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"Troponin Elevation in Coronary Ischemia and Necrosis"

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Abstract Detection of a rise and/or fall of cardiac troponin (cTn) is the cornerstone in the diagnosis of myocardial infarction (MI). For the acute risk, it is hypothesized that cTn mirrors activated coagulation and platelet reactivity and indicates the presence of a ruptured plaque, which may help to identify patients at high risk who benefit particularly from aggressive pharmacological treatment and early invasive strategy. High-sensitivity assays using the 99th percentile as the threshold for positivity can achieve sensitivity at presentation of 90 % or more, and performance further improves with subsequent measurements within 3 to 6 h. By 3 h, negative predictive values of almost 100 % have been reported. However, use of assays with higher sensitivity lead ultimately to a loss of clinical specificity. Thus, other conditions than MI, such as stroke, pulmonary embolism, sepsis, acute perimyocarditis, Takotsubo, acute heart failure and tachycardia also can go with elevated troponin levels. The detection of brief rise and subsequent fall of troponin concentration in marathon runners, and even in healthy subjects, after a standardized exercise test has cast doubts on the hypothesis that troponin is released only upon irreversible damage. This kind of troponin leakage may originate from a cytosolic compartment of the cells and not from the necrosis of thin filaments.

Keywords Myocardial infarction · Troponin · Cardiovascular risk marker

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Introduction

Acute myocardial infarction is a condition where there is evidence of myocardial necrosis. The condition is defined as detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischemia, new or presumed new significant ST-segment and T wave changes or new left bundle branch block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy [1•].

With the new high-sensitivity troponin methods, very minor damage on the heart muscle can be detected. Thus, also other conditions than acute myocardial infarction can go with elevated troponin levels. In the clinical work it may be difficult to interpret an elevated troponin in conditions such as stroke, pulmonary embolism, sepsis, acute perimyocarditis, Takotsubo, acute heart failure and tachycardia.

Cardiomyocyte necrosis is accompanied by biphasic troponin release, with a rapidly appearing first peak resulting from the loosely bound troponin pool with a second long-lasting elevation due to degradation of the contractile apparatus [2]. However, in participants of extreme sports, troponin leaks into the circulation at levels high above the accepted 99th-percentile limit have been reported [3, 4], and even a standardized exercise test may be associated with significant elevations of troponins in healthy subjects [5]. Therefore, it has been hypothesized that troponin under these conditions is released due to degradation of "cytosolic" troponin or increased permeability of the cell membranes of myocytes under stress rather than cardiomyocyte death.

In this review we will discuss troponin elevation in coronary ischemia and necrosis.

