Review

Bench-to-bedside review: Significance and interpretation of elevated troponin in septic patients

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Abstract

Because no bedside method is currently available to evaluate myocardial contractility independent of loading conditions, a biological marker that could detect myocardial dysfunction in the early stage of severe sepsis would be a helpful tool in the management of septic patients. Clinical and experimental studies have reported that plasma cardiac troponin levels are increased in sepsis and could indicate myocardial dysfunction and poor outcome. The high prevalence of elevated levels of cardiac troponins in sepsis raises the question of what mechanism results in their release into the circulation. Apart from focal ischemia, several factors may contribute to the microinjury and minimal myocardial cell damage in the setting of septic shock. A possible direct cardiac myocytotoxic effect of endotoxins, cytokines or reactive oxygen radicals induced by the infectious process and produced by activated neutrophils, macrophages and endothelial cells has been postulated. The presence of microvascular failure and regional wall motion abnormalities, which are frequently observed in positive-troponin patients, also suggest ventricular wall strain and cardiac cell necrosis. Altogether, the available studies support the contention that cardiac troponin release is a valuable marker of myocardial injury in patients with septic shock.

Introduction

In 2000, the Joint European Society of Cardiology/American College of Cardiology Committee proposed a new definition of myocardial infarction based predominantly on the detection of the cardiospecific biomarkers troponin T and troponin I in the appropriate clinical setting [1]. Given that cardiac troponin is highly sensitive for detecting even minimal myocardial-cell necrosis, these markers may become 'positive' even in the absence of thrombotic acute coronary syndromes [2]. This may occasionally be related to a spurious troponin elevation but may also be due to several non-thrombotic cardiac and systemic diseases [2-4]. Sepsis and other systemic inflammatory processes may lead to myocardial depression and cellular injury, greatly increased oxygen consumption, reduced microvascular circulation, and decreased oxygen delivery to the heart, ultimately resulting in the release of troponin into the systemic circulation [5]. The aim of this review is to go from bench to bedside to determine what evidence and interests are able to incite intensivists to evaluate the cardiac troponin plasma marker in the context of sepsis.

Limitations in cardiac assessment at the bedside

Abnormalities of cardiac function are frequent in patients with sepsis. Approximately 50% of patients with severe sepsis and septic shock may develop impairment of ventricular performance. Whereas evaluation of myocardial performance during septic shock is of critical importance to select the best therapeutic options, several factors complicate the diagnosis of sepsis-induced myocardial dysfunction in humans. Making accurate measurements of cardiac function is difficult and this is confounded by the inherent difficulty of excluding patients with true coronary insufficiency with sepsis. The available evaluation methods have their strengths and limitations, leading to an absence of consensus regarding the gold standard technique to assess cardiac function. In addition, most of the contractility indexes are affected by peripheral vasodilatation and changes in loading conditions observed in septic shock. In addition, catecholamine stress observed in sepsis stimulates the myocardium and may, therefore, mask myocardial depression. Since alteration of myocardial performance in sepsis may be related to structural abnormalities of the heart, biochemical markers could thus be useful in the diagnosis of sepsis-induced myocardial dysfunction. Recently, plasma cardiac troponin has been proposed as a biomarker that accurately detects myocardial dysfunction and provides prognosis information in septic patients.

IL = interleukin; TNF = tumor necrosis factor.

What are troponins?

Cardiac troponins are regulatory proteins that control the calcium-mediated interaction of actin and myosin. The troponin complex consists of three subunits: troponin T, which binds to tropomyosin and facilitates contraction; troponin I, which binds to actin and inhibits actin-myosin interactions; and troponin C, which binds to calcium ions [2,6]. The amino acid sequences of the skeletal and cardiac isoforms of cardiac troponin T and troponin I are sufficiently dissimilar and, therefore, differentially detectable by monoclonal antibody based assays. Troponin C is not used clinically because both the cardiac and skeletal muscle share troponin C isoforms. Cardiac troponin I is 13 times more abundant in the heart than creatine kinase MB isoenzyme, so the signal-to-noise ratio associated with troponin I is much more favorable for the detection of minor amounts of cardiac damage. Cardiac troponin T is as abundant as troponin I in the heart [7].

Origin of cardiac troponin release

Normally, cardiac troponins T and I are not detectable in the blood of healthy persons. Release of these troponins can occur when myocytes are damaged by a variety of conditions, such as trauma, exposure to toxins, inflammation, and necrosis due to occlusion of a portion of the coronary vasculature [2-4,8]. The majority of cardiac troponin T and cardiac troponin I is bound to myofilaments, and the remainder is free in the cytosol. When myocyte damage occurs, the cytosolic pool is released first, followed by a more protracted release from stores bound to deteriorating myofilaments [9].

