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REVIEW

Frontiers in cardiovascular medicine

Troponin elevation in coronary vs. non-coronary disease

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Acute myocardial infarction is defined as myocardial cell death due to prolonged myocardial ischaemia. Cardiac troponins (cTn) are the most sensitive and specific biochemical markers of myocardial injury and with the new high-sensitivity troponin methods very minor damages on the heart muscle can be detected. However, elevated cTn levels indicate cardiac injury, but do not define the cause of the injury. Thus, cTn elevations are common in many disease states and do not necessarily indicate the presence of a thrombotic acute coronary syndrome (ACS). In the clinical work it may be difficult to interpret dynamic changes of troponin in conditions such as stroke, pulmonary embolism, sepsis, acute perimyocarditis, Tako-tsubo, acute heart failure, and tachycardia. There are no guidelines to treat patients with elevated cTn levels and no coronary disease. The current strategy of treatment of patients with elevated troponin and non-acute coronary syndrome involves treating the underlying causes. The aim of this paper is to review data from studies of non-ACS patients with acutely elevated troponin who in clinical practice may be difficult to discriminate from ACS patients.

Keywords Troponin • Myocardial infarction

Introduction

Acute myocardial infarction (MI) is defined as myocardial cell death due to prolonged myocardial ischaemia. The ESC/ACCF/AHA/WHF task force[1] for the redefinition of MI agreed on the following definition of MI; Detection of rise and/or fall of cardiac biomarkers (preferably troponin) above the 99th percentile of the upper reference limit together with evidence of ischaemia with at least one of the following: Ischaemic symptoms, electrocardiography (ECG) changes of new ischaemia, development of pathologic Q-waves in the ECG or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality. In the task force document clinical classification of five different types of MI were defined (*Table 1*). Type 2 MI is defined as MI secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension. In addition, there are numerous causes of troponin release due to myocardial damage not related to myocardial ischaemia. Discrimination of Type 2 MI from troponin release due to non-coronary diseases is challenging. However, discrimination is paramount in order to provide timely and appropriate treatment.

The new high-sensitivity troponin methods allow detection of very minor damages on the heart muscle increasing numbers of patients with elevated troponin concentrations and thus hamper interpretation of troponin results. In clinical practice it may be difficult to interpret dynamic changes of troponin in conditions such as stroke, pulmonary embolism (PE), sepsis, acute perimyocarditis, Tako-tsubo, acute heart failure (HF), and tachycardia (*Table 2*).

The aim of this paper is to review data from studies of non-ACS patients with acutely elevated troponin who in clinical practice may be difficult to discriminate from ACS patients.

Troponins for diagnosis of myocardial injury

Cardiac troponin is composed of three subunits T, I, and C, which are the products of different genes. The total mass of the troponin complex is minuscule when compared with the protein mass of other myofibrillar proteins like actin and myosin. However, both

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Table 1 Clinical classification of different types of myocardial infarction

Type 1
Spontaneous myocardial infarction related to ischaemia due to a primary coronary event such as plaque erosion and/or rupture, fissuring, or dissection
Type 2
Myocardial infarction secondary to ischaemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anaemia, arrhythmias, hypertension, or hypotension
Type 3
Sudden unexpected cardiac death, including cardiac arrest, often with symptoms suggestive of myocardial ischaemia, accompanied by presumably new STelevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood
Type 4a
Myocardial infarction associated with PCI
Type 4b
Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy
Type 5
Myocardial infarction associated with CABG

Table 2 Reasons for acutely elevated troponins

Acute coronary syndrome
Acute heart failure
Pulmonary embolism
Stroke
Acute aortic dissection
Tachyarrhythmias
Hypotension / Shock
Sepsis
ARDS
Perimyocarditis
Endocarditis
Tako-tsubo cardiomyopathy
Radiofrequency catheter ablation
Cardiac contusion
Strenuous exercise
Sympathomimetic drugs
Chemotherapy

troponin T and I are ideally suited for the detection of myocardial damage as they are expressed as cardio-specific isoforms. There is a distinct release kinetics following MI show a first peak resulting from the loosely bound troponin pool and a second prolonged elevation due to degradation of the contractile apparatus.[2] Patients with large reperfused MI typically show such a biphasic time-release pattern of cardiac troponin (cTn) T when compared with the monophasic pattern seen with cTnI.[2] The release pattern of cTnT is different in non-reperfused MI and may vary with small MIs. Although the exact reason for this different release kinetics is still illusive, cTnT differs from cTnI with respect to higher molecular weight, higher fraction of unbound cTnT, less degradation, whereas cTnI is more frequently found as binary or tertiary complex in blood (*Figure 1*). There is evidence that the early appearing pool may give information on the quality of micro-vascular reperfusion, while the concentration of cTn on Day 3 or 4 reflects myocardial infarct size.[3] Experimental data strongly suggest that troponin leaks out of the cell only after membrane disruption following myocardial cell death.[4] The detection of brief rise and subsequent fall of troponin concentration during marathon running[5] and rise after inducible myocardial ischaemia[6] has cast some doubts on the hypothesis that troponin is released only upon irreversible damage. However, there are neither consistent experimental nor clinical data providing proof of this concept, so far.