High-Sensitivity (hs) cTn Assays

Several years ago, manufacturers started to develop novel high-sensitivity generations of cTn assays in order to comply with the precision criteria of the ESC/ACC [6••]. To achieve a higher analytical sensitivity and precision, previous assay generations were refined or completely re-formatted. For example, the analytical performance of the former fourth generation cTnT assay was optimized for sensitivity and precision by increase of the sample volume, increasing the ruthenium concentration of the detection antibody, and by lowering the background signal by buffer optimization. Interferences with heterophilic antimouse antibodies (HAMA) or autoimmune-antibodies were minimized by replacement of the constant C1 region of the FAB by a human IgG-C1 region resulting in a mouse-human chimeric detection antibody [7]. Other manufacturers followed different strategies such as addition of a second detection or capture antibody to reach a higher analytical sensitivity [8]. As with previous, less sensitive, assay generations, cTnI assays lack standardisation and assays from various manufacturers differ substantially regarding configuration and epitope location of the detection antibodies. In addition, cTnI is present in several isoforms and is prone to conformational change due to degradation, oxidation and phosphorylation [8]. Accordingly, recovery of known cTn concentrations spiked into serum or plasma varies substantially and assays differ largely regarding the release kinetics following myocardial injury, or with respect to bio-variability [9]. Therefore, analytical characteristics including 99th percentile value, limit of detection (LoD), limit of blank (LoB), or limit of quantitation (LoQ) have to be assessed individually for each cTnI assay, and—given heterogeneity of assay characteristics—every assay should prove its clinical performance in controlled clinical trials. In direct comparison, 19 cTn assays were found to show very heterogenous analytical characteristics regarding the 99th percentile value and their analytical sensitivity as reflected by the proportion of detectable cTn concentrations in a healthy reference population [10]. Another issue addresses the definition of high sensitivity itself. A 'scorecard' concept has been introduced by Fred Apple to provide a systematic classification and objective platform for users [11]. An assay was proposed to be 'highly sensitive' if it met two basic criteria—first, total imprecision at the 99th percentile value should be ≤10 %; second, measurable concentrations below the 99th percentile should be attainable with an assay at a concentration value above the assay's limit of detection for at least 50 % (and ideally >95 %) of healthy individuals. Sensitive assays that lack features of 'high sensitivity' should be classified as 'contemporary' (level 1) assays, whereas older, less sensitive assays should be classified according to the total imprecision at the 99th percentile as guideline acceptable (≤10 %), clinically usable (>10 % to ≤20 %), or not acceptable (>20 %). It has been proposed that a cTn assay should be designated as a 'high-sensitivity' assay if cTn can be measured in at least 50 % of healthy individuals, in order to ensure a high clinical sensitivity [11]. These high-sensitivity assays are characterized by a substantially higher analytical sensitivity than conventional assays allowing measurement of cTn in nanograms per litre rather than micrograms per litre [12].

In an early study of the diagnostic performance of several cTn assays in unselected patients with ACS, hs-cTnT and several contemporary cTnI assays (including investigational products) outperformed the conventional fourth-generation cTnT assay [13]. However, in one study, a striking difference was found in the prediction of long-term outcomes favouring hs-cTnT over a contemporary hs-cTnI assay [14]. Whether the clinical performance of various hs-cTn assays is similar has not been determined, as few studies have involved head-to-head comparisons of hs-cTn assays for detection of reversible ischemia [15], diagnosis and prognosis [13, 14, 16, 17].

Timing and Measurement of hs-cTn in ACS

At least two measurements of hs-cTn are required in order to comply with the recommendations of European Guidelines [6••], and the most recent third version of the 'universal definition of myocardial infarction' [1•]. Serial measurements are required in order to discriminate a stable from an acute cTn rise. Before the implementation of hs assays, protocols recommended an initial measurement at the time of presentation and a second measurement after 6 to 9 h. The use of hs-Tn assays were found to detect the majority of patients with an evolving NSTEMI at presentation and almost all patients with an evolving NSTEMI within 3 h [16, 18–20]. Accordingly, recent ESC guidelines [6••] recommend the implementation of hs-Tn assays with a second sample after 3 h or, optionally, after 6 h in order to diagnose NSTEMI earlier than with standard cTn assays. The workflow distinguishes two scenarios (Fig. 1). First, in patients presenting within 6 h after the last episode of symptoms suggestive of ACS with a hs-Tn value below the 99th percentile, a second measurement has been advocated after 3 h or, optionally, after 6 h. A rise of hs-Tn above the 99th percentile with a concentration change of 50 % of the 99th-percentile value is considered relevant indicating a diagnosis of NSTEMI and favouring an invasive strategy. In patients with persistently negative hs-Tn results, or in the absence of a relevant change, a diagnosis of unstable angina may be made. Further management requires a risk stratification that includes assessment of a clinical multivariable score, ECG and evolution of symptoms. Accordingly, an asymptomatic low-risk patient may be sent home after a pre-discharge or early post-discharge stress test. In patients presenting more

Fig. 1 Flow-chart in suspected ACS

Accelerated diagnostic protocols: rule-in of MI is the issue !

