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Interpretation of cardiac troponin levels regarding the fourth universal definition of myocardial infarction published in 2018

Interpretacja stężeń troponin sercowych w świetle czwartej uniwersalnej definicji zawału serca z 2018 roku

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Abstract

Cardiac troponin (cTn) is a laboratory test routinely used in patients with suspected acute coronary syndrome (ACS). Unfortunately, wide variety of laboratory assays and different cut-off values regarding gender may result in difficulties with diagnosis and delay the treatment. Troponin I and less specific troponin T are used to diagnose ACS. Dynamic changes in cTn concentration are required to confirm the diagnosis of myocardial infarction (MI). The fourth universal definition of myocardial infarction defines five major types of MI — atherosclerotic plaque disruption, imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis, cardiac death with symptoms suggestive of myocardial ischaemia and new ischaemic electrocardiographic changes, MI connected with percutaneous coronary intervention or coronary bypass grafting. Considering this definition, increased cTn concentrations are not always related to abnormal findings in coronary angiography and can be associated with many conditions. Increased high sensitivity cTn values in healthy individuals can be induced by intense physical activity, which is confirmed by studies performed in marathoners. While elevated cTn levels are observed in 20–60% of patients with acute ischemic stroke and are associated with an increased long-term mortality, acute MI is diagnosed only in 3,5% of patients. Elevated cTn levels often accompany chronic kidney disease, however changes in serial testing are obligatory for acute MI diagnosis. Deterioration of kidney function is more connected with elevated TnT rather than TnI levels. Regardless of the reason, increased cTn concentration is a negative predictive factor. Patients with elevated cTn levels need further diagnosis, risk stratification and a long-term follow-up.

Key words: troponin, myocardial infarction, acute coronary syndrome

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Introduction

Cardiac troponins (cTn) were first described in 1963 [1], and at the end of the 1970s and 1980s they were considered to be indicators of myocardial injury. In 1999, it was suggested that the cTn level should be determined and used to diagnose ACS; one year later, they were recognised as the biomarkers of choice in the diagnosis of myocardial infarction [2, 3]. Due to the difficulties in the interpretation of troponin concentration for the purposes of diagnosing

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ACS, the European Society of Cardiology proposed to differentiate myocardial injury from myocardial infarction (MI) in the document on the fourth universal definition of myocardial infarction, published in 2018.

Myocardial injury is defined as the state in which cTn concentration in the blood is above the 99th percentile upper reference limit (URL). It is considered acute if there is an increase and/or decrease in cTn values.

Myocardial infarction is myocardial injury diagnosed based on the abnormal cTn values in a clinical situation in which the symptoms of acute myocardial ischaemia are observed [4] (Table 1). It is therefore necessary to relate cTn results to the clinical picture and to be aware of the difficulties in the interpretation of the elevated cTn level. The article presents available data on the interpretation and significance of cardiac troponin results.

Biochemical characteristics

The sarcomere is the basic contractile unit of the heart that is composed of thick filaments (myosins) and thin filaments (actins). The thin filament is a helix composed of two filamentous actins (F-actins), which are polymers of globular actin subunits (G-actin). The F-actin helix groove contains tropomyosin to which troponin is attached. Myofibrillar contraction is activated by the depolarisation and then modulated by the interaction of calcium ions (Ca^{2+}) with specific regulatory sites on the contractile apparatus of striated muscles of the heart [5]. These sites are troponin complexes immobilised on the thin filament, which acts in an allosteric manner to regulate the Ca2+-dependent interaction between filaments of actin and myosin [6]. Cardiac troponin I (cTnI) and troponin T (cTnT) are part of the contractile apparatus of myocardial cells and they are expressed almost exclusively in the heart [7, 8]. No increases in the cTnI level were observed after an injury to tissues other than the striated muscle of the heart.

In case of cTnT, the situation is more complex. Skeletal muscles express proteins which are detected by the assay used to determine the cTnT level. For this reason, skeletal muscles may be the source of increased cTnT values [9]. New data indicate that the frequency of elevated cTn values without ischaemic heart disease may be higher than initially thought [10, 11]. The preferred biomarkers used to evaluate myocardial injury are cTnI and cTnT, high-sensitive cardiac troponins (hs-cTn) are recommended to be used in [12] clinical practice [7].

