Troponin Elevation Beyond Coronary Arteries

14

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Contents

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Abstract

Cardiac troponins are protein complexes that have become the gold standard biomarkers in the detection of myocardial injury. The use of new-generation high-sensitivity assays, which can detect even small increases in troponin levels, resulted in an increase in the number of patients with elevated troponin concentrations. However, in this case there are more false-positive results. This makes it of paramount importance to set differential diagnosis among several noncoronary entities such as stroke, pulmonary embolism (PE), sepsis, acute perimyocarditis, Takotsubo, acute heart failure (HF), and tachycardia. Technological progress of high-sensitivity troponin assays may be helpful in detecting even slight elevations of troponin in individuals, a condition that is met in several different clinical pathologies. However, despite the fact that troponin elevation is indicative of myocardial necrosis, it does not elucidate the pathophysiologic mechanism that causes myocardial damage. The purpose of this chapter is to report clinical pathologies where elevated troponin concentrations are found and to cite studies that have used troponin in the prediction and evaluation of future events.

Keywords

Troponin elevation • Sepsis • Stroke • Cardiomyopathies • End-stage renal disease

Abbreviations

ACC	American College of Cardiology
ACS	Acute coronary syndromes
AMI	Acute myocardial infraction
AV	Atrioventricular
CAD	Coronary artery disease
CKD	Chronic kidney disease
cTn	Cardiac troponin
ESC	European Society of Cardiology
ESRD	End-stage renal disease
HF	Heart failure
IL	Interleukin
MI	Myocardial infraction
MRI	Magnetic resonance imaging
PE	Pulmonary embolism
PSVT	Paroxysmal supraventricular tachycardia
SAH	Subarachnoid hemorrhage
SIRS	Systemic inflammatory response
SRCs	Stress-related cardiomyopathies
TAVI	Transcatheter aortic valve implantation
Tn	Troponin
TNF-α	Tumor necrosis factor-α
VARC	Valve Academic Research Consortium

Key Facts

- Troponin elevation occurs in patients with ESRD, tachyarrhythmias, acute HF, aortic stenosis, pericarditis and myocarditis, acute pulmonary embolism, stress-related cardiomyopathies, sepsis, stroke, strenuous exercise, and cardiac contusion apart from coronary events.
- Etiology of troponin elevation is multifactorial.
- Most of recently available data support the prognostic value of troponin on patients' outcome.

Definitions

Acute heart failure Acute heart failure is a cardiac pathology that is characterized by the inability of the heart to provide enough volume in order to satisfy the body's needs. Several entities are implicated with acute heart failure such as valvulopathies, coronary artery disease, and a damaged or inflamed heart.

End-stage renal disease End-stage renal disease is a clinical pathology that is characterized from declined function of kidneys. The function is not adequate for the everyday needs of the human body resulting to either hemodialysis or need for kidney transplantation. It is usually the subsequent consequence of chronic kidney disease, kidney injury/trauma, or major blood loss.

High-sensitivity troponin assay High-sensitivity troponin assays are troponin tests that have been designed to sense even slight elevations in concentrations in total population comparing with the conventional ones. The coefficient of variance (CV) of $<10\,\%$ at the 99th percentile value in the population of interest has been proposed by experts.

Subarachnoid hemorrhage Subarachnoid hemorrhage is the blood concentration in the subarachnoid space. This space is found among the brain and the thin tissues that cover the brain. It might be a result of several bleeding types (arteriovenous malformation, bleeding disorder, bleeding from a cerebral aneurysm, head injury).

TAVI Transcatheter aortic valve implantation constitutes an alternative treatment option for patients with severe symptomatic aortic stenosis who cannot undergo surgery due to the fact that they are either considered as "high risk" or inoperable. It can be performed via the femoral or subclavian artery or direct through the ascending aorta or transapical.

Introduction

Troponins are protein complexes that are composed of three subunits (troponins I (TnI), T (TnT), and C (TnC)). TnT binds to tropomyosin, TnC binds to calcium ions, and TnI binds to actin by preventing actin–myosin interaction (Antman 2002).

Troponins are specific for skeletal and cardiac muscle but not for smooth muscle. A percentage of 7 % of cardiac TnT (cTnT) and 3.5 % of cTnI is found in the myocyte cytoplasm of the heart. cTnT content per gram of myocardium is almost twofold higher than that of cTnI (Adams et al. 1993; Antman 2002). Besides, different genes produce cardiac and skeletal troponins in each type of muscle. However, the amino acid sequence of TnC is not different among two types of muscle. Therefore, its detection is not diagnostic (Schreier et al. 1990).

Both cTnI and cTnT are myocardial injury-specific markers. However, the used troponin assays differ significantly as far as sensitivity and specificity are concerned. Assays of cTnT that are industrially made by a single producer present with relatively uniform cut-off concentrations. However, first-generation troponin assays may have falsely detected skeletal muscle troponin as elevated cardiac troponin. In addition, cTnI assays, given the fact that different kits are used to detect different epitopes, differ concerning cut-off concentrations and standardizations (Ammann et al. 2003). As far as the upper reference limit of cTns is concerned, it was initially defined as the 97.5th percentile of the values measured in the normal control population (1). However, a later definition was that acute myocardial infarction (MI) is diagnosed when cTnI or cTnT concentrations, that are identified within 24 h after the initial event, are higher than the 99th percentile using a coefficient of variation of 10 % or less (Panteghini et al. 2004; Thygesen et al. 2012). However, values in the intermediate zone are indicative of minor myocardial damage (Ammann et al. 2003).