Troponin assays

The Joint ESC/ACCF/AHA/WHF Task Force has promoted the use of the 99th percentile and state that a cTn imprecision $\leq$10% at the 99th percentile is desirable.[1] During the time period when troponin assays were insufficiently precise at very low levels, some institutions advocated the use of the lowest value at which the assay achieved a 10%CV rather than the 99th percentile value. As a consequence several diagnostic companies have improved assay sensitivity to comply with these recommendations.[7] The criteria defining a hsTn assay are still under debate. According to our understanding hsTn assays—by virtue of their higher analytical sensitivity—possess the capability to identify more patients with hitherto undetectable cTn concentrations (with or without ACS) and also allow detection of low cTn concentrations in many if not all healthy subjects. These hsTn assays comprise hsTnI assays from Singulex, Nanosphere, Beckman-Coulter (Access), Centaur Troponin I Ultra and Vista (both Siemens), cTnI (Ortho Vitros), and TnThs (Roche).[8,9] Additional criteria may serve for subclassification such as the scorecard classification proposed by Apple.[9]

Analytical issues

By definition, using the 99th percentile as the reference limit, an elevated troponin value may be encountered in 1% of a healthy reference population. A cTn elevation reflects acute or chronic myocardial damage but is not exclusive for ACS thus causing some problems with interpretation of results. Sometimes the term false-positive is being used to describe a patient with suspected ACS and elevated troponin but subsequently absence of significant coronary disease on coronary angiogram. In this setting several differential diagnoses have to be considered where troponin elevation may be related to underlying cardiac but non-coronary pathology or extracardiac disease, such as severe renal dysfunction.[10]

Rarely, elevated troponin concentrations cannot be explained despite thorough clinical examination. These rare instances are referred to as truly false-positives, and are most frequently related to heterophilic antibodies or other analytical issues.[11]

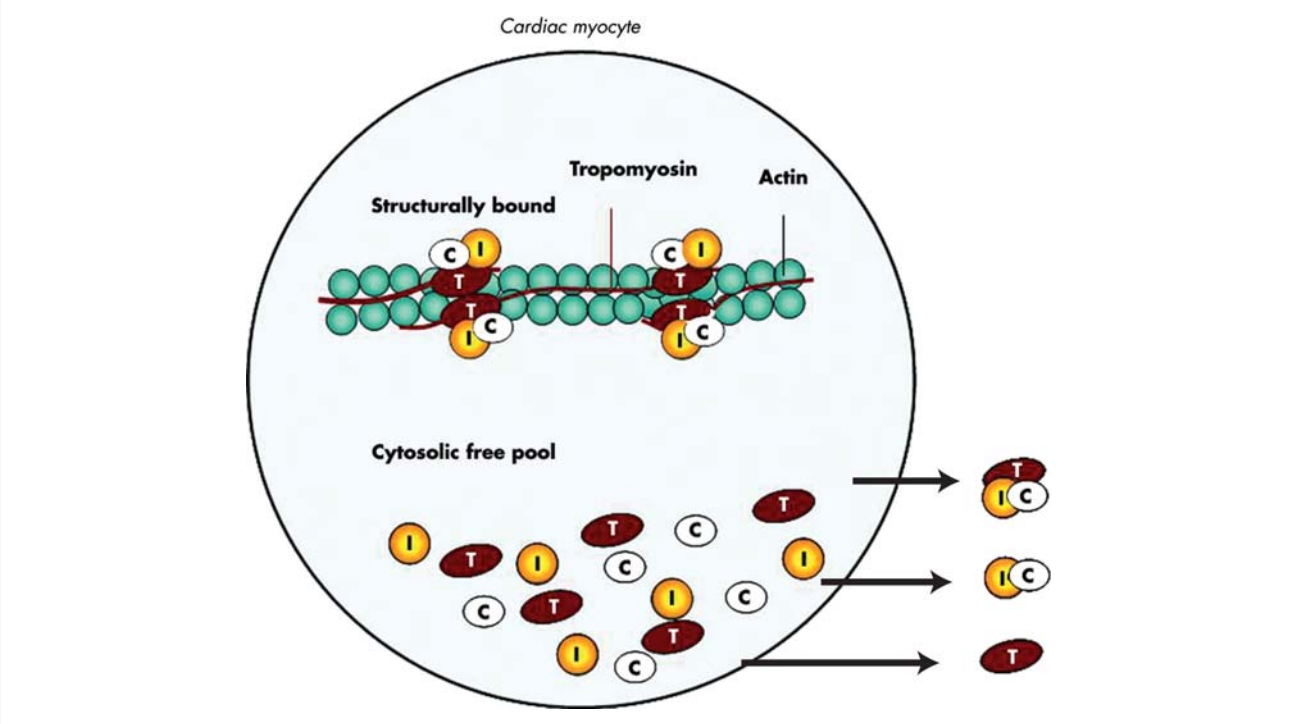

Figure 1 Schematic representation of the cardiac myofibrillar thin filament. Cardiac troponins exist in a structural (bound) form and in a free cytosolic pool. Cardiac troponins are released from myocytes as complexes or as free protein. Permission received from the authors and BMJ.