Positive values

The 99th percentile URL was adopted as the cut-off point for myocardial injury. This point must be specified precisely

Table 1. Types of myocardial infarction (MI) (source [4])

Myocardial infarction	Definition	Comments
Type 1	The term "acute myocardial infarction" should be used in the case of acute myocardial injury with clinical symptoms of acute myocardial ischaemia if there is an increase and/or decrease in the cTn level in the blood with at least one value above the 99th percentile URL and at least one of the following criteria is met: • development of symptoms of myocardial ischaemia • presence of new ischaemic changes in ECG • development of pathological Q waves in ECG • imaging of a new loss of viable myocardium or new regional systolic dysfunction the location of which corresponds to the ischaemic aetiology • detection of a thrombus in the coronary artery during coronary angiography or autopsy (not applicable to type 2 and 3 MI)	Post-mortem identification of acute coronary atherothrombosis in the artery supplying the infarcted area of the myocardium meets the criteria for type 1 MI
Type 2	Identification of an imbalance between myocardial oxygen supply and demand that is not related to the acute coronary atherothrombosis	
Type 3	Cardiac death in patients with symptoms suggestive of myocardial ischaemia and presumably new ischaemic changes in ECG before the cTn level is determined or before it becomes abnormal	
Type 4a	Myocardial infarction related to percutaneous coronary intervention (PCI)	
Type 4b	Myocardial infarction caused by stent thrombosis	
Type 4c	Myocardial infarction caused by in-stent restenosis	
Type 5	Myocardial infarction related to coronary artery bypass grafting (CABG)	

cTn — cardiac troponin; URL — upper reference limit; ECG — electrocardiography

for each assay [13]. However, for all cTn assays, including high-sensitivity cTn assays, there is still no expert opinion on the criteria for how to define the 99th percentile URL [14]. It is therefore necessary to rely on changes in the values obtained during serial cTn testing. Significantly lower cTn values are observed in women than in men, which is why sex-specific 99th percentile URL values are recommended for high-sensitivity cTn assays [13, 14].

cTn evaluation time

The cardiac troponin level should be determined during the first assessment of the patient's condition and repeated during evaluation. According to the recent NSTE-ACS guidelines using 0 h/1 h algorithm (best option) is recommended to rule in/out MI. 0 h/2 h algorithm (second best option) is recommended alternatively, if an hs-cTn test with a validated 0 h/2 h algorithm is available. Time — 0 h, 1 h or 2 h — refers to blood sampling [15]. To diagnose acute MI, an increase and/or decrease with at least one value above the 99th percentile URL in the cTn level has to be observed, combined with a high likelihood of myocardial ischaemia based on the clinical assessment and/or ECG test. High-sensitivity cTn methods shorten the time to diagnose myocardial infarction in many patients to less than 3 hours from the onset of symptoms. However, there are still patients in whom MI is diagnosed late, after 6 hours. In patients with suspected acute MI who are assessed more than 12–18 hours after the onset of symptoms, it may take longer to detect the changing cTn level due to the downward phase of the cTn-concentration curve [16]. As a result of the implementation of hs-cTn assays, there is an increase in the frequency of diagnosing NSTEMI and a decrease in the frequency of diagnosing unstable angina [17].

Types of myocardial infarction

Table 1 shows the types of myocardial infarction and their definitions according to the current fourth universal definition of myocardial infarction.

Table 2. Clinical conditions increasing the cardiac troponin level other than MI (source [5])

Direct myocardial cell injury	**Infiltrative cardiac diseases** — direct compression of cardiomyocytes, regional loss of myocardium
	Chemotherapy — cardiotoxicity
Excessive myocardial strain	**Chronic heart failure** — myocardial wall stress
	Systemic hypertension — increased LV afterload (pressure overload)
	Aortic stenosis — increased LV afterload (pressure overload)
	Pulmonary hypertension — increased RV afterload (pressure overload)
	Valvular regurgitation — increased preload (volume overload)
	Chronic kidney disease and end-stage renal failure — chronic activation of the RAA system, excessive activation of the sympathetic nervous system (volume and pressure overload)
Myocardial ischaemia (reduced oxygen supply)	**Chronic heart failure and adverse cardiac remodelling:** • impaired coronary reserve • subendocardial ischaemia
	Coronary artery disease: • endothelial dysfunction and atherosclerosis • clinically silent microinfarctions
	Hypotension — reduced perfusion pressure
	Hypovolaemia — reduced filling pressure, output
	Anaemia — reduced oxygen supply
	Diabetes mellitus — vascular complications (endothelial dysfunction and coronary artery disease)
Increased oxygen demand	**Chronic heart failure and cardiac remodelling:** • reduced myocardial compliance during diastole and contractile dysfunction (collagen deposition, focal fibrosis) • subendocardial ischaemia
	Atrial fibrillation — increased myocardial oxygen consumption
	Chronic kidney disease — excessive sympathetic activity and release of catecholamines
	Stroke — excessive sympathetic activity and release of catecholamines

