

## REVIEWS

# Serum Troponin - a Sensitive Indicator of the Cardiac Involvement in Septic States

Andrei Seri<sup>1</sup>, Adrian Madalan<sup>1</sup>, Isabela Tiglea<sup>1,2</sup>, Daciana Marta<sup>3</sup>

## Abstract

Troponin, a serum marker specific for myocardial necrosis, is useful in evaluation of the myocardial involvement during sepsis using noninvasive methods. The aim of this paper is to review the recent studies on troponin release in sepsis. We also inquire the possible mechanistic connection between the excessive amounts of troponin released in the circulation, and the septic states that prompted this clinical laboratory anomaly.

**Keywords:** troponin, sepsis

## Rezumat

Troponina este un marker seric specific de necroză miocardică, util în evaluarea afectării miocardice în sepsis prin metode noninvazive. Scopul articolului este o prezentare a studiilor referitoare la eliberarea de troponină în stările septice. Sunt analizate mecanismele care ar putea explica valorile serice ridicate ale troponinei în aceste circumstanțe.

**Cuvinte cheie:** troponină, sepsis

## INTRODUCTION

Troponins (Tn) are protein associations located on the filaments of the movement-generating apparatus in the striate (both cardiac, and skeletal) musculature. There are three distinct proteins coded by separate genes: TnC, TnI, TnT. They are important regulatory components of the myocardial contraction machine. Their nomenclature reflects the role each of them plays in contraction<sup>1</sup>.

Troponin C (TnC) binds calcium ions in order to generate movement. Troponin T (TnT) binds tropomyosin and forms the troponin-tropomyosin complex. Troponin I (TnI) binds to actin and has the role of anchoring the troponin-tropomyosin complex. The excitation of the striate muscle triggers an action potential that opens the calcium channels and releases the calcium ions into the sarcoplasm. Then, some of this calcium binds to troponin, inducing a conformational

change that relocates tropomyosin in such a manner that the myosin bridges can attach to actin, generating the contraction.

The troponins T and I dosage is well suited for early detection of myocardial damage. Cardiac troponins (cTn) are the most sensitive and specific biochemical markers of the myocardial injury<sup>2</sup>. The aim of this paper is to review data from studies (inclusive of ours) regarding troponin level elevation in sepsis.

## Elevated troponin levels in cardiac diseases

Research in the last several years has shown that the release of cTnI and cTnT from cardiomyocytes indicates serious and irreversible heart muscle damage, and that the augmentation of their blood levels occurs not only in ischemia, but in all myocardial lesions in general<sup>3</sup>.

The introduction of the hs-cTnT (high-sensitivity cTnT) assay in the current clinical practice has reve-

<sup>1</sup> "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

<sup>2</sup> "St. Pantelimon" Emergency Clinical Hospital, Bucharest, Romania

<sup>3</sup> "Victor Babes" National Institute of Pathology, Bucharest, Romania

## Corresponding author:

**Daciana Marta**

"Victor Babes" National Institute of Pathology, 99-101 Splaiul Independenței, 050096, Bucharest, Romania.

E-mail: daciana.marta@ivb.ro

aled a large proportion of patients with minor cardiac troponin increases, the majority of whom do not have myocardial infarct<sup>4</sup>.

The determination of cTn could be useful in a wide range of conditions: acute coronary syndromes, including myocardial infarction, myocarditis, mechanical, chemical, and electrical lesions (contusions, percutaneous transluminal coronary angioplasty, cardiac surgery, cardiac biopsy, defibrillation, cardiotoxic substances exposure)<sup>2</sup>.

### Troponin level increases in non-cardiac conditions

According to the data presented by Thyssen K., and collaborators, elevated levels of troponins are present in sepsis, rhabdomyolysis, kidney failure, pulmonary embolism, pulmonary hypertension, chronic obstructive pulmonary disease, stroke, and under certain medication regimens (e.g. sulfasalazine)<sup>5</sup>.

High values of troponin T have been reported in 12-34% of the stroke patients. A possible cause could be the cardiac injury determined by the autonomic dysregulation following the vascular accident, with massive catecholamines release, leading to the global dysfunction of the left ventricle<sup>6</sup>.

The acute pulmonary embolism is associated with elevated serum cTn levels<sup>7</sup>. The purported mechanism of the resulting right ventricular diastolic insufficiency involves the increased troponin, caused by the microvascular thrombosis.

Recent progress in cancer therapy (anthracycline, biologic agents, e.g. trastuzumab, and multikinase inhibitors, e.g. sunitinib) has extended patient survival, but it has also increased the incidence of the long-term cardiotoxicity<sup>8</sup>.

Sepsis represents one of the most common etiologies of the multiple organ dysfunction syndrome, a very severe condition which requires external support (in the setting of the intensive care unit) in order to maintain the homeostasis of the organism. Anomalies of the cardiac function inherently occur in such demanding conditions, the estimates in the literature placing the figure for the incidence of this ultimate complication around 50% of the subjects afflicted with serious sepsis<sup>9,10</sup>. At the septic shock stage, hypovolemia excluded, pressor medication is characteristically indispensable to maintain satisfactory systemic arterial pressure. Cardiac function monitoring, usually by measurement of the left ventricular ejection fraction, identifies only the advanced-stage myocardial lesions. In contrast, hs-cTnT can predict incipient, more subtle changes in the myocardial structure.