Cardiac troponins have raised to be the gold standard for the detection of myocardial injury (Thygesen et al. 2012) especially after the introduction of new generation, high-sensitivity assays in use that can detect even minor elevations in troponin concentrations (Giannitsis et al. 2010). The new high-sensitivity troponin methods give the opportunity to detect even minor damages on the cardiac heart muscle increasing the number of patients with elevated troponin concentrations. In this case, there is higher percentage of false-positive results. This makes it of paramount importance to differentiate the diagnosis among several non-coronary entities, especially when troponin levels are high (Fig. 1).

Aetiology of Troponin Elevations

Troponin Levels in Patients with End-Stage Renal Disease

Patients with chronic kidney disease (CKD) (particularly those with end-stage renal disease [ESRD]) have a greater frequency of persistently elevated cardiac troponin comparing to patients who do not have CKD. The controversial issue related to the troponin elevation, as mentioned above, is that this is not due to reduced renal clearance but due to myocardial injury (Wang and Lai 2008; Newby et al. 2012). Kidneys cannot easily clear large molecules such as troponin molecule, a fact that makes difficult troponin to be cleared from serum. Nevertheless, it has been proposed that the troponin molecule is fragmented into smaller parts that can be easily identified by the troponin assays and it may be cleared from kidneys. The mechanism

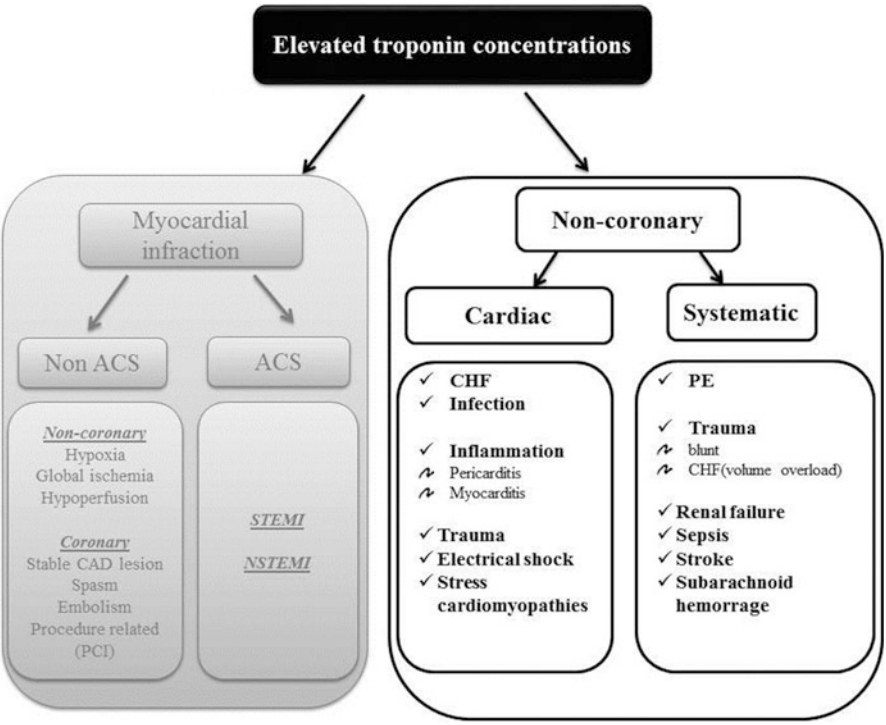

Fig. 1 Troponin elevation in coronary and non-coronary syndromes. Troponin concentrations are elevated in many pathological entities that they can be both coronary and non-coronary. The new high-sensitivity troponin methods give the opportunity to detect even minor damages on the cardiac heart muscle increasing the number of patients with elevated troponin concentrations. This makes it of paramount importance to set a differential diagnosis along than among several non-coronary entities

above may explain the elevation of troponin in severe renal failure (Diris et al. 2004). However, another study (Ellis et al. 2001) did not record a statistically significant difference among the half-life and the elimination rate of troponin I in patients with MI and ESRD when compared to those with MI and normal kidney function. Therefore, elevated troponin concentrations in patients with CKD should be assessed in the concept of acute coronary syndrome's (ACS) suspicion though they may also be due to other cardiac diseases associated with myocardial injury. This is highly prevalent among CKD patients, especially when the levels do not alter quickly over time (Jaffe 2006). In particular, in patients with CKD but without suspected ACS, micro-infarctions, microvascular disease, subendocardial ischemia associated with left ventricular hypertrophy and diastolic dysfunction, as well as non-ischemic cardiomyopathic processes could also be responsible for detectable small increases in troponin. Therefore, a change in the cTn concentration of more than 20 % has been considered as the main criterion for the diagnosis of MI in patients with ESRD with elevated cTn concentrations after symptoms' onset (Xu et al. 2013). This has

been considered an indicative change of three standard deviations (Wu et al. 2007). To be more specific, in a cohort of asymptomatic patients with ESRD, troponin levels exceeded the 99th percentile value using the new hs TnT assay in the entity of patients (Jacobs et al. 2009). Therefore, the wide variation in assays and thresholds along with the absence of comparative studies has not fully elucidated the relation among troponin concentrations and ischemia in patients with ESRD.

Tachyarrhythmias

Troponin elevation is commonly observed after episodes of tachyarrhythmias. However, the mechanism of tachycardia-induced troponin elevation is not fully understood (Ben Yedder et al. 2011). A widely proposed mechanism is that tachycardia increases myocardial oxygen demand with simultaneously decreased myocardial oxygen delivery, as a result of the short duration of diastole, which is the time when myocardial perfusion occurs. This results to reduced myocardial perfusion and release of cTnI (Carlberg et al. 2011). In animal studies, a second possible mechanism which is implicated with tachycardia-induced elevation of troponin concentrations proposes myocardial stretch. This is supported by the finding of a direct association with both a rise in natriuretic peptide and troponin concentrations (Qi et al. 2000). A probable scenario was that cTnI release from viable cardiomyocytes may be mediated by triggering stretch-responsive integrins. Their role is to link the extracellular matrix to the intracellular cytoskeleton (Hessel et al. 2008).