Positive cTn values — a variety of causes

Cardiac troponin is a biomarker that is "organ-specific", not "disease-specific" [5]. Therefore, an elevated cTn level indicates myocardial cell injury, but it does not determine its mechanism. The term "myocardial injury" better describes elevated cTn levels in patients without ACS and those with no imbalance between myocardial oxygen supply and demand. The cTn level may increase as a result of mechanical stretch caused by a preload or physiological stresses on a healthy heart [4]. The effect of repeated periods of increased preload on myocyte loss may be significant, and it may lead to cell hypertrophy and myocardial dysfunction in the absence of ischaemia. Histological symptoms of myocardial injury can be detected in clinical conditions with a non-ischaemic aetiology [2, 18].

The coexistence of various causes of elevated cardiac troponin values is often observed in everyday clinical practice (Table 2). Particular attention should be paid to the interpretation of elevated cTn values in athletes, ischaemic stroke (IS) and chronic kidney disease (CKD).

Elevated cardiac troponin values in athletes

According to the analysis of the results of the studies conducted from 2008 to 2013 (as many as 10 studies were analysed, the total number of subjects was 392), hs-cTn values above the 99th percentile were observed in about 70% of marathon runners after the end of the run (the values were determined within 0–6 hours after the end of the run). The hs-cTnT level was assessed in the majority of runners, and the hs-cTnI level in a much smaller group [19]. In the study involving the Brighton marathon participants, higher hs-cTnT values were observed in relation to greater exercise intensity [20]. In another study on the participants of this marathon, there were no differences in the hs-cTnT level between the control group, the group with diagnosed heart diseases, and runners who collapsed after the run [21].

An elevated exercise-induced hs-cTn level results from the prolonged stress on the cell membrane of cardiomyocytes, the release of reactive oxygen species and decreased pH [22]. Initially, it was believed that small-degree necrosis occurred, but there is no evidence to confirm this theory — no late gadolinium enhancement (LGE) areas were found in cardiac magnetic resonance and there is still a lack of histopathological examinations.

The clinical significance of positive exercise-induced hs-cTn values remains unclear. Most data indicate that an increase in the hs-cTn level after intensive exercise is physiological and does not affect the short-term prognosis. However, there is still no evidence of the effect of increased exercise-induced hs-cTn values on long-term prognosis [19, 21].

Significance and interpretation of positive cardiac troponin values in acute ischaemic stroke

Elevated cTn values in patients with acute ischaemic stroke (AIS) are usually of little clinical significance even

