome. An elevation of cTn indicates the presence of, but not the underlying reasons for, myocardial injury. Abnormal values have been described in various conditions not related to acute coronary disease, like myocarditis, pulmonary embolism, etc. In this case, it has diagnostic and prognostic values.

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OSLOBADANJE TROPONINA VAN AKUTNOG KORONARNOG SINDROMA

Snezana Ćirić Zdravković
Klinika za kardiovaskularne bolesti, Klinički centar Niš

SAŽETAK

Srčani troponin T i I su najspecifičniji i najsenzitivniji laboratorijski markeri miokardnog ćelijskog oštećenja. Shodno tome, definicija akutnog miokardnog infarkta je bazirana na povećanju srčanog troponina u krvi u okolnostima ishemijske. Akutni koronarni sindrom bez ST-segment elevacije je merenjima troponina dao centralnu ulogu u dijagnostici i terapijskom odlučivanju. Rezultati testa moraju biti raspoloživi u okviru 30 do 60 minuta zato što su povećani troponini neophodni u

identifikaciji bolesnika koji će imati najveću korist od rane invazivne strategije, upotrebe glikoprotein antagonista IIb/IIIa, niskomolekularnog heparina (LMWH). Povećanje troponina je u većini, ali ne uvek, povezano sa ishemičnim ćelijskim oštećenjem u akutnom koronarnom sindromu. Povećanje cTn indikuje prisustvo, ali ne i postojeći razlog, za miokardno oštećenje. Abnormalne vrednosti bile su opisane u različitim stanjima koja nisu povezana sa akutnom koronarnom bolešću kao miokarditis, plućni embolizam, akutna srčana insuficijencija, septički šok, kao rezultat kardiotoksičnih lekova, kao i posle terapijskih procedura kao što su koronarna angioplastika, elektrofiziološka ablacija ili električna kardioverzija. U jedinicama intenzivne nege plućni embolizam i perimiokarditis predstavljaju najvažnije diferencijalno dijagnostičke probleme u stanjima sa povećanim nivoima troponina. U akutnom plućnom embolizmu porast troponina je verovatno vezan za akutno opterećenje desne komore. Porast troponina kraće traje nego u nestabilnoj angini, a najviše vrednosti povezane su sa ishodom. U histološki potvrđenom miokarditisu troponini su skoro redovno povećani, kao i u oko polovine bolesnika sa klinički suspektim miokarditisom.

Ključne reči: akutni koronarni sindrom, troponini T i I, nekoronarno povećanje troponina