Paroxysmal supraventricular tachycardia (PSVT) is a commonly found arrhythmia. Usually, it is not dangerous; thus, it rarely leads to adverse clinical outcomes. However, a percentage of patients (30 %) with PSVT presented to have significantly elevated troponin concentrations (Ben Yedder et al. 2011). Furthermore, they presented with symptoms of chest pain and chest discomfort that were falsely diagnosed as acute ACS and consequently treated inappropriately with antiplatelet and antithrombotic therapies. Nevertheless, coronary angiography did not reveal serious pathology of coronary arteries in the majority of patients. Even more, it has been shown that patients with PSVT did not have risk factors that could increase cardiovascular risk (Ben Yedder et al. 2011). However, some predisposing factors that are closely related to troponin elevation, such as maximal PSVT heart rate, ST-segment depression $\geq$1 mm during the episode of PSVT, and impaired left ventricular systolic function, have been recorded (Chow et al. 2010; Ben Yedder et al. 2011).

Prolonged episodes of supraventricular tachyarrhythmias (SVT) have also been related with troponin elevation even in presumably healthy individuals. However, several limitations apply to these observations since no coronary angiography, stress testing, or hemodynamic measurements were performed in all patients, and continuous values of troponin changes were not available. In conclusion, whether tachycardia alone may cause a troponin release despite the absence of many cardiac entities (e.g., structural heart disease, significant CAD, and inflammatory mediators) or whether it is related to a disproportion between

oxygen demand and supply in patients with subclinical heart disease has not been fully elucidated yet.

Acute Heart Failure

Acute heart failure is a cardiac pathology where troponin elevation is rather common. However, the pathophysiologic substrate of troponin elevation in acute HF remains unclear. A possible scenario is based on the fact that increased ventricular preload triggers myocardial strain that may consequently result to troponin release (Feng et al. 2001). Another hypothesis is that the detectable elevated level of cTnT is due to myocardial damage as a result of necrotic and apoptotic processes. Thus, it has been estimated that 1 g of myocardial mass is being lost every year in the human heart (Olivetti et al. 1995). However, the present data have not fully clarified the question of whether the incidence of elevated troponin concentration and the width of increase/decline are significantly higher in acute comparing to chronic HF.

A number of studies have been realized in order to evaluate the possible relation among troponin elevation and adverse events. In particular, during the Acute Decompensated Heart Failure National Registry (ADHERE) Registry (Peacock et al. 2008), 67,924 HF patients were evaluated in order to discriminate the relationship among elevated troponin concentrations and adverse events. Out of them, 4,240 patients (6.2 %) had elevated troponin levels but using the less sensitive assays for cTnT or cTnI measurements. These patients when compared with those who did not have elevated troponin concentrations manifested lower values of systolic blood pressure and ejection fraction on admission and higher percentages of in-hospital mortality. Elevated troponin concentrations have been proved to be an independent predictor of mortality when adjusted for variables. These findings had previously been shown in another international pooled analysis of 1,256 acute destabilized HF patients (Januzzi et al. 2006).

Aortic Stenosis-Transcatheter Aortic Valve Implantation

Aortic stenosis constitutes a pathology that it is included in the most frequently encountered valvulopathies. Until recently, surgical valve replacement was the gold standard for the management of patients with symptomatic severe aortic stenosis. However, out of them, some patients are characterized either as “high operative risk” or “inoperable.” These patients are treated with transcatheter aortic valve implantation (TAVI), a technique that constitutes a well-established therapeutic alternative (Vavuranakis et al. 2010). In the setting of TAVI, myocardial biomarkers, like troponin, have also been incorporated in the current guidelines of the Valve Academic Research Consortium (VARC) for the detection of peri-procedural myocardial infarction (Leon et al. 2011). In some patients, TAVI is performed via transapical approach. This involves direct myocardial injury that may have increased troponin concentrations and consequently prognosis. Furthermore, the influence of

pre-interventional troponin levels on subsequent troponin release and outcome after TAVI has not been studied yet. Thus, the assessment of baseline values of cTn and its influence on outcome after TAVI are crucial to enlighten the role of troponins. In a study of 198 consecutive patients who underwent successful transfemoral TAVI, the relation of cTnT with procedural and 12-month outcome has been evaluated using a new-generation troponin T assay before and after TAVI. Furthermore, the relation of cTnT to the long-term outcome of the procedure has also been recorded. They showed that post-interventional cTnT levels increased significantly and peaked at day 3 after transfemoral TAVI, and they subsequently declined. Furthermore, they showed that baseline renal function, the duration of rapid ventricular pacing, as well as baseline cTnT values predicted the width of post-interventional cTnT concentrations. Despite the fact that cTnT levels did not prove to be an independent predictor of short-term mortality, pre-interventional as well as post-interventional cTnT concentrations predicted 1-year mortality, independently of procedural success (Chorianopoulos et al. 2014). In the first Department of Cardiology, a study that evaluated a total of 115 consecutive patients who were chosen for TAVI and were separated into groups according to post-procedural cTnI levels, was conducted. Patients with elevated TnI appear to have increased DQTc. DQTc was defined as that difference among the final and the pre-procedural value of QTc. It has been well recognized that QT prolongation is a marker of myocardial injury induced by ischemia, but in this study it probably represents myocardial necrosis induced both by ischemia or mechanical stress. Indeed, the presence of microembolization during balloon valvuloplasty and hypotension during rapid right ventricular pacing or even the use of medication that changes myocardial function during sedation/anesthesia may be implicated with myocardial necrosis even in the absence of significant epicardial coronary artery disease. Furthermore, new onset first-degree atrioventricular (AV) block appeared to be with higher. To conclude, the primary finding of this study was that TnI elevation after TAVI may be related to conduction abnormalities. The proposed mechanism for their appearance is probably associated with minor myocardial injury that affects the conduction system of the heart (Vavuranakis et al. 2013).