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 ablation, or electrical cardioversion [3]. The mechanisms of release and clearance of cardiac troponins T and I are complex and incompletely understood in these pathological conditions. Although both are structural proteins, it has been suggested that cytosolic pools of these proteins are released into the circulation after cell injury. The cytosolic pool for cardiac troponin T was estimated at 6% to 8% of total cardiac troponin and that for soluble cardiac troponin I at 2.8% of total cardiac troponin. Release of cardiac troponin T may be related to transient leakage from the cytosolic component due to loss of sarcolemmal integrity during reversible ischaemia, or from its continuous release when ischaemic injury is irreversible [3,10].

How is heart tissue damaged in sepsis?

The high prevalence of elevated serum levels of cardiac troponins in septic shock raises the question of what mechanism results in troponin release in septic shock. Proposed mechanisms include focal ischemia, and direct cardiac myocytotoxic effects of endotoxins, cytokines or reactive oxygen radicals [4,11]. In addition, activation of many intracellular pathways may cause degradation of free troponin to lower molecular weight fragments, which are released into the systemic circulation because of increased membrane permeability [9,11]. The current understanding of myocardial dysfunction in sepsis is that there is no evidence of global coronary hypoperfusion. Tools for assessing tissue and heart dysfunction have, however, evolved and enable us to reconsider the above assumption as a universal concept. In this respect, microvascular dysfunction is now considered an intrinsic aspect of sepsis sequelae. Indeed, evidence suggests that sepsis may induce perturbations in regional coronary blood flow and microvascular failure leading to myocardial ischemia [12].

Myocardial depressant substances

The phenomenon of myocardial depression can be mediated by circulating depressant substances, which until now have been incompletely characterized. Among those possible candidates, tumor necrosis factor (TNF), IL-1β and IL-6 play a central role in septic myocardial dysfunction [13]. TNF-α, alone or in association with IL-1β, has been implicated in the pathophysiology of septic myocardial dysfunction [13]. Proposed mechanisms of TNF-α-induced myocardial depression include the activation of the neutral sphingomyelinase, and suppression of the calcium transient and nitric oxide pathways. TNF-α can also modulate tissue destruction and biosynthesis/activation of intracellular proteases [13]. For example, TNF-α may induce activation of calpains and caspases that could participate in the degradation of crucial cardiac contractile proteins, including troponins. Upon activation by calcium, active calpain is released by calpastatin and cleaves cardiac troponin I at the carboxyl terminus to produce the cardiac troponin I degradation fragment [13]. Caspases, the executioners of apoptotic cell death, also induce sarcomere disarray and are involved in the cleavage of α-actin, α-actinin and troponin T [14]. Alternatively, TNF-α may have an important role in cardiac injury through a variety of mechanisms, including second messenger pathways, arachidonate metabolism, protein kinases, oxygen free radicals, nitric oxide, transcription of a variety of cytotoxic genes, regulation of nuclear regulatory factors, ADP-ribosylation and, potentially, DNA fragmentation [13]. In this setting, histology of transgenic mice specifically overexpressing TNF-α in the heart shows hypertrophied interstitial connective tissue cells associated with focal myocyte degeneration and injury [13,15]. Transmission electron microscopy further demonstrated myofibril disarray and breakdown in TNF-α transgenic mouse heart [13,16]. Altogether, these derangements in heart tissue architecture could participate in the breakdown of sarcomeric proteins and their release in the systemic circulation.

Leukocyte and reactive oxygen species

Reactive oxygen species may play a role in the induction of several types of organ failure, including that of the heart,

following the development of sepsis. Leukocyte derived superoxide and its daughter molecules are thought to be a major cause of heart injury in sepsis [17]. In addition, activated NADPH oxidase complexes and mitochondria are also potential sources of free radicals in the septic heart, which may have multiple potential sites of action [18]. Under pathophysiological conditions, dramatically elevated levels of reactive oxygen species may cause significant damage to cellular proteins and membranes as well as to nucleic acids, leading to single strand breaks and chromosomal alterations, which are all likely to induce cardiac cell death. Consistent with this hypothesis are the fascinating findings of Ammann and colleagues [19], who reported that plasma troponin levels became positive during leukocyte recovery in aplastic patients with septic shock and indicated poor outcome.

Myocardial perfusion abnormalities

Typically, global myocardial ischaemia has not been considered a critical factor of septic heart dysfunction [20,21]. Detailed analysis of existing literature may, however, lead to the contrasting conclusion that myocardial ischemia or microcirculation abnormalities are present in septic shock. Experimental studies suggest that generalized microvascular dysfunction is a prominent feature of septic shock and is probably an important factor in the heart, as elsewhere [22]. This could lead to relative ischaemia, microvascular shunting, or flow heterogeneity secondary to mechanisms such as endothelial dysfunction, leucocyte plugging of capillaries, interstitial edema and free radical production. Growing evidence suggests that reversible mismatched perfusion metabolism areas inherent to local redistributive microcirculatory adjustment are present in experimental sepsis, suggesting an ischemic component is partially responsible for heart dysfunction [23-25]. Specifically, decreased myocardial microcirculatory flow and random oxygen consumption have been experimentally demonstrated by means of positron emission tomography imaging in endotoxic shock [24].