First Author	Trial	Assay	N=	ADP	NPV (%)	PPV (%)	Ref
Keller T	German multicenter	hsTnI (Architect Abbott)	1818	3 hour	83.7* (δ250%)	95.8	JAMA 2012
Reichlin T	APACE	hsTnT	718	3 hour	98	42	NEJM 2009
Aldous SJ	ASPECT	hsTnT	939	2 hour	98.2	55.9	Clin Chem 2011
Biener M	Single center	hsTnT	459	3 hour	92	52.1	Int J Cardiol 2013
Reichlin T	APACE	hsTnT	872	1 hour	100	76	Arch Int Med 2012
Than M	ASPECT	POCT cTnI (TRIAGE, Alere)	3582	2 hour	99.1	12.9	Lancet 2011
Cullen L	ADAPT	hsTnI (Architect Abbott)	1635	2 hour	99.7	25.6	JACC 2013
Cullen L	APACE	hsTnI (Architect Abbott)	909	2 hour	99.7	27.8	JACC 2013

than 6 h after the last episode of symptoms, it appears unlikely that a negative initial hs-Tn result will eventually become positive. Therefore, a second blood draw may eventually be omitted. Nevertheless, patients should only be discharged after a pre-discharge or an early post-discharge stress test, if estimated risk is low and in the absence of recurrent symptoms.

When the hs-Tn result is above the 99th percentile at admission, a second blood draw is recommended after 3 h or, optionally, after 6 h, in order to discriminate an acute from a chronic cTn elevation. A concentration change of 20 % or more is regarded as relevant. This change represents a significant change, i.e. >3 standard deviations of the variation associated with an elevated baseline concentration, in cTn on the basis of a 5–7 % analytical total CV [21]

Patients with very high hs-Tn concentrations are candidates for a timely invasive strategy as very high cTn concentrations render differential diagnoses other than NSTEMI unlikely [22, 23]. In order to accelerate coronary angiography, a second measurement of cTn may eventually be obviated. Patients with chronic stable cTn elevations should receive a diagnostic work-up to identify the underlying reason as an elevated troponin is prognostically relevant, regardless of whether the reason is ACS or unrelated to myocardial ischemia [24]. Use of more sensitive cTn assays offers the potential to detect lower cTn concentrations at earlier time points. This has propelled accelerated diagnostic protocols to rule-out MI earlier which is particularly helpful to reduce observation times in overcrowded and busy chest pain units or emergency departments. Now, several investigators propose diagnostic protocols with repeat blood sampling after only 1 h [25•] or 2 h [26, 27] for diagnosis of MI, at least for patients at low or very low risk [26, 27]. Recently, the usefulness of an accelerated protocol within 2 h using hs-TnT was tested in two independent study populations [28]. In consistency with previous reports the accelerated protocols allowed to rule out MI with a very high NPV. On the other hand, specificities and positive predictive values (PPVs) were very low, limiting the value of early serial sampling for rule-in of MI in patents presenting with an elevated cTn (Fig. 2).

Pathophysiology of Myocardial Ischemia

The etiology of acute coronary syndromes (ACS) is complex and involves multiple interrelated mechanisms of which many have not yet been fully understood. Our current understanding is that a plaque may rupture or erode in response to inflammation leading to local occlusive or non-occlusive thrombosis [29]. Depending on the degree and reversibility of this dynamic obstruction, the clinical manifestations of ACS comprise a continuous spectrum of risk that progresses from unstable angina (UA) to non-ST elevation myocardial infarction (NSTEMI) to ST-segment elevation myocardial infarction (STEMI). NSTEMI is distinguished from unstable angina by ischemia sufficiently severe in intensity and duration to cause myocyte necrosis, which is recognized by the detection of cardiac troponin, the most sensitive and specific biomarker 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 as compared to the protein mass of other myofibrillar proteins like actin and myosin. However, both troponin T and I are ideally suited for the detection of myocardial damage as they are expressed as cardio-specific isoforms, which are encoded by separate cardiac troponin T and I genes [30]. The vast