Pericarditis and Myocarditis

cTn has been recorded to be increased in 32–49 % of cases of acute pericarditis. Despite the fact that troponin is not present in the pericardium, probably this is due to the fact that the epicardium participates in the inflammatory process (Brandt et al. 2001).

Concerning the pathophysiologic mechanism of myopericarditis with sero-epidemiologic studies, data are limited. This suggests that most of patients with Coxsackie B virus infection are not detected and the inflammatory cascade is not widely expanded. Elevated troponin concentration is roughly related to inflammatory process but without adverse events in myopericarditis (Remes et al. 1990). Indeed, the finding above had been confirmed (Imazio et al. 2008); thus, acute

pericarditis and myopericarditis after 1 year had similar percentages of complications with echocardiography, ECG, and treadmill testing findings returning to normal patterns in most of cases. Nevertheless, the mechanism of myocarditis remains unclear, and cTn levels may have a significant range from normal levels up to high levels. To be more precise, primary myocarditis is supposed to be triggered either by acute viral infection or post-viral autoimmune response. This may of course predispose to coronary vasospasm too (Yilmaz et al. 2008). This partly justifies atypical chest pain in individuals with myocarditis that makes difficult the differential diagnosis with ischemic events. However, we should not underestimate the fact that MRI in endocarditis shows involvement from the epicardial layers, while ischemia is located in the endocardial layers extending toward the epicardial.

Acute Pulmonary Embolism

Elevated cardiac troponin levels in PE are present even in hemodynamically stable patients. The exact mechanism of troponin release in PE has not been fully elucidated yet. One explanation is that right ventricular strain that develops acutely due to increase in pulmonary artery resistance may be implicated for elevated troponin concentrations. Indeed, it has been recorded (Meyer et al. 2000) that a percentage of 63 % of patients with PE and right ventricular dilation manifested elevated cTnI concentrations, while 29 % of patients with positive cTnI test had a normal right ventricular end-diastolic diameter. Furthermore, an equally significant finding was that a positive cTnI level was associated with more segmental defects on ventilation–perfusion scintigraphy. Another scenario is that perfusion–ventilation mismatch induces hypoxemia that leads to hypoperfusion due to both impaired output and diminished coronary blood flow. In addition, the exploration of cTnT release mechanism in patients with PE indicated that peak values of the enzyme were lower comparing to those of individuals with acute MI and maintained high in blood for a shorter period (Muller-Bardorff et al. 2002). In particular, the mechanism of myocardial injury and cTnT release in patients with significant PE differs from the one in patients with ACS. In a meta-analysis (Becattini et al. 2007) of 20 studies in 1985 on patients with PE, it was found that increased cTn levels were adversely related with short-term mortality. They were also associated with a higher mortality in the subgroup of hemodynamically stable patients. Indeed, patients who were categorized as intermediate risk were hemodynamically stable but with right ventricular dysfunction or elevated troponins. This has been observed in a study where normal echocardiogram when combined with a negative cTnI was positively related with lower risk for early death (Kucher et al. 2003).

Stress-Related Cardiomyopathies

Stress-related cardiomyopathies (SRCs) are recorded as cardiac pathologies including Takotsubo cardiomyopathy or apical ballooning syndrome, subarachnoid

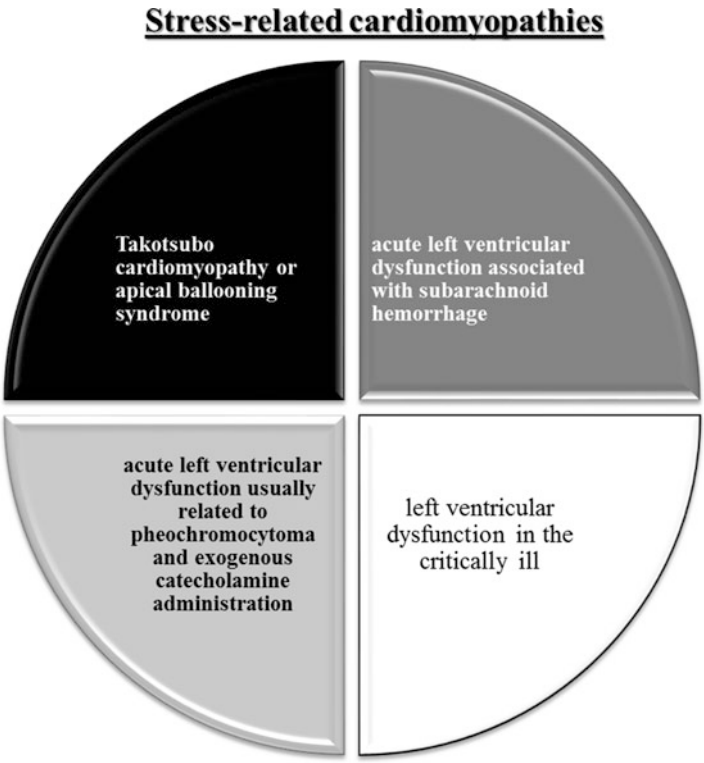

Fig. 2 Stress-related cardiomyopathies include Takotsubo cardiomyopathy or apical ballooning syndrome, acute left ventricular dysfunction associated with subarachnoid hemorrhage, acute left ventricular dysfunction usually related to pheochromocytoma and exogenous catecholamine administration, and acute left ventricular dysfunction in the critically ill