Heart apoptosis

Despite extremely low levels of myocyte nuclear apoptosis, caspase activation has been implicated in sarcomere disarray and contractile dysfunction in various models of myocardium injury [26]. Caspase activation participates in the regulation of cardiac contractility and its inhibition might reverse depressed contractility. Many putative caspase cleavage sites in cardiac contractile and structural proteins may be identified through data bank research with caspase cleavage motifs. The existence of such cleavage sites explains the findings that exposure of myofibrillar proteins to active caspase 3 results in α-actin, α-actinin and troponin T and myosin light chain cleavage [14]. In experimental sepsis, our studies suggest that activation of caspase 3 plays an important role in endotoxin-induced cardiomyocyte dysfunction, which is related to changes in calcium myofilament response, troponin T cleavage and sarcomere disorganization [26].

What mechanisms of troponin increase are possible in clinical sepsis?

Does cardiac ischemia occur in septic patients?

Two elegant studies have shown that coronary blood flow is increased and not decreased in septic shock, even if energetic substrate extraction is altered [20,21]. Preservation of coronary flow, net myocardial lactate extraction, and increased availability of oxygen to the myocardium argue against global ischemia as a cause of septic myocardial depression. In addition, nuclear magnetic resonance studies have shown normal myocardial high energy phosphate levels. In these studies, however, myocardial ischemia is difficult to rule out. First, the results of these studies suggest evidence of myocardial hypoxia (zero or negative lactate uptake) in 15% of studied patients [21]. Second, autopsies of septic patients provide circumstantial evidence that histological changes can be related to heart ischemia. For example, in a retrospective review of autopsy findings in 71 patients, Fernandes and colleagues [27] noted abnormalities in the myocardium, including interstitial myocarditis (27%), interstitial edema (28%), and muscle-fiber necrosis (7%). These data also support an opinion that structural injury to the contractile apparatus or microcirculation of the heart may contribute, at least partly, to myocardial dysfunction in sepsis [28].

Does demand ischemia exist in septic shock?

Cardiac output is typically increased in sepsis, meaning increased work for the cardiac pump, that is, increased oxygen demand. Tachycardia can further decrease oxygen supply because diastolic time, during which myocardial perfusion occurs, is reduced. Coronary flow reserve can thus be reduced, with a potential mismatch between oxygen demand and supply causing demand ischemia. In addition, aggressive inotropic treatment to boost systemic oxygen delivery may increase the incidence of cardiovascular complications and adversely affect outcome in fluid resuscitated septic patients. It is quite possible that elaborate attempts at prolonged resuscitation could either cause or disclose ischemic myocardial damage. Increased cardiac filling pressures and increased wall stress may contribute to myocyte damage and microinjury in septic shock [2].

Could increase of cardiomyocyte permeability explain troponin leakage?

Circulating mediators such as TNF-α have been implicated in increased permeability of sarcolemmic cardiomyocyte membrane, a phenomenon that could explain troponin release without irreversible injury [9]. TNF-α may increase the permeability of endothelial monolayers to macromolecules and lower molecular weight solutes and it is likely that similar alterations in permeability also occur at the level of myocyte cell membranes, thus leading to leakage of cardiac troponin I [12]. Indeed, release of myocardial enzymes from mammalian myocardiocytes into cell supernatant has been demonstrated during limited periods of hypoxia [29]. In human volunteers, no correlation between plasma levels of TNF-α and troponin

could be found in endotoxin-treated volunteers, suggesting that TNF-α alone may not be sufficient to induce increased permeability [30]. In sharp contrast, levels of TNF-α, its soluble receptor and IL-6 are significantly higher in troponin-positive septic shock patients than those of troponin-negative patients, suggesting that cytokines in combination may provoke an increase in membrane permeability and troponin release [19].

Are increased troponin levels related to ischemic cardiac tissue damage in clinical sepsis?

Many studies in sepsis have shown that continuous ECG monitoring and transthoracic echocardiography examination at diagnosis do not disclose developing ischemia and exclude myocardial infarction [19,31-37]. In troponin-positive septic shock patients, the presence of myocardial ischemia has been excluded based upon results of stress echocardiography [19,31,38]. It should be pointed out, however, that stress echocardiography cannot definitely exclude microembolization from non-flow limiting unstable plaques as well as local wall motion abnormalities as a cause of elevated troponins. In this specific context, even very small episodes of myocardial necrosis (<1 g) may be associated with significant troponin increases [2].