The development of three-site sandwich immunoassays needed for the generation of some of more sensitive troponin assays involving two capture and one detection antibody or two detection and one capture antibody is associated with an increased susceptibility to heterophile interference.[12] Conversely, interference of troponin with cTnI- and less frequently cTnT-autoantibodies may result in falsely negative results or lower concentrations of detectable cTn.[13] Haemolysis may interfere with cTn and cause measurement of higher or lower cTn concentrations. This issue is not relevant with mild haemolysis[7,11] or high cTn concentrations but may be relevant with more severe haemolysis (>100 mg/dL), particularly at concentrations near the 99th percentile value, and in clinical settings where haemolysis is more prevalent like in emergency departments.[14,15] There are several other analytical issues that may confound the result and need attention including non-specific binding, effect of matrix selection, lot-to-lot variation.

Lowering the cut-off value in patients with acute coronary syndrome

Applying the 99th percentile cut-off using highly sensitive assays in ACS patients has now been substantiated in several studies.[16–18] It has been demonstrated beyond doubt that lowering the decision cut-off allows earlier detection of MI, increases numbers of cases with MI, and decreases numbers of cases with unstable angina proportionately.[7]

However, the ESC/ACCF/AHA/WHF infarct definition gives no recommendations for use of the 99th percentile value for risk assessment. Previous studies suggested that lowering the decision cut-off from the 10%CV to the 99th percentile gradually improved risk stratification, treatment, and selection of early invasive vs. selective invasive strategy among patients with ACS in randomized clinical trials.[19–22]

However, measurements were made with cTn assays with an imprecision ≥20%. More recently, the MERLIN-TIMI-38 trial that randomized 4513 ACS patients to ranolazine or placebo found that using a hsTnI assay concentrations above the 99th percentile value predicted an adverse prognosis.[23]

The problem of diagnosing myocardial injury in minor elevations: the role of kinetic changes

Given the lack of a clear definition of rise and fall of cTn, many clinicians have operated with a change in the cTn concentration of ≥20% as a practical cut-off. MacRae *et al.*[24] could demonstrate the usefulness of a 20% delta change in a cohort of 258 patients with suspected ACS. Recent studies suggest that this cut-off value regarding significant rise of troponin level needs to be higher in the lower cTn range.[25,26]

Two strategies to determine the required delta change appear promising. The first strategy requires that pre-specified or receiver-operating characteristic (ROC)-optimal delta change values obtained from ACS studies have to be validated with respect to their diagnostic and prognostic performance. Apple *et al.*[25] tested the utility of a delta

change of cTnI of ≥10%, ≥20, and ≥30%, and found that ≥30% change improved specificity and risk assessment. In another study, concentration changes of hsTnT within 3 h were compared between patients with a final diagnosis of non-STEMI who initially presented with a negative troponin and in patients with a final diagnosis of unstable angina (*Figure 2*). In this study, ROC analysis demonstrated that a delta change ≥117% from the baseline to the subsequent sample within 3 h increased clinical specificity.[26] Forthcoming studies should validate criteria for delta change and should address interesting aspects such as the question for the minimal value for change to allow a diagnosis of MI, or other criteria such as discrimination by absolute differences, or maximal concentrations (*Figure 3*).

The second strategy requires the measurement of normal biological variability of troponin concentrations in order to calculate the reference change value (RCV) from intraindividual and interassay variability.[27] Due to biochemical differences of cTnI assays RCV has to be established individually for each commercially available cTnI assay. In addition, RCV values have to be calculated for different automated analysers as technologies may differ substantially regarding precision. Wu *et al.*[27] calculated the RCV and derived parameters of a cTnI assay using a single molecule detection system and found a RCV of 46% for an increasing cTn and 32% for a decreasing cTnI value. More recently, Vasile *et al.*[28] reported a log-normal RCV of 85%, and calculated a delta change of 58% for an increasing cTnT, and 57.5% for a decreasing cTnT using the hsTnT assay.