hemorrhage associated with acute left ventricular dysfunction, pheochromocytoma or critical state of patient, as well as exogenous catecholamine administration (Fig. 2). In these cases, cardiac toxicity mediated by catecholamines burdens left ventricular function and is accompanied by troponin release. Takotsubo cardiomyopathy has been characterized as a cardiomyopathy that is closely related with stress. Other characterizations for this syndrome include broken heart syndrome or transient left ventricular apical ballooning syndrome. Its prevalence is reported to range from 0.7 % to 2.5 % in patients presenting with acute coronary syndromes (Pilgrim and Wyss 2008). The typical Takotsubo cardiomyopathy syndrome includes women of older age with an acute emotional or physiologic stress (Fig. 3). Nevertheless, its clinical profile varies a lot and includes both younger patients and men (Sharkey et al. 2010). Emotionally or physically stressful events immediately before hospitalization are not always well defined in all patients with Takotsubo cardiomyopathy (Sharkey et al. 2010). The pathophysiology of syndrome has not been fully enlightened until recently; thus, several mechanisms have

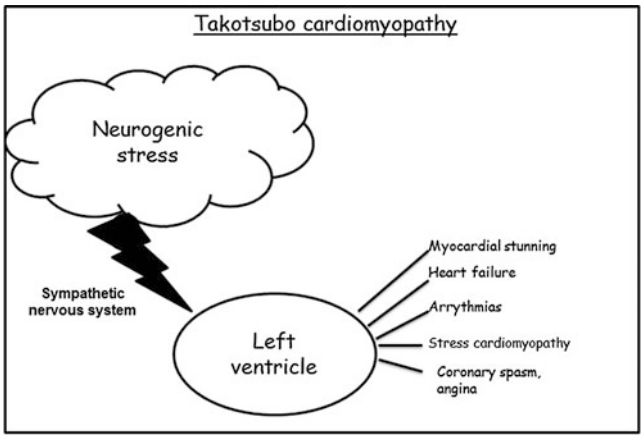

Fig. 3 The typical Takotsubo cardiomyopathy syndrome includes women of older age with an acute emotional or physiologic stress. Nevertheless, its clinical profile varies a lot and includes both younger patients and men

been suggested. Among them, catecholamine-induced myocardial stunning, ischemia-mediated stunning due to multi-vessel epicardial or microvascular spasm, aborted acute myocardial infarction (AMI), and focal myocarditis are included. The selective involvement of apical and/or midportion of the left ventricle with relative sparing of basal segments has not been fully clarified. Additionally, this might be partially enlightened by the fact that apical myocardium responds more to sympathetic stimulation. In these patients, symptoms including ischemic chest pain or dyspnea are usually present. The majority of patients with Takotsubo cardiomyopathy present a modest increase in cTn that reaches its peak within 24 h (Ramaraj et al. 2009). The paradox of this syndrome is that the elevation of ischemia biomarkers is lower for the degree of acutely induced regional wall motion abnormalities that appears acutely and remarkably lower than the one observed in ACS (Ramaraj et al. 2009). A prospective study was conducted in order to evaluate the extent of troponin T and I elevation in differentiating between Takotsubo cardiomyopathy and ACS. In that study, it was found that those with values of TnT over 6 ng/mL or with values of TnI over 15 ng/mL had smaller possibility to present Takotsubo cardiomyopathy (Sharkey et al. 2008). There is no specific therapy for Takotsubo cardiomyopathy except for supportive therapy. This leads to improvement of systolic dysfunction as well as regional wall motion abnormalities in a small period (Sharkey et al. 2010).

Acute LV dysfunction associated with subarachnoid hemorrhage is referred as neurocardiogenic stunning (Bybee and Prasad 2008). Its predictors are four and include severe neurologic injury, plasma troponin increase, brain natriuretic peptide elevation, and female gender (Tung et al. 2004). The diagnosis of neurogenic SRC is highly related to the onset of several, even fatal arrhythmias as well as an elevated risk of vasospasm of cerebral arteries. The prolongation of QT interval, the elevation

of ST segment, and T-wave inversion with symmetrical pattern are concomitant with an increase in cardiac troponin. They are recorded in approximately two thirds of patients with severe subarachnoid hemorrhage (Bybee and Prasad 2008). Unlike Takotusbo cardiomyopathy, the differential diagnosis between neurogenic SRC and acute MI is usually difficult. However, a slight elevation in cardiac troponin in combination with the onset of non-coronary distributed wall motion abnormalities favors the diagnosis of neurocardiogenic stunning.

Furthermore, acute LV dysfunction presents in an approximately 33–50 % of critically ill patients who are hospitalized. Its main characteristic is the onset of a global LV dysfunction. When dilated cardiomyopathy is excluded from differential diagnosis, the mechanisms of global LV dysfunction can be partially elucidated by a direct catecholamine myocardial toxicity in several situations. These include tachycardia-induced cardiomyopathy, hypertensive crisis, sepsis, multiorgan dysfunction, and post-cardiac arrest syndrome. In the entities above, a high prevalence of myocardial injury as determined by cTnI levels was recorded despite the absence of ACS on admission to the intensive care unit (Ammann et al. 2003; Quenot et al. 2005). Furthermore, it has been observed that this myocardial injury was an independent predictor of in-hospital mortality even when adjusted for co-variables (Quenot et al. 2005).