The presence of some degree of focal cardiac necrosis in septic patients has been emphasized by recent anatomopathological findings. Indeed, troponin-positive septic shock patients tend to show more pronounced histological abnormalities than troponin-negative septic shock patients [31,37]. Specifically, contraction band necrosis, an early marker of irreversible myocyte injury, and sarcoplasmic fibril rupture are more frequent in troponin-positive septic shock patients [37]. Contraction band necrosis is believed to result from calcium overload and its presence is typically associated with focal ischemia reperfusion injury and the use of high catecholamine concentrations.

Does increased troponin level indicate cardiac dysfunction and poor outcome in clinical sepsis?

A correlation between troponin level and requirements for inotropic support has been mentioned by some authors [36,39], whereas others have shown opposite results [37,38]. In patients with increased troponin levels, evaluation of myocardial performance during septic shock has been performed by the means of left ventricular stroke work index calculation [5,39] and evaluation of systolic function by echocardiography [19,33,35,37,38,40]. Consistently, estimates of left ventricular ejection fraction and fractional area contraction correlate negatively with increased levels of cardiac troponin I in both adults and children with septic shock [35,38,41,42]. Also, serial determinations of cardiac troponin I show a negative correlation between serum concentrations of cardiac troponin I and myocardial function (echocardiography fractional area contraction less than 50%) [41]. However, a correlation between left ventricular dysfunction and increased levels of cardiac troponin I is not a universal finding in septic shock patients [43]. The reason for these contrasting results has not been reconciled. However, it should be pointed out that several factors may complicate the diagnosis of sepsis-induced myocardial dysfunction in humans and echocardiography derived parameters may not reflect actual myocardial contractility and dysfunction [41,42].

In addition to global systolic and diastolic performance evaluation, tissue velocity imaging for myocardial strain and strain rate imaging is an important development in the field of cardiac ultrasound that provides quantitative information for analysis of myocardial motion. Increased wall strain and regional wall motion abnormalities in septic shock could be part of the septic myocardial dysfunction pattern and account for cardiac myolysis. Although regional wall motion abnormalities have been observed in some positive-troponin cases [36], there is no information with respect to perturbations in tissue Doppler derived myocardial strain and strain rate in septic shock patients.

Eventually, a prognosis of sepsis depends on the severity of organ dysfunctions, in particular, cardiovascular failure. Whether an elevated troponin level represents a critical and independent parameter of outcome has been debated in many clinical studies [5,8,20,34,36,40-43]. Studies in unselected critically ill patients yield the consistent information that mortality among troponin-positive patients is higher than troponin-negative patients, irrespective of the cause of troponin increase. In studies restricted to patients with sepsis, elevated troponin levels have been shown to be related to the severity of the disease. Overall, these results are very similar in showing that troponin elevation indicates a worse myocardial function and unfavourable outome [5,19,31,34,36,37,39].

It should be pointed out, however, that the relative expected and documented ranges of troponin that can be seen in sepsis are rather difficult to depict because there is huge variability in the sensitivity of assays (Table 1). The appropriate cut-off value for each assay is unique and cannot be compared with any other. These differences are due in part to the heterogeneity of the antibodies and matrix components of the assays. They are also due to the fact that there are various fragments of troponin that circulate, and the antibodies used in the various assays detect these fragments differently [3,7,10].

Conclusion

Although the mechanisms of troponin release into plasma during sepsis are not clearly established, cardiac troponin I is an indicator of myocardial injury in septic patients and is potentially associated with myocardial depression and poor outcome. There is evidence from several small studies that

Table 1

Summary of clinical studies on cardiac troponin levels in patients with sepsis and septic shock

Authors	Year	Troponins	Cut-off (μg/l)	Range (μg/l)
Spies *et al*. [5]	1998	cTnT	0.2	0.04-3.3
Fernandes *et al*. [34]	1999	cTnI	0.6	
Turner *et al*. [39]	1999	cTnI	0.4	2.4 (median)
Arlati *et al*. [32]	2000	cTnI	0.5	0.5-11.2
Ver Elst *et al*. [37]	2000	cTnI	0.4	0.8-6.8
		cTnT	0.1	0.2-1.5
Ammann *et al*. [31]	2001	cTnI	0.1	0.2-15.4
Ammann *et al*. [19]	2003	cTnI	0.1	
		cTnT	0.1	
Mehta *et al*. [36]	2004	cTnI	1.0	1-10.8

cTn, cardiac troponin.

elevated cardiac troponin levels in patients with sepsis indicate myocardial dysfunction and a poor prognosis. However, further studies are needed to elucidate the potential of troponins to characterize the severity and course of the septic cardiomyopathy. Cardiac troponin I, in association with markers of myocardial depression such as natriuretic peptides, seems to be an early factor of prognosis and cardiac dysfunction in patients with sepsis.

Competing interests

The authors declare that they have no competing interests.

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