Troponin concentration changes in patients with end-stage renal disease

Only for the subset of patients with end-stage renal disease (ESRD), the NACB guidelines[29] have recommended a change in the cTn concentration of ≥20% for the diagnosis of MI in those who present with elevated cTn, 6–9 h after presentation, as indicative of a relevant concentration change because it represents a significant (3 SD) change in cTn on the basis of a 5–7% analytical CV. However, the NACB made recommendations utilizing less sensitive troponin assays and it is not clear if those recommendations still fit for the more sensitive assays. Recently, in a cohort of asymptomatic patients with ESRD a troponin concentration exceeding the 99th percentile value using the new hsTnT assay was found in 100% of patients.[30]

Tachycardias

In clinical practice, elevated troponin concentrations are sometimes observed after prolonged episodes of supraventricular tacharrhythmias (SVT), even in presumably healthy individuals. The most likely mechanism for troponin elevation following tachycardia may be shortening of diastole with subsequent subendocardial ischaemia.[31] In animal studies, myocardial stretch is believed to represent a second possible mechanism for tachycardia-mediated troponin elevation as there exists a direct association between a parallel rise in natriuretic peptide and troponins concentrations in patients with various tachycardias.[32] It has been hypothesized that cTnI release from viable cardiomyocytes may be mediated by stimulation of stretch-responsive integrins, mechanotransducer molecules that link the extracellular matrix to the intracellular cytoskeleton.[33]

Bakshi *et al.*[34] reported on 21 patients with normal coronary angiograms in whom tachycardia was believed to account for the observed troponin elevation in 28% of patients. Bukkapatnam *et al.*[35] studied 104 patients with a diagnosis of SVT of whom 48% had elevated cTn. However, no difference in the diagnosis

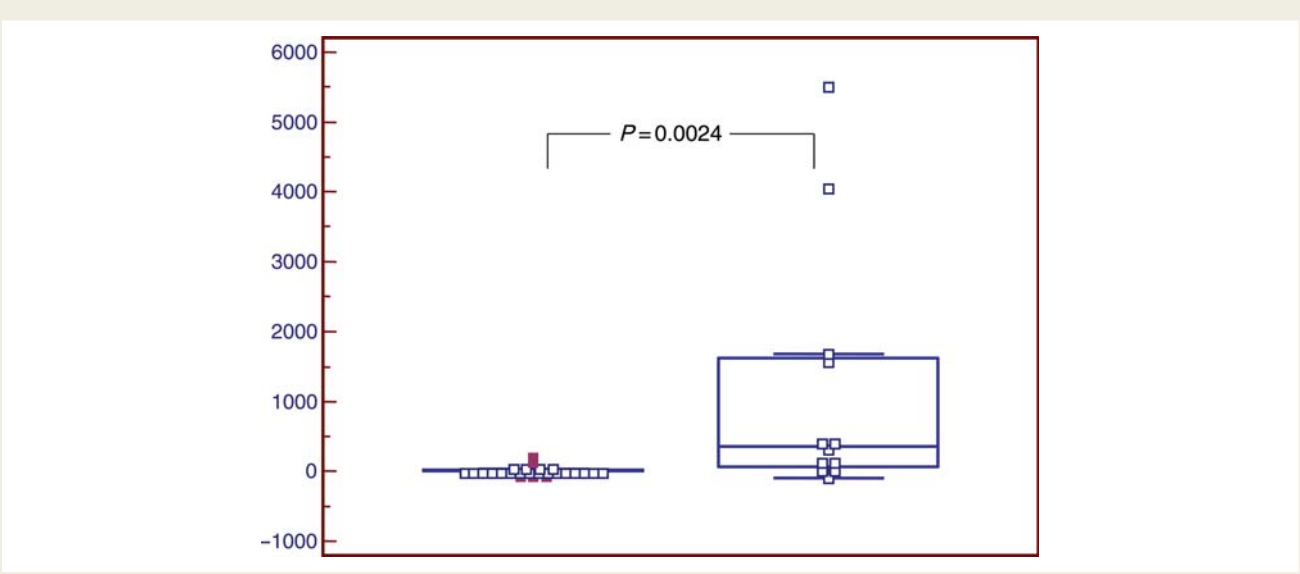

Figure 2 Box and whiskers plot showing delta change between presentation and subsequent blood sample obtained within 3 h in patients with a diagnosis of unstable angina (left, $n = 25$) and evolving non-STEMI (right, $n = 12$). Diagnosis of myocardial infarction was based on fourth generation cTnT (≥0.03 ng/mL). hsTnT concentration increased significantly ($P = 0.0024$) from a mean of 10.66% (SEM 10.8, median 0%, range −84.6 to 192.8%) to a mean of 1176.9% (SEM 520.9, Median 358.4%, range: −96.6 to 5503.6%).

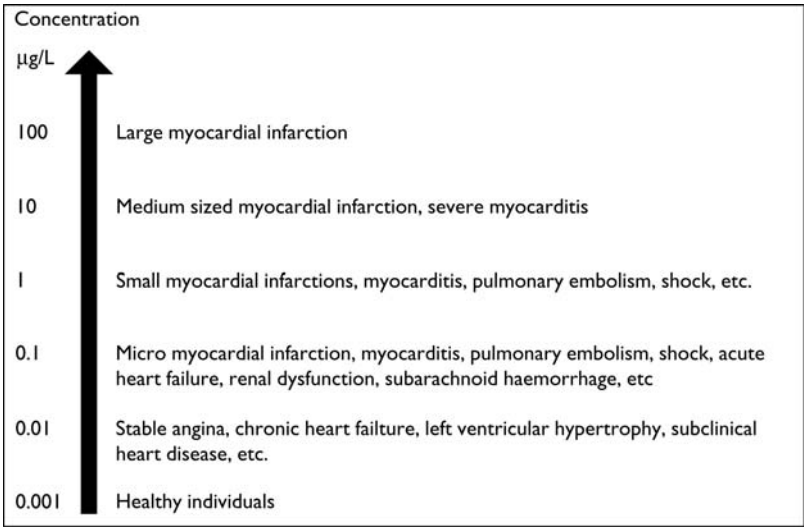

Figure 3 Relation between troponin level and possible causes.