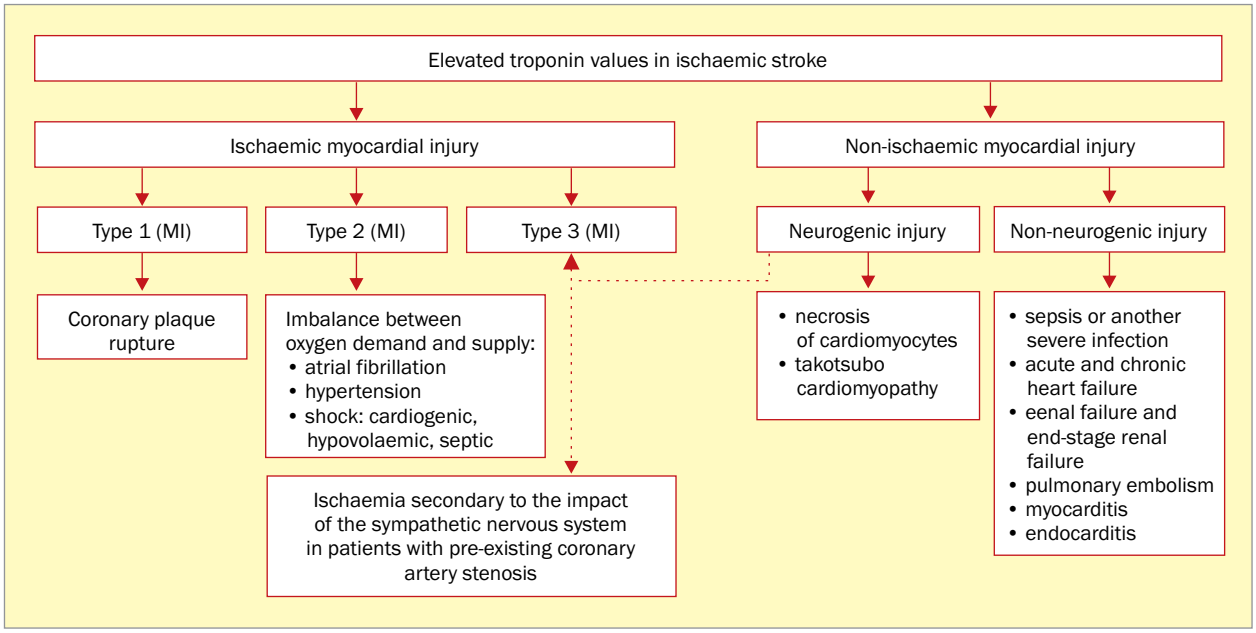

Figure 1. Possible mechanisms leading to an increase in the cTn level in ischaemic stroke; MI — myocardial infarction (source [26])

though they are observed in 20–60% of these patients [23–25].

An increase in the cTn level during a stroke may be associated with ischaemic or non-ischaemic myocardial injury (Figure 1) [26]. These processes are not mutually exclusive. Neurocardiogenic mechanisms may contribute to myocardial ischaemia or sudden cardiac death.

In a clinical trial involving almost 2,000 patients with ischaemic stroke, elevated cTn values were observed in as many as 353 individuals. Acute myocardial infarction was diagnosed in 16% of patients with ischaemic stroke and elevated cTn values, who represented 3.5% of all patients with AIS. However, it was shown that elevated cTn levels are associated with long-term mortality rates that are twice as high as those in patients with ischaemic stroke and normal cTn values. Acute ischaemic stroke may act as a kind of indirect stress test for underlying coronary artery disease. This type of stress test is closely associated with the 30-day mortality rate. Despite the clinically mild nature of stroke in the analysed population, as many as 60% of patients with ischaemic stroke and positive cTn values died within 3 years [27]. Importantly, the TRELAS (Troponin Elevation in Acute Ischaemic Stroke) study showed that only 24% of 29 patients with AIS and positive cTn values had significant changes in coronary angiography [28].

Recent reports also indicate that positive troponin results are primarily associated with cardioembolic ischaemic stroke. In other types of strokes, positive cTn values are observed much less frequently [29]. Therefore, patients with AIS require special attention, risk stratification and detailed cardiological evaluation.

Significance and interpretation of positive cardiac troponin values in chronic kidney disease (CKD)

Persistently elevated cardiac troponin levels are often observed in patients with CKD. This can be caused by the myocardium through increased release, as well as by the kidneys through reduced clearance of cTn [30]. This especially applies to hs-cTnT, the level of which is elevated more often than that of hs-cTnI [31, 32].

It was found that hs-cTnT demonstrates a 24-hour variation — its level decreases during the day, and then increases at night until it reaches the highest value again in the morning. The deterioration of renal function is more strongly associated with elevated cTnT levels than cTnI levels, which may suggest that renal function plays a role in the 24-hour clearance of cTn [33].

In recent studies it was shown that impaired renal clearance may be important in case of a significantly elevated cTn level in response to acute episodes of myocardial injury [34]. The injury mechanisms include increased ventricular pressure, impaired patency of small coronary vessels, anaemia, hypotension and possibly direct toxic effects on the myocardium associated with the uraemic state [35]. An elevated cTn level is therefore frequent; it has a high prognostic value in long-term observation due to the fact that it reflects myocardial injury [31]. Diagnosing MI in patients with CKD and elevated cTn values may be difficult if there are no clinical symptoms or changes in ECG indicating myocardial ischaemia. However, the study results suggest that changes in the cTn level based on serial measurements make it possible to diagnose MI in patients with CKD as effectively as in individuals with normal renal function [36, 37].

Impaired renal clearance is therefore not the main cause of persistently elevated TnT values and it is important to have comprehensive tests carried out in all patients with elevated cTn levels, regardless of their eGFR [30].

Prognostic significance of elevated cTn values

In the recent study conducted by Chapman et al. [38] on more than 2,000 patients with an elevated TnI level, it was shown that approximately two thirds of patients with type 2 MI or myocardial injury died within 5 years. However, most of the deaths were from non-cardiovascular causes. The prevalence of nonfatal myocardial infarction or cardiovascular death in patients with type 2 MI and myocardial injury was similar to that in patients with type 1 myocardial infarction. Major adverse cardiac events (MACE) occurred in one third of patients with elevated cardiac troponin levels, regardless of whether myocardial cell necrosis was spontaneous or secondary to another acute disease. The risk of MACE in patients with type 1 myocardial infarction was highest, but there was no difference in its level between patients with type 2 MI and patients with myocardial injury. Patients with type 2 MI or myocardial injury with diagnosed coronary artery disease were at the highest risk of cardiovascular events [38].