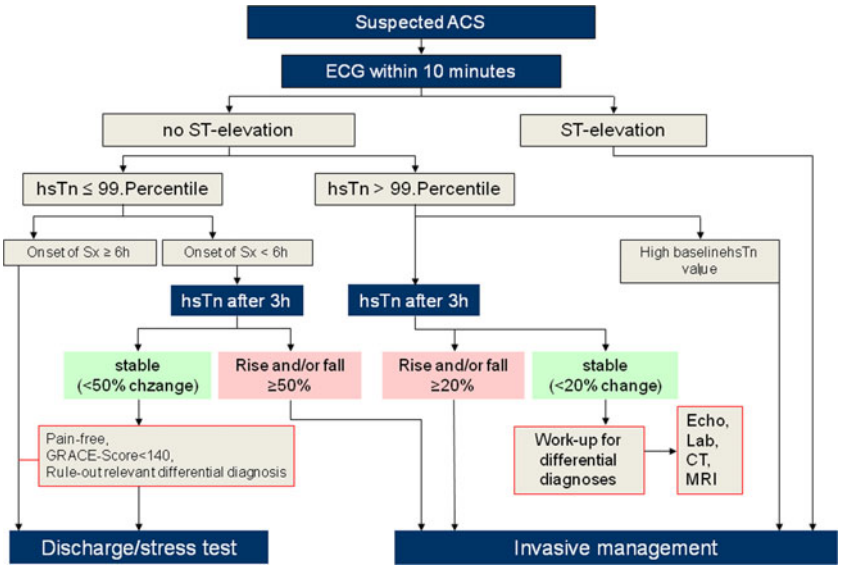

Fig. 2 Summary of studies evaluating the performance of an accelerated diagnostic protocol for rule-out and rule-in of MI

majority of the troponin complex is immobilized in the sarcomere of striated muscle and only a minor fraction exists as a soluble pool, which eventually represents a precursor pool of sarcomere assembly.

In patients with myocardial infarction, distinct release kinetics have been described, with a rapidly appearing first peak resulting from the loosely bound troponin pool and a second long lasting elevation due to degradation of the contractile apparatus [31]. A biphasic pattern has been observed for cTnT whereas a monophasic release has been demonstrated for cTnI [31]. Although the exact reason for the different release kinetics is still illusive, cTnT differs from cTnI with respect to higher molecular weight, higher fraction of unbound cTnT, and less degradation, whereas cTnI is more frequently found as binary or tertiary complex in blood. There is evidence that the early appearing pool may give information on the quality of micro-vascular reperfusion [32], while the concentration of cTn on day 3 or 4 reflects myocardial infarct size [33]. Experimental data strongly suggest that troponin leaks out of the cell only after membrane disruption following myocardial cell death [34].

Definition of Myocardial Infarction

Acute myocardial infarction is a condition where there is evidence of myocardial necrosis. The condition is defined as detection of a rise and/or fall of cardiac biomarker values (namely cardiac troponin) with at least one value above the 99th percentile upper reference limit and with at least one of the following: symptoms of ischemia, new or presumed new significant ST-segment–T wave changes or new left bundle branch block, development of pathological Q waves in the ECG, imaging evidence of new loss of viable myocardium or new regional wall motion abnormality or identification of an intracoronary thrombus by angiography or autopsy [1•].