of CAD was found between those with when compared with those without CAD. However, several shortcomings limit the value of these observations as the diagnostic work-up including coronary angiography, stress testing, and haemodynamic measurements was not routinely performed in all patients, and serial troponin results to support an acute and reversible concentration change were not available. Therefore, it is still illusive if tachycardia alone may cause a troponin release in the absence of underlying structural heart disease, significant CAD, myodepressive factors, and inflammatory mediators or whether troponin release is due to an imbalance between oxygen demand and supply (Type 2 MI) in patients with subclinical heart disease. Recently, the GISSI-Atrial Fibrillation (AF) investigators found that higher concentrations of myocardial strain or injury markers like hsTnT, MR-proANP, NT-proBNP, and endothelin predicted higher risk of a first recurrence of AF in 382 patients having sinus rhythm but with a history of recent AF.[36] These data suggest that presence of underlying structural heart disease is closely related to recurrence of AF. No data are presently available to address whether AF itself has any effect on the concentration change over time.

Acute heart failure

The ADHERE Registry[37] examined 67 924 acutely decompensated HF patients and explored the relationship between elevated troponin concentrations and adverse events. Using less sensitive formulation of the cTnT assay or cTnI assays, 4240 patients (6.2%) were positive for troponin. These patients had lower systolic blood pressure on admission, a lower ejection fraction, and higher in-hospital mortality (8.0 vs. 2.7%, $P < 0.001$) than those who were negative for troponin. The adjusted odds ratio (OR) for death in the group of patients with a positive troponin test was more than two-fold (OR 2.55) higher, independent of other predictive variables. These findings on the important prognostic role of troponins in patients with acutely decompensated HF were confirmed in another international pooled analysis of 1256 acute destabilized HF patients.[38] Reasons for higher prevalence of cTnT in acute HF are still unsettled. It has been speculated that increased ventricular preload causing myocardial strain may cause troponin release.[39]

It is tempting to speculate that a detectable baseline level of cTnT is the result of physiological loss of myocardium by necrosis and apoptosis. About 1 g of myocardial mass, corresponding to 64 million cells, is being lost per year in the human heart.[40] However, the relative contribution of necrosis and apoptosis is difficult to ascertain. In a study that included 40 patients with acute HF, Miller *et al.*[41] could demonstrate that baseline concentrations of cTn were significantly lower in those with dilated cardiomyopathies than in those with ischaemic cardiomyopathies. No data are currently available to clarify whether prevalence of elevated troponin and magnitude of rise and/or fall are higher in acute vs. chronic HF.

Pericarditis and myocarditis

Despite the fact that troponins are not present in the pericardium, cTn has been reported to be elevated in 32–49% of cases of acute pericarditis, as a consequence of the involvement of the epicardium in the inflammatory process.[42] Troponin elevations reflect myocardial lesion, thus an acute pericarditis with signs of myocarditis (evidenced by global or regional myocardial dysfunction or elevated cTn) is called myopericarditis. Clinical studies in patients with myopericarditis are sparse. Imazio *et al.*[43] have reported data on 274 consecutive cases of idiopathic or viral acute pericarditis. At presentation, when patients with pericarditis and myopericarditis were compared, patients with myopericarditis were younger, they were more often male, they had more often had recent febrile syndrome with gastrointestinal symptoms and/or skeletal muscle myalgia and ST-segment elevation at presentation was more common. They had also more often a deteriorated

ejection fraction and arrhythmias, but less frequently pericardial effusion compared with those with pericarditis.

Limited data have been published on the natural history of myopericarditis. Seroepidemiologic studies suggest that the majority of cases of Coxsackie B virus infection are subclinical and have a benign course. In the majority of patients, the inflammatory process is apparently self-limited without short-term, overt sequelae. Troponin increase is roughly related to the extent of myocardial inflammatory involvement, but unlike acute coronary syndromes it does not seem to carry an adverse prognosis in patients with myopericarditis. Remes *et al.*[44] have reported a good clinical outcome in a long-term follow-up of 18 patients with Coxsackievirus myopericarditis. Also in the larger study by Imazio *et al.*[43] the prognosis was good. After 12 months the frequency of complications was similar in acute pericarditis and myopericarditis, with normalization of echocardiography, ECG, and treadmill testing in the majority of cases.