In another study conducted by the same author, the TnI value of 5 ng/L (Abbott Architect STAT assay) was considered as a cut-off point for risk stratification in patients admitted with suspected acute coronary syndrome. The hs-cTnI value below 5 ng/L on admission identified patients with low risk of myocardial infarction or cardiac death within 30 days [38].

Furthermore, the HiSTORIC study carried out on a group of more than 30,000 patients showed that it is possible to exclude myocardial infarction on the basis of only one hs-cTnI result below 5 ng/L (Abbot Architect STAT assay), measured on admission to the emergency department. Such a strategy showed 99.5% accuracy in excluding MI during the 30-day observation. In patients with hs-cTn levels from 5 ng/L to the 99th percentile, hs-cTnI was measured again

after 6 hours, whereas those with values above the 99th percentile in the first hs-cTnI measurement were admitted to the hospital. While applying this diagnostic scheme a low risk of cardiovascular events was observed during the 12-month period. Additionally, the number of patients discharged from the emergency department increased by 57% (from 53% to 74%) [40].

Conclusion

To sum up, elevated cardiac troponin values may result not only from coronary artery disease, but also from many different conditions that are often comorbid conditions. The prognostic significance of elevated hs-cTn values induced by intensive exercise remains unclear. However, it should be kept in mind that poor long-term prognosis and high mortality rates are common in the majority of patients with elevated cTn values, even without clinical or ECG markers of myocardial infarction. It is necessary perform detailed diagnostics of these patients for coronary artery disease and comorbidities, and to take preventive and therapeutic measures to improve their prognoses.

Conflict of interest

Authors do not declare the conflict of interest.

Streszczenie

Stężenia troponin sercowych (cTn) oznacza się rutynowo w diagnostyce ostrego zespołu wieńcowego (ACS). Rozpoznanie ACS mogą jednak utrudniać różne rodzaje testów laboratoryjnych oraz inne punkty odcięcia wartości patologicznych u kobiet i mężczyzn. W diagnostyce ACS znajdują zastosowanie troponina I (TnI) oraz mniej specyficzna troponina T (TnT). Do potwierdzenia zawału serca (MI) konieczne jest stwierdzenie dynamicznych zmian stężenia cTn. W czwartej uniwersalnej definicji zawału serca wyróżnia się pięć głównych typów MI w zależności od patomechanizmu: związany z pęknięciem blaszki miażdżycowej, związany z dysproporcją między podażą a zapotrzebowaniem mięśnia sercowego na tlen, zgon sercowy u pacjentów z objawami sugerującymi niedokrwienie mięśnia sercowego i nowymi zmianami niedokrwiennymi w elektrokardiografii oraz MI towarzyszący angioplastyce wieńcowej i pomostowaniu aortalno-wieńcowemu. Zgodnie z tą definicją podwyższone stężenie cTn nie zawsze wynika z obecności istotnych zwężeń w tętnicach wieńcowych i może towarzyszyć wielu stanom. Wzrost wartości cTn oznaczanej metodą wysokoczułą u zdrowych osób może być indukowany intensywnym wysiłkiem fizycznym, co potwierdzają badania maratończyków. Podwyższone stężenie cTn występuje u 20–60% pacjentów z udarem niedokrwiennym mózgu i wiąże się z wyższą śmiertelnością odległą, jednak ostry MI w tej grupie chorych diagnozuje się jedynie u 3,5% osób. Podwyższone stężenie troponin sercowych często towarzyszy przewlekłej chorobie nerek, jednak w przypadku podejrzenia ACS znaczenie ma dynamika seryjnych pomiarów. Pogorszenie funkcji nerek ma większy wpływ na wzrost stężenia cTnT niż cTnI. Niezależnie od przyczyny podwyższone wartości cTn stanowią niekorzystny czynnik rokowniczy. Pacjenci, u których stwierdzono wzrost wartości cTn, wymagają rozszerzenia diagnostyki, stratyfikacji ryzyka i długoterminowej obserwacji.

Słowa kluczowe: troponiny, zawał serca, ostry zespół wieńcowy

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