Sepsis

Half of patients with severe sepsis and septic shock may present declined ventricular function that is associated with elevated cTn concentrations (Mehta et al. 2004). Among patients with sepsis or systemic inflammatory response syndrome (SIRS) who were hospitalized in intensive care units, high levels of cTn have been noted in frequencies ranging from 12 % to 85 % (Lim et al. 2006). Several factors including the different underlying causes of sepsis, the variety of used troponin assays, and the different applied cut-off values for cTn may contribute to the wide range of incidence. Furthermore, this study has indicated that elevated cTn concentration is an independent predictor of mortality in sepsis patients (Lim Qushmaq et al. 2006). The high incidence of cTn elevations in septic patients raises the question of the mechanism that leads to troponin release (Figs. 4 and 5). A possible scenario is the one of global myocardial ischemia that results to the release of cTn from damaged myocardial cells due to oxygen supply–demand mismatch due to fever and tachycardia. This results in reduced oxygen supply of the myocardium as a result of systemic hypoxemia from respiratory failure, microcirculatory dysfunction, hypotension, and sometimes anemia. Except for ischemia, there are many other parameters that may result in myocardial injury in the substrate of septic shock. Troponins that are in small quantities in cytosol may leak through the myocardial membrane independently of any damage to myofibril (Turner et al. 1999). Furthermore, a possible mechanism includes the direct cardiac injury and myocytotoxic effect of endotoxins, cytokines (interleukins (IL) 1β, IL-6, and tumor necrosis factor (TNF)-α), nitric oxide and endotoxins (Ammann et al. 2001) as well as activation of caspase

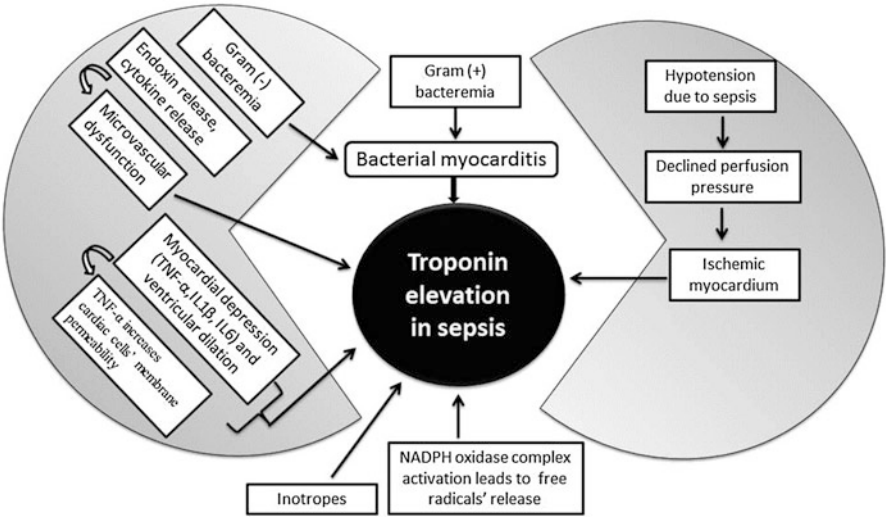

Fig. 4 The pathophysiologic mechanisms of sepsis. The high incidence of cTn elevations in septic patients raises the question for the mechanism that leads to troponin release. One of the possible mechanisms includes hypoxemia from respiratory failure, microcirculatory dysfunction, hypotension, and anemia. Another scenario is that small quantities of cytosolic troponins may leak though the myocardial membrane independently of any damage to myofibril. Myocytotoxic effect of endotoxins, cytokines (interleukins (IL) 1β, IL-6, and tumor necrosis factor (TNF)-α), nitric oxide, and endotoxins due to gram-negative bacteremia and sepsis results to myocardial depression and ventricular dysfunction. Another scenario includes the release of reactive oxygen radicals due to activation of NADPH oxidase complexes and mitochondria. These free radicals in combination with leucocyte-derived superoxide radicals are implicated with myocardial cell damage and apoptosis. Furthermore, a possible mechanism includes the direct cardiac injury. Finally, increased cardiac filling pressures and increased wall stress due to sepsis have been implicated with intracellular signaling cascade activation that leads to cardiac myocytes apoptosis, myocytes damage, and micronecrosis

3 (Communal et al. 2002) in case of gram-negative bacteremia and sepsis. Based on the fact that TNF-α increases the permeability of endothelial cells to macromolecules and lower molecular weight solutes, a similar increase in permeability of myocardial cell membrane could be expected (Brett et al. 1989). Additionally, IL1β, IL-6, and TNF-α have been proposed to play a central role in sepsis-mediated myocardial depression (Prabhu 2004). Indeed, in a recent study (Altmann et al. 2010), it has been shown that in a small group of patients with SIRS, sepsis, and septic shock, there were no differences among cTnI-positive and cTnI-negative patients when compared for coagulation parameters with thromboelastometry. They proposed that cytokines release from myocardial membrane, especially TNF-α, IL1β, and IL-6 play a crucial role in mediating hemodynamic effects and increase of cardiac troponin in patients with severe sepsis and septic shock. Another scenario includes the release of reactive oxygen radicals (Natanson et al. 1989) due to activation of NADPH oxidase complexes in mitochondria (Levy et al. 2005; Chagnon et al. 2006). These free

Fig. 5 Theories of cTn elevation in sepsis. Several theories have been proposed in order to elucidate troponin elevation in sepsis. These include: the demand and supply mismatch theory, the stress-mediated elevation of troponin during sepsis, the myocarditis and the role of cytokine vasopressor theory, the microthrombosis theory, and the ventricular wall stress-mediated theory

radicals in combination with leucocyte-derived superoxide radicals are implicated in myocardial cell damage and apoptosis (Levy et al. 2005). Finally, increased cardiac filling pressures and increased wall stress due to sepsis have been implicated in intracellular signaling cascade activation that leads to cardiac myocyte apoptosis (Horwich et al. 2003), myocyte damage, and micronecrosis (Brett et al. 1989). Whether cTn is indicative of reversible or irreversible myocardial damage remains unclear. However, in a recent meta-analysis (Sheyin et al. 2015) of 17 studies with total sample size of 1,857 patients, elevated troponin was proved to be an independent predictor of mortality (risk ratio, 1.91; 95 % CI, 1.65e2.22; $p < 0.05$).