In addition there is a clinical classification with five types of myocardial infarction. Type 1 is a spontaneous myocardial infarction related to atherosclerotic plaque rupture, ulceration, fissuring, erosion, or dissection with resulting intraluminal thrombus in one or more of the coronary arteries leading to decreased myocardial blood flow or distal platelet emboli with ensuing myocyte necrosis. The patient may have underlying severe CAD but, on occasion, non-obstructive or no CAD. Type 2 is myocardial infarction secondary to an ischemic imbalance. Type 3 is myocardial infarction resulting in death when biomarker values are unavailable. Type 4a is myocardial infarction related to percutaneous coronary intervention (PCI). Myocardial infarction associated with PCI is arbitrarily defined by elevation of cTn values >5×99th percentile URL in patients with normal baseline values. In addition, either (i) symptoms suggestive of myocardial or (ii) new ischemic ECG changes or new LBBB; (iii) angiographic loss of patency of a major coronary artery, a side branch, persistent slow, no-flow or embolization; or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required. Myocardial infarction associated with stent thrombosis is detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL. The latter type is type 4b. Type 5 is myocardial infarction related to coronary artery bypass grafting (CABG) in which myocardial infarction is arbitrarily defined by elevation of cardiac biomarker values >10×99th percentile URL in patients with normal baseline cTn values. In addition, either (i) new pathological Q waves or new LBBB, (ii) angiographic documented new graft or new native coronary artery occlusion, (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is present [1•].

cTns in Acute Coronary Syndrome (ACS)

As described above, the acute myocardial infarction diagnosis is based on detection of a rise and/or fall of cardiac biomarker values (namely cardiac troponin) with at least one value above the 99th percentile upper reference limit. Accordingly, unstable angina is defined by the clinical context of acute myocardial ischemia among patients with cTn values persistently below the 99th percentile, or among patients with baseline elevations of cTn but without relevant concentration changes. Numerous trials [7, 13, 18, 35–37] and a recent meta-analysis [38] now provide substantial evidence that high-sensitivity assays using the 99th percentile as the threshold for positivity can achieve sensitivity at presentation of 90 % or more, and performance further improves with subsequent measurements within 3 to 6 h. By 3 h, negative predictive values (NPVs) of almost 100 % have been reported, supporting the usefulness of earlier rule-out protocols [13, 18–20]. In a study comparing four cTn assays head-to-head with any of the more sensitive prototype assays, contemporary assays and hs-TnT performed significantly better than the conventional fourth generation cTnT assay that served as a reference [13]. However, use of assays with higher sensitivity lead ultimately to a loss of clinical specificity [39]. Serial measurements were found to compensate for this loss of clinical specificity [19, 40]. Still, PPVs to discriminate MI from non-ACS related causes of troponin elevation are disappointingly low, unless very high delta change values between 100 % [40] and 250 % [19, 40] are used. In that case, specificity and PPV can exceed 90 % [19].

Regarding risk stratification, there is established evidence beyond any doubt from earlier conventional assay generations that cTn provides excellent information for short-term and long-term risk of death or MI [41]. For the acute risk, it is hypothesized that cTn mirrors activated coagulation and platelet reactivity and indicates the presence of a ruptured plaque. For long-term risk, cTn is linked to more complex plaque composition, presence of multi-vessel coronary artery disease or left main disease [42]. Intracoronary angioscopy consistently confirmed a relationship between presence and magnitude of cTn with presence and extent of intracoronary thrombus [43]. New hs assays used at the 99th percentile have now been found to improve risk stratification further. They allow an excellent prediction of the risk for death or MI [24, 35–37], even in patients with cTn levels below the lower limit of detection of conventional assays [24, 35].

Regarding guidance of therapy using cardiac troponin, there is a huge amount of evidence coming from trials using standard assays that cTn can help to identify patients at thrombotic risk who benefit particularly from anticoagulation with low molecular weight heparins [44], GP IIb/IIIa inhibitors [45, 46], early invasive strategy and early reperfusion [46, 47].