The pathophysiology of myocarditis is poorly understood and cTn levels may vary from normal levels up to high levels. Primary myocarditis is presumed to be caused by an acute viral infection or a post-viral autoimmune response. An increased prevalence of coronary vasospasm has been demonstrated in patients with myocarditis.[45] Thus, myocardial inflammation or virus persistence, or both, may cause a coronary vasomotility disorder enabling the occurrence of coronary vasospasm. This vasospasm may be the reason for atypical chest pain in subjects with myocarditis, which in turn may lead to some confusion in whether or not the aetiology of a given troponin elevation is due to myocarditis or due to an ischaemic aetiology.

Magnetic resonance imaging (MRI) is a powerful diagnostic tool for acute myocarditis, based on delayed enhancement imaging findings. Delayed enhancement usually involves the subendocardial layer in MI, whereas it usually spares the subendocardial layer in myocarditis.[46,47]

Acute pulmonary embolism

Despite that most patients with acute PE have an uncomplicated clinical course, this condition has a wide spectrum of clinical outcome varying from an early recovery of symptoms to sudden death. Patients with PE and signs of shock or hypotension have high mortality rates. It is generally accepted that these high-risk patients should be considered for thrombolytic therapy.[48] In patients with absolute contraindications to thrombolysis and in those in whom thrombolysis has failed to improve haemodynamic status, surgical embolectomy is the preferred therapy. If this is not immediately available, catheter embolectomy or thrombus fragmentation may be considered.[48]

Routine use of thrombolysis in non-high-risk patients is not recommended, but it may be considered in selected patients with intermediate-risk PE and after thorough consideration of conditions increasing the risk of bleeding.[48] Patients with intermediate-risk PE are characterized as patients with a stable circulation but with right ventricular dysfunction or elevated troponins. Kucher *et al.*[49] concluded that a normal echocardiogram combined with a negative cTnI level was most useful to identify patients at lowest risk for early death.

Among patients with stable circulation at admission, right ventricular dysfunction at echocardiography identifies patients with elevated risk for in-hospital mortality.[50] Several observational studies have reported elevated cardiac troponin levels in PE, even in haemodynamically stable patients. The reason for cTn release in PE is still unclear. The acute right ventricular strains secondary to increase in pulmonary artery resistance may cause a troponin elevation in PE. In the study by Meyer *et al.*[51] 63% of those with right ventricular dilation had an increased cTnI level whereas 29% of positive cTnI levels had a normal right ventricular end-diastolic diameter. Also significant was the finding that a positive cTnI level correlated with having more segmental defects on ventilation–perfusion scintigraphy. However, another explanation to an elevated troponin in PE patients might be hypoxaemia due to perfusion–ventilation mismatch, hypoperfusion as a consequence of low output and reduced coronary blood flow, as well as paradoxical embolism from systemic veins to the coronary arteries, usually via a patent foramen ovale. Transmural right ventricle infarction despite patent coronary arteries has been found in autopsies of patients who died of massive PE.[52] Studies investigating the release of kinetics of cTnT in patients with PE showed that the peak cTnT was lower and persisted for a shorter period of time compared with cTnT values in acute MI.[53] Thus, the mechanism of myocardial damage and cTnT release in patients with significant PE is different from that in patients with ACS. Whether cTnT in PE patients originates from the cytosolic pool or from a different readily accessible cell pool or whether troponin release in PE is attributable to severe reversible or irreversible myocardial ischaemia is unknown.

Several studies have reported an association between elevated troponin levels and a poor prognosis in patients with PE. Becattini *et al.*[54] has performed a meta-analysis of 20 studies in 1985 patients with PE. Elevated cTn levels were significantly associated with short-term mortality, death resulting from PE and other adverse events. Increased cTn values were also associated with a higher mortality in the subgroup of haemodynamically stable patients. Another more recent metanalysis focused on normotensive patients with acute symptomatic PE.[55] In this analysis, consisting of 1366 patients, elevated troponin level resulted in a four-fold increased risk of short-term death.

Tako-tsubo

Tako-tsubo cardiomyopathy has been called stress-induced cardiomyopathy, broken heart syndrome or transient left ventricular apical ballooning syndrome. The Prevalence is reported to be 0.7–2.5% in patients presenting with acute coronary syndromes.[56] The typical Tako-tsubo cardiomyopathy patient has been characterized as an older woman with an acute emotional or physiologic stress commonly preceding the clinical presentation of Tako-tsubo cardiomyopathy. However, the clinical profile of Tako-tsubo cardiomyopathy is broader including both younger patients and men[57] and emotional or physically stressful events immediately before hospitalization can not be identified in all patients with Tako-tsubo cardiomyopathy.[57]

The pathophysiology of Tako-tsubo cardiomyopathy is not well understood. Several mechanisms for the reversible

cardiomyopathy have been proposed, including catecholamine-induced myocardial stunning, ischaemia-mediated stunning due to multivessel epicardial or microvascular spasm, aborted acute myocardial infarction (AMI), and focal myocarditis. The reason of selective involvement of apical and/or midportion of the left ventricle with relative sparing of basal segments is unknown and might be partly explained by the evidence that apical myocardium has increased responsiveness to sympathetic stimulation.