Stroke

All types of stroke [ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH)] are characterized by increased cTn levels (Sandhu et al. 2008). In particular, in a recent meta-analysis of 15 studies that involved 2,901 patients with acute stroke, a percentage of 18 % of them had elevated cTn concentrations with range from 0 % to 35 % probably due to different exclusion criteria and cTn cut-

offs (Kerr et al. 2009). The levels of cTn and adverse outcomes are closely related in the majority of studies that examine the relation among cTn and stroke (including SAH). In particular, in a recent meta-analysis (Kerr et al. 2009) on acute stroke patients with a positive troponin level, it seemed to express features representative of myocardial ischemia on the ECG and had poorer survival when compared with stroke patients without troponin elevation. Furthermore, several studies proved a strong positive correlation between cTn elevation and severity of the stroke (Ay et al. 2006). This constitutes cTn as a valuable biomarker for the evaluation of stroke severity despite the fact that the mechanism of increased cTn in the substrate of stroke has not been fully clarified. Undoubtedly, the extent of the ischemic plaque of the brain as well as the location of stroke influences the prognosis. Nevertheless, when patients survive after a stroke, other cardiovascular entities including coronary artery disease may affect the long-term survival (Dixit et al. 2000). cTn increase maybe also provoked by heart and renal failure rather than MI. cTn increase is also attributed to left ventricular systolic dysfunction which is encountered in all three kinds of strokes. Left ventricular dysfunction may be due to either exaggerated catecholamine release. This may also lead to a form of an unrestrained myocardial stress test that reveals ischemia by obstructive stable coronary plaques or can trigger Takotsubo disease.

Strenuous Exercise

Strenuous exercise may induce the release of cTn immediately after prolonged running (Scharhag et al. 2005; Sahlen et al. 2009). The proposed mechanism is that prolonged exercise causes muscular fatigue that is expressed as rapidly decreased systolic and diastolic function which is the so-called cardiac fatigue (Douglas et al. 1987). In particular, runners with elevated troponin concentrations after the race have also been proved to have more signs of right and left ventricular dysfunction including regional wall motion abnormalities (Neilan et al. 2006). In a meta-analysis, a percentage of 47 % of individuals had elevated troponin T after endurance exercise (Shave et al. 2007). Nevertheless, in another recent study using high-sensitivity troponin assays, the majority of marathon runners (80–86 %) had increased levels after racing (Mingels et al. 2009). In general, high-sensitivity troponin assays have indicated that even a short-duration exercise may result to elevated troponin concentrations if the intensity is high. To be more specific, it has been shown that a 30 min of high-force exercise led to small TnI elevations in 75 % of participant (Shave et al. 2010). However, others have proved that the troponin release is not necessarily indicative of myocardial injury. This is based on the fact that since the elevation usually normalizes within 24–48 h, at least in case of non-high-sensitive troponin assays (Scharhag et al. 2005). The proposed mechanism is that the released troponin is the product of degraded "cytosolic" troponin under stress. Undeniably, data from a murine model of forced physical stress support the above hypothesis (Chen et al. 2000). Fatigue symptoms are usually observed in long-distance runners. Therefore, the setting of troponin elevation combined with dizziness, chest pain, or collapse should constitute a challenging

Table 1 Mechanisms and characteristics of cTn elevation according to exercise intensity

Intense exercise
• Strenuous exercise may induce the release of cTn immediately especially after during prolonged running (Scharhag 2005, Sahlen 2009) • Runners with elevated troponin concentrations after the race have also been proved to have more signs of right and left ventricular dysfunction including regional wall motion abnormalities (Neilan et al. 2006) • 47 % of individuals had elevated troponin T after endurance exercise (Shave 2007) • The majority of marathon runners (80–86 %) had increased levels after racing (Mingels 2009)
Short duration exercise
• Short-duration exercise may result in elevated troponin concentrations if the intensity is high • It has been shown that 30 min of high-force exercise led to small TnI elevations in 75 % of participants while others have proved that the troponin release is not necessarily indicative of myocardial injury (Shave 2010) • The elevation usually normalizes within 24–48 h, at least in case of non-high sensitive troponin assays (Scharhag et al. 2005) • The proposed mechanism is that the released troponin is the product of degraded "cytosolic" troponin or prolonged staying of the myocytes' cell membranes under stress

diagnostic issue (Shave et al. 2005). The mechanisms of cTn elevation according to exercise intensity are summarized in Table 1.