The correct evaluation of the myocardial performance in septic shock is very important when considering the best therapeutic options, but there are a few confounding factors that could impact the diagnostic of the sepsis-induced myocardial dysfunction<sup>11</sup>. Precise measurement or accurate computation of the ventricular function is difficult. The current diagnostic methods have limitations which are responsible for the lack of the consensus regarding the "gold standard" test in the evaluation of the cardiac function. Furthermore, most of the contractility indices are susceptible to peripheral vasodilatation, and the catecholamine stress manifest in sepsis stimulates the myocardium, masking its depression<sup>12</sup>.

Recently it has been shown that cTnT can be used as a routine clinical biomarker to assess the prognosis of the patients with sepsis<sup>13</sup>. A meta-analysis performed recently by Shegin et al. has concluded that the patients with high troponin values face a poorer prognostic - the augmented marker is an ominous predictor of increased mortality<sup>14</sup>.

Several mechanisms have been envisioned to account for troponin release in sepsis. As expected, one model of the process relies on the global myocardial ischemia. Fever and tachycardia increase the oxygen demand, while the oxygen delivery is impaired due to systemic hypoxemia from respiratory failure, microcirculation dysfunction, and hypotension<sup>2</sup>.

The dysfunction manifest at the level of the microcirculation can lead to ischemia and impaired myocardial reperfusion<sup>15</sup>. ver Elst et al. have found that the values of TnI  $\geq 0.1$  correlate with the APACHE II (acute physiology and chronic health evolution) score, and with the degree of hypotension, and they are an independent predictor of the left ventricular dysfunction<sup>10</sup>. Elevated TnI was also reported<sup>16</sup>.

Troponin buildup in plasma can also be determined by other factors which cause microinflammation, or minimal cardiac cell injury. A possible direct injury has been evoked, by myocytotoxic effect due to the bacterial endotoxins, cytokines, or free oxygen radicals generated by the neutrophils, macrophages, and the inflammation of the endothelium<sup>17</sup>.

Current pathophysiological theories regard the microvascular dysfunction, and particularly the endothelial dysfunction, as a central element in initiation, progression, and maintenance of the pathological processes involved in sepsis<sup>18</sup>. The endothelial malfunction causes coagulopathy in the microvasculature bed, the adhesion and migration of the leukocytes, excessive generation of reactive oxygen species, nitric oxide-dependent vasodilatation, cytokines production, and pro-

motes systemic inflammation<sup>19</sup>. The large amounts of nitric oxide generated by the inducible NO-synthase can cause severe liver damage and promote the synthesis of inflammatory cytokines.

The phenomenon of myocardial depression could be mediated by circulating depressant factors, currently incompletely characterized. Among the putative depressant factors: TNF $\alpha$ , and the interleukins IL1 $\beta$  and IL6<sup>20</sup>.

TNF $\alpha$  can increase the permeability of the sarcolemma of cardiomyocytes. The mechanisms of TNF $\alpha$ -induced myocardial depression include activation of the neutral sphingomyelinase, and suppression of the nitric oxide activation. TNF $\alpha$  can also modulate the tissue destruction, and the biosynthesis of intracellular proteases. TNF $\alpha$  is able to induce the activation of the calpains and caspases involved in the contractile proteins degradation, including troponin degradation. Active calpain is released by calpastatin, and further cleaves the cTnI at the carboxy-end. Caspases, the main enzyme effectors involved in the execution stage of the apoptotic process, are activated in two ways: by a mechanism requiring mitochondria participation, or via death receptors. They also contribute in the cleaving of alpha actin, alpha actinin, and troponin T<sup>21</sup>.

The presence of a certain degree of focal cardiac necrosis in septic patients has been established by pathology examination, recognizing the breakage of the sarcoplasmic fibrils, and the necrosis of the contraction bandelets, typically associated with focal reperfusion ischemia and high catecholamines levels<sup>22</sup>.

Interleukin-27 is elevated in the sepsis-induced myocardial dysfunction, and mediates inflammation<sup>23</sup>.

A major cause for the myocardial damage occurred in sepsis can be traced to the superoxide anion and its derived reactive species, formed in large amounts by the activated leukocytes. The oxygen species inflict

structural damage, both at the level of the nucleic acids and the proteins, contributing in this way to the death of the cardiac cells. Under normal circumstances, the reactive oxygen species are inactivated by the cell antioxidant defense systems, but in sepsis these systems are overwhelmed<sup>24</sup>.

Irregardless of the mechanisms of troponin liberation in the blood, the high values of the troponin I or T almost always portend a grim prognostic<sup>25</sup>.

Research done on troponin in patients with septic states has shown the utility of monitoring its levels<sup>26</sup>. Preliminary data from a study done on 111 patients with sepsis, 61 of which associated thrombosis, show a significant difference ( $p < 0,001$ ) between the two lots, with average values of 0,33 ng/l, and 4,26 ng/l, respectively<sup>27</sup>.

## CONCLUSIONS

The clinical studies under course in the last few years have demonstrated that the troponin levels escalate in sepsis, and these abnormally high values have a prognostic signification. Evaluation of the incidence, and understanding of the clinical connotation of the troponin elevations in sepsis are necessary, in the view of the increasing usage of this marker in the clinical practice. Due to the fact that the increased values of cTnT and cTnI associate high rates of mortality, studies enrolling higher numbers of patients are needed for the evaluation of this biological marker as a prognostic factor of cardiac ischemia, especially in severe systemic infections.

Monitoring of the troponin, a marker of myocardial injury, contributes to the recognizing of the myocardial involvement during sepsis using a noninvasive method.

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