However, the question of whether very low decision cut-offs using hs assays warrant a change of management or selection of an invasive strategy versus medical treatment is still unresolved. The GUSTO IV trial [48] reported an excess of death/MI among patients who underwent an early invasive treatment as compared to a conservative approach if patients were stratified as low-risk patients as suggested by undetectable cTnT levels and low NT-proBNP values. On the other hand, the TACTICS-TIMI 18 trial [46] found that rates of death and MI were significantly reduced in patients who received tirofiban and underwent an early invasive treatment within 48 h if cTnT values were above the lower detection limit. As a limitation, total imprecision at the lower detection limit was unacceptably high with the cTnT assay used at that time. At present, there is some evidence that hs assays may be useful to improve in-hospital management and outcomes, particularly in the intermediate range of cTn elevation [49]. In addition, a biomarker sub-study from the Platelet Inhibition and Patient Outcomes (PLATO) trial [50] investigated the relationship between hs-TnT status and benefits of ticagrelor, a more potent P2Y12 inhibitor, as compared to clopidogrel across the entire spectrum of ACS. Patients with hs-cTnT values above the 99th percentile and a diagnosis of NSTEMI derived benefits from ticagrelor by reducing cardiac endpoints, regardless of whether they underwent an invasive or a conservative treatment [50]. Conversely, patients testing negative for hs-cTnT (unstable angina) derived the same amount of benefit from ticagrelor as compared to clopidogrel [50]. If treated invasively during index hospitalization, there was an increase of the primary endpoint driven by higher rates

Table 1 Reasons for acutely elevated troponins

Acute myocardial infarction
Acute heart failure
Pulmonary embolism
Stroke
Acute aortic dissection
Tachyarrhythmias
Hypotension/Shock
Sepsis
ARDS
Perimyocarditis
Endocarditis
Takotsubo cardiomyopathy
Radiofrequency catheter ablation
Cardiac contusion
Strenuous exercise
Recent exercise test
Sympathomimetic drugs
Chemotherapy

of procedure-related MIs and significant excess of major bleeds, particularly procedural non-CABG related major bleeding [51]. Thus, it appears that patients with unstable angina represent a low-risk cohort that may not benefit from treatment strategies outlined for the NSTEMI cohorts. In agreement, the current ESC guidelines [6••] recommend not to perform an early routine coronary angiography in cTn-negative patients, but to base the decision on the recurrence of chest pain or on a positive stress test.

cTns in Non-Ischemic Clinical Conditions

Several other conditions than acute myocardial infarctions are associated with acute elevation of troponin levels (Table 1) [52•]. Thus, it is very important to keep in mind that elevated troponin for certain is not equivalent with a coronary plaque rupture. The troponin release in non-ischemic conditions has been reviewed previously.

The detection of brief rise and subsequent fall of troponin concentration in marathon runners [3, 4], and even in well-trained and young healthy subjects [53] and healthy middle-aged subjects [5], after a standardized exercise test has cast doubts on the hypothesis that troponin is released only upon irreversible damage. This kind of troponin leakage may originate from a cytosolic compartment of the cells and not from the necrosis of thin filaments.. However, there are neither consistent experimental nor clinical data providing proof of this concept so far.

Conclusions

A detection of a rise and/or fall of cardiac troponin (cTn) is the cornerstone in the diagnosis of myocardial infarction (MI). For the acute risk, it is hypothesized that cTn mirrors activated coagulation and platelet reactivity and indicates the presence of a ruptured plaque, which may help to identify patients at high risk who benefit particularly from aggressive pharmacological treatment and early invasive strategy.

High-sensitivity assays using the 99th percentile as the threshold for positivity can achieve sensitivity at presentation of 90 % or more, and performance further improves with subsequent measurements within 3 to 6 h. By 3 h, negative predictive values of almost 100 % have been reported. However, use of assays with higher sensitivity lead ultimately to a loss of clinical specificity. Thus, other conditions than MI, such as stroke, pulmonary embolism, sepsis, acute perimyocarditis, Takotsubo, acute heart failure and tachycardia can also go with elevated troponin levels.

The detection of brief rise and subsequent fall of troponin concentration in marathon runners and even in healthy subjects after a standardized exercise test has cast doubts on the hypothesis that troponin is released only upon irreversible damage.

Compliance with Ethics Guidelines

Conflict of Interest Stefan Agewall has received honorarium from: Astra-Zeneca, Sanofi, Siemens, Pfizer, Boehringer-Ingelheim, Orion Pharma

Evangelos Giannitsis has received honorarium from Roche Diagnostics

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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