Cardiac Contusion

Cardiac contusion that is a frequent enough entity is induced by blunt trauma on the chest wall. From the data of the literature, the frequency ranges from 5 % to 50 % with traffic accidents being one of the most usual reasons of cardiac contusion as a result of violent fall, aggressive impacts, and the practice of risky sports (Fabian et al. 1988). The range of post-traumatic cardiac lesions varies from no symptoms to decrease in cardiac function. The early diagnosis of cardiac contusion is achieved with continuous electrocardiographic monitoring, serial electrocardiograms, echocardiography, and measurement of serum biochemical cardiac markers such as troponin as well as radionuclide imaging and coronary angiography. However, significant complications had been recorded in patients with blunt chest trauma in whom ECG findings were normal and serial assessment of cTn was within reference intervals (Schultz and Trunkey 2004). Furthermore, cTnI and cTnT were compared with less-specific biomarkers for superiority in the detection of cardiac damage due to myocardial contusion in patients with blunt chest trauma and hemodynamic stability. Furthermore, it was investigated whether they were associated with significantly worse long-term prognosis (Bertinchant et al. 2000). It has been shown that despite improved specificity of cTnI and cTnT, the main problem with the use of these biomarkers was the low-sensitivity as well as low predictive values in diagnosing myocardial contusion (Bertinchant et al. 2000). Levels of cTnI were further evaluated in children with thoracic non-accidental trauma. It has been shown that the elevation of cTnI level could be indicative of sufficient chest trauma and

independent of the presence of cardiac decompensation or shock from other causes (Bennett et al. 2011).

Potential Applications to Prognosis and Other Diseases or Conditions

Troponins T and I are perfectly appropriate for the detection and prediction of myocardial injury because they are cardiac-specific proteins. Detection of a rise and/or fall of the cTn levels is crucial for the diagnosis of acute MI (Jaffe 2006); thus, increased cTn levels are defined as a value exceeding the 99th percentile of a normal reference population and must be determined for each specific assay with appropriate quality control in each laboratory (Apple et al. 2007). The criteria for cTn elevated values are assay dependent including high-sensitivity assays. Nevertheless, they can be defined from the precision profile of each assay (Thygesen et al. 2010). These biomarkers reach their peak values shortly after MI and maintain them for a prolonged time. In large reperfused MI, typically the biphasic time-release pattern of cTn, as described above, is usual (Thygesen et al. 2010). The early appearing peak may inform for the quality of microvascular reperfusion, while the levels of cTn on day 3 or 4 are indicative of myocardial infarct size (Giannitsis et al. 2008). It is strongly proposed that troponin is released from cardiac myocyte cell immediately after the membrane is disrupted as a result of myocardial cell death (Fishbein et al. 2003). However, the fact that troponin is elevated during marathon running (Giannitsis et al. 2009) doubts the scenario that it is released only due to irreversible damage. Finally, cTn can be useful in detection of myocardial injury during intervention for structural heart diseases. However, their significance concerning the prognostic value of adverse events have not been thoroughly evaluated yet.

Conclusion

Troponin is considered to be a very powerful diagnostic tool that helps the differential diagnosis of acute coronary syndromes from other entities. Despite the fact that it is cell specific for the cardiac muscle, troponin is observed to be high in conditions that are not included in ACS. High-sensitivity troponin assays appear to have apart from strengths and unique characteristics, some limitations that can cause problems into clinical practice. The technological progress of high-sensitivity troponin assays may be helpful for their widespread use with high potential to detect even slight elevations of troponin in healthy individuals that is met in several different clinical pathologies. However, despite the fact that troponin elevation is indicative of myocardial necrosis, it does not elucidate the pathophysiologic mechanism that causes myocardial damage. Therefore, the need for ameliorating the tests used as well as for discovering more specific biomarkers for the differential diagnosis of clinical entities is mandatory.

Summary Points

- This chapter focuses on troponin elevation beyond coronary artery disease.
- Troponins are protein complexes that are composed of three subunits (TnI, TnT, and TnC).
- Cardiac troponins are the gold standard biomarkers in the detection of myocardial injury.
- The use of new high-sensitivity assays detects even small increases in troponin levels increasing the number of patients who are detected with elevated troponin concentrations.
- Troponin concentrations are elevated at several noncoronary entities such as stroke, pulmonary embolism, sepsis, acute perimyocarditis, Takotsubo, acute heart failure, tachycardia, and cardiac contusion.
- Patients with chronic kidney disease have a greater frequency of persistently elevated cardiac troponin probably because troponin molecule is too large for the kidneys to be cleared from serum.
- The most predominant scenario for troponin elevation in episodes of tachyarrhythmias is the imbalance between oxygen demand and supply to the myocardium when myocardial perfusion occurs.
- The pathophysiologic substrate of troponin elevation in acute HF is based either on the fact that increased ventricular preload triggers myocardial strain that may consequently result to troponin release or due to myocardial damage as a result of necrotic and apoptotic processes.
- Elevated cardiac troponin levels in PE are present even in hemodynamically stable patients. The proposed scenarios for the pathophysiologic mechanism are two. The first is based on the fact that increased pulmonary artery resistance results to acute right ventricular strains and to elevated troponin concentrations. The second one is that hypoxemia leads to increased troponin levels. Patients with acute PE and elevated troponin had worse outcome than those without.
- In stress-related cardiomyopathies, cardiac toxicity mediated by catecholamines burdens left ventricular function and is accompanied by troponin elevation.
- Patients with severe sepsis and septic shock usually present with declined ventricular function which is related with elevated cTn concentrations. There are several proposed mechanisms for the pathophysiologic cascade.
- All types of stroke [ischemic, intracerebral hemorrhage, and subarachnoid hemorrhage (SAH)] are characterized by increased cTn levels.
- Strenuous exercise may induce the release of cTn immediately, especially after prolonged running.
- Cardiac contusion following blunt chest trauma is not rare and ranges from no symptoms to decrease in cardiac function with cardiogenic shock being a rarely encountered manifestation. The diagnosis is set with continuous electrocardiographic monitoring, serial electrocardiograms, echocardiography, and measurement of serum biochemical cardiac markers such as troponin as well as radionuclide imaging and coronary angiography.

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