These patients frequently present with symptoms consistent with ischaemic chest pain or dyspnoea. Electrocardiography often shows minimal ST elevation in the precordial leads and most patients exhibit a small elevation of troponin.[58] Studies evaluating the ability of the ECG to differentiate Tako-tsubo cardiomyopathy and ACS have been unsuccessful in identifying reliable differences between the two groups to diagnose Tako-tsubo cardiomyopathy based on the ECG alone.[58] In most reports of Tako-tsubo cardiomyopathy, echocardiography during the acute phase (within 72 h of admission) demonstrates findings with dyskinetic or akinetic apical and midventricular wall motion abnormalities and basal hyperkinesis.

Magnetic resonance imaging examination may also be used to identifying the typical regional wall motion abnormalities. It also allows a precise quantification of right and left ventricular function enables the assessment of myocardial perfusion and can be used to exclude other disease processes. Late gadolinium enhancement (LGE) on MRI is considered as indicative of myocarditis or embolic infarction, depending on the mural distribution of enhancement. Most reports suggest that LGE rules out Tako-tsubo cardiomyopathy, but there are studies reporting LGE in patients with Tako-tsubo cardiomyopathy.[59]

Most patients with Tako-tsubo cardiomyopathy have a modest rise in cTn that peaks within 24 h.[58,60] The magnitude of increase in the biomarkers is less than that observed with a STEMI and disproportionately low for the extensive acute regional wall motion abnormalities that characterize Tako-tsubo cardiomyopathy.[58] One prospective study evaluated the magnitude of troponin T and I elevation in differentiating between Tako-tsubo cardiomyopathy and ACS. In this analysis, those with troponin T $>$ 6 ng/mL or troponin I $>$ 15 ng/mL were unlikely to have Tako-tsubo cardiomyopathy.[60]

The optimal management of Tako-tsubo cardiomyopathy has not been established, but supportive therapy invariably leads to spontaneous recovery. The systolic dysfunction and the regional wall motion abnormalities are transient and often resolve completely within a matter of days to a few weeks.[57]

Sepsis

Approximately 50% of patients with severe sepsis and septic shock may develop impairment of ventricular performance. Elevations in cTn correlate with the presence of left ventricular systolic dysfunction.[61,62]

Among patients who are treated in intensive care units for sepsis or systemic inflammatory response syndrome, elevated cTn have been detected in 12–85%, with a median frequency of 43% according to a recent meta-analysis of 3278 patients in 20 studies.[63] This wide range of prevalence is probably due to the different underlying causes of sepsis, the different troponin assays used, and the different cut-off values that were applied. Several studies have demonstrated that an elevated cTn predicts mortality in sepsis patients.[63]

The high prevalence of elevated serum levels of cTn in septic patients raises the question of what mechanism results in troponin release in septic shock. One theory of myocardial dysfunction in sepsis has been based on the hypothesis of global myocardial ischaemia. The release of cTn from damaged myocardial cells might be an oxygen supply–demand mismatch of the myocardium. As a consequence of fever and tachycardia the 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. Thus, there are reasons for a Type II MI. However, studies using thermodilution catheters placed in the coronary sinus in patients with septic shock allowing measurement of coronary flow and myocardial metabolism report preservation of myocardial blood flow, net myocardial lactate extraction, and diminished coronary artery–coronary sinus oxygen difference compared with controls.[64] Thus, these observations argue against global ischaemia as a cause of septic myocardial depression. Apart from ischaemia, several factors may contribute to microinjury and minimal myocardial cell damage in setting of septic shock. A possible direct cardiac injury and myocytotoxic effect of endotoxins,[65] cytokines,[66] or reactive oxygen radicals induced by infectious process and produced by activated neutrophils, macrophages, and endothelial cells have been postulated.

It is not clear whether higher cTn represents reversible or irreversible myocardial injury in septic shock. ver Elst *et al.*[62] did not find evidence of irreversible myocyte necrosis in autopsy cases of septic shock where there was a positive premortem cTn. These authors suggested the possibility of cTn release as reversible injury in these patients.

There is no consensus on the appropriate approach and management of an elevated cTn level in the intensive care unit (ICU) setting. A plaque rupture MI (Type I) and a MI secondary to ischaemia due to either increased oxygen demand or decreased supply (Type II) must always be considered. A history of coronary artery disease with typical ischaemic ECG changes may indicate a Type I MI. Patients at ICU can rarely communicate classic ischaemic symptoms because of endotracheal intubation, sedation, or analgesia, underscoring how difficult it might be to decide whether an increased cTn is caused by cardiac ischaemia or not.

Stroke

Increases in cTn have been reported in all types of stroke [ischaemic, intracerebral haemorrhage, and subarachnoid haemorrhage (SAH)].[67] In a recent meta-analysis of 15 studies including 2901 patients with acute stroke, 18% of the patient had a positive cTn. The prevalence varied from 0 to 35% most likely due to different exclusion criteria and different cTn cut-offs.[68] Also contractile dysfunction and ECG changes such as ST-segment depression and T-wave inversion (ST–T changes) are common in stroke patients.[69]

The majority of studies relating cTn and stroke (including SAH) demonstrate an association between raised cTn level and adverse

outcomes. In the meta-analyses made by Kerr *et al.*,[68] acute stroke patients with a positive troponin level were more likely to have features suggestive of myocardial ischaemia on the ECG and had a greater risk of death than those without a troponin rise. Even when adjusted for potential confounding factors, a positive cTn level was associated with an overall increased mortality. A strong positive correlation between the rise in cTn and the severity of the stroke has also been observed in several studies,[70,71] and increased cTn levels may therefore represent a surrogate marker for the severity of a stroke.

Although the aetiology of increased cTn in the setting of stroke has not been entirely elucidated, there are a number of possible causes of raised cTn after stroke. After AMI, stroke incidence is markedly increased, particular early after the cardiac event.[72] Certainly the extent of the ischaemic penumbra of the brain and the location of the stroke affects the prognosis, however, in patients surviving a stroke, other manifestations of cardiovascular disease, particularly coronary artery disease, are the main causes of long-term mortality.[73] Thus, patients with ischaemic stroke may have had antecedent MI perhaps complicated by AF.[69] However, it is clear that this could not be the whole explanation. In a recent study of 244 patients with acute ischaemic stroke but without overt ischaemic heart disease, perfusion abnormalities on myocardial perfusion scintigraphy were not more frequent or pronounced in acute stroke patients with elevated cTn compared with acute stroke patients with normal cTn.[74] The authors suggested that heart and renal failure rather than MI are the most likely causes to elevated cTn levels in patients with acute stroke.

Left-ventricular systolic dysfunction has been observed in all three kinds of strokes. In patients with SAH and wall motion abnormalities no perfusion defects were observed at myocardial scintigraphy[75] and in another study no abnormalities were found during coronary angiography.[76] The observed wall motion abnormalities were reversible.[76]

It has also been proposed that the observed cardiac abnormalities are secondary to increased/disturbed sympathetic activity provoked by acute stroke. An exaggerated catecholamine release may lead to excessive release of intracellular calcium ions and subsequent reversible myocyte dysfunction. An alternate explanation is that the catecholamine surge acts as an uncontrolled severe myocardial stress test, which essentially reveals stable coronary plaques or induces a Tako-tsubo disease. Animal studies have documented that acute stroke trigger an acute release of catecholamines, which is followed by a severe decrease in cardiac function accompanied by a significant increase in cTn.[77] Similar findings have been found in patients with SAH.[78] Banki *et al.*[75] reported that LV systolic dysfunction in humans with SAH was associated with normal myocardial perfusion and abnormal sympathetic innervation.

Strenuous exercise

cTn can be elevated immediately after strenuous exercise, a phenomenon that has been studied mainly in the setting of prolonged running.[79–81] Troponin elevation has been found to occur mainly in participants with less training and in those with a lack of prior endurance racing.[81,82] Prolonged exercise induces a state of muscular fatigue. Involvement of cardiac muscle in this process is manifested as transiently decreased systolic and diastolic function, so-called cardiac fatigue.[83] Interestingly, runners with increased levels of troponin post-race have also been reported to exhibit more pronounced signs of right and left ventricular dysfunction including regional wall motion abnormalities.[82]

The proportion of individuals with increased troponin concentration has varied widely between studies. In a meta-analysis using a third-generation troponin assay, 47% of individuals had elevated troponin T after endurance exercise.[84] However, in a recent study using high-sensitivity troponin methods almost all (80–86%) marathon runners had increased levels after racing.[85] Data obtained using high-sensitivity troponin methods have shown that even a brief bout of exercise may lead to troponin elevation if the intensity is high. In a study by Shave *et al.*,[86] 30 min of high-intensity exercise resulted in small troponin I elevations in six out of eight participants.

Several authors have shown that the kinetics of exertional troponin release do not necessarily indicate true cardiac damage since the increase is typically transient and levels usually normalize within 24–48 h, at least when non-high sensitive troponin methods have been used.[79] Therefore, it has been hypothesized that troponin is released due to degradation of 'cytosolic' troponin or increased permeability of the cell membranes of myocytes under stress. Indeed, data from a murine model of forced physical stress support the notion that troponin is depleted from the cytosolic pool as serum levels rise.[87]

Exertional symptoms are relatively common in long-distance runners and troponin elevation in the setting of dizziness, chest pain or collapse may therefore constitute a considerable diagnostic challenge.[88] Currently, there is no data suggesting that endurance exercise should be discouraged in individuals with elevated post-exercise troponins.

Cardiac contusion

Troponins may be elevated after thoracic trauma. No significant complications occurred in patients in whom ECG findings were normal and serial measurements of cTn were within reference intervals.[89] Thus, a patient with chest trauma and an absence of other injuries or haemodynamic instability, with normal ECG and cTn can be discharged, whereas increased cTn may serve to identify patients at increased risk of mortality.[90]

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