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NON-CORONAROGENIC CAUSES OF INCREASED CARDIAC TROPONINS IN CLINICAL PRACTICE

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Cardiospecific isoforms of troponins are the most sensitive and specific biomarkers for the diagnosis of myocardial infarction. However, though elevated troponin levels indicate myocardial damage, they do not determine the cause and mechanism of the damage. With the new highly sensitive methods, very minor damages of the heart muscle can be detected. Myocardial damage can occur in many non-coronarogenic diseases. In this review, we discuss the mechanisms of elevation, the diagnostic value of cardiac troponins in the renal failure, tachyarrhythmias, endocarditis, myocarditis, pericarditis, sepsis, neurogenic pathologies (stroke), pulmonary embolism. In addition, we pay attention to the main reasons for a false-positive increase of the concentration of cardiac troponins: heterophilic antibodies, rheumatoid factor, alkaline phosphatase, cross-reactions with skeletal muscle troponins.

Keywords: *troponins, renal failure, endocarditis, myocarditis, sepsis, stroke, subarachnoid hemorrhage, pulmonary embolism, false-positive results.*

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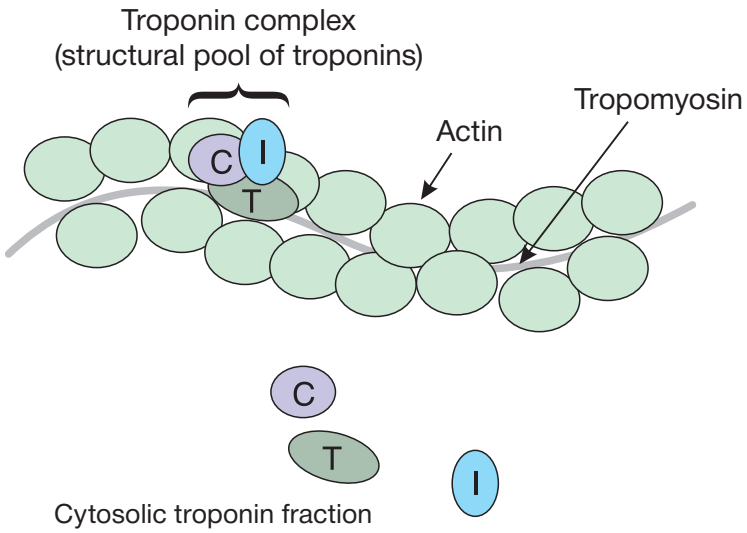
INTRODUCTION

The troponin complex comprises three subunits (T, I, C) that regulate the contractile activity of the myocardium (Fig. 1). Cardiac troponin T, a tropomyosin-binding subunit, fixes the troponin complex to produce thin actin filaments. Troponin C, a calcium-binding subunit, binds calcium ions entering the cytoplasm from the sarcoplasmic reticulum upon the stimulation of contraction. Troponin I, an inhibitory subunit, blocks the hydrolysis of adenosine triphosphate, which is necessary for the interaction of actin and myosin. In the absence of calcium ions in the cytoplasm (relaxation phase), troponin I interferes with the interaction of actin and myosin. The optimal functioning of troponin proteins is determined by the correct amino acid structure. Even minor genetic abnormalities that cause changes in one or more amino acids in the composition of troponins are accompanied by severe disorders of myocardial contractility. Hence, currently, more than 100 mutations in genes encoding the amino acid sequence of troponins have been discovered, which lead to the development of contractile myocardial dysfunction and cardiomyopathies [1]. Additionally, approximately 4%–6% of troponin proteins (of the entire mass of troponins inside the cardiomyocyte) are in the cytoplasm of the cardiomyocyte, which are not part of the troponin complex and are not involved in myocardial contraction — the cytosolic troponin fraction (Fig. 1). The molecular weight of troponin proteins is relatively small (23.8 kDa for troponin I, 37 kDa for troponin T, and 20 kDa for troponin C). Troponins T and I are consid-

Fig. 1. Location of troponins in a cardiomyocyte



ered ideal biomarkers for detecting myocardial injury, since they are cardiospecific isoforms [2, 3].

Until recently, it was believed that troponins are released from cardiomyocytes after the death of cardiomyocytes. Increased troponin concentrations during prolonged and intense exertion (marathon, triathlon) [4, 5] and after psycho-emotional stress [6] formulate the hypothesis that troponin is released only upon irreversible damage to myocardial cells.

The advent of new, more sensitive methods (highly sensitive and ultra-sensitive immunoassays) has changed some ideas about the biology of troponins. Cardiac troponins are determined in the blood of all healthy individuals using modern ultra-sensitive tests at a concentration of less than the 99th percentile ("troponin-negative" results are no longer observed) and therefore can be considered products of normal myocardial metabolism. The mechanisms of troponins release into the bloodstream from the myocardium of healthy individuals are unknown. Presumably, this occurs during the processes of regeneration or renewal of cardiomyocytes, increased permeability of cell membranes, minor necrotic and apoptotic processes in the subclinical course of inflammatory and ischemic diseases, excessive physical exertion, and stress [5–7].

Highly sensitive and ultra-sensitive methods determine significantly low serum troponin concentrations; hence, the lower limits of determination for highly sensitive and ultra-sensitive immunoassays are 2–5 ng/L and 0.01–0.2 ng/L, respectively. In 2012, experts from the International Federation of Clinical Chemistry and Laboratory Medicine designated those immunoassays as highly sensitive, which can detect troponin in greater than 50% of healthy individuals. Furthermore, the manufacturers continued to work on increasing the sensitivity of their immunoassays and achieving a quantitative determination of cardiac troponins in the blood serum of 95%–100% of healthy individuals. Such immunoassays are called ultra-sensitive. The use of highly sensitive and ultra-sensitive immunoassays for the early diagnosis of acute myocardial infarction (AMI) (one-hour and three-hour algorithms) is regulated in the guidance document "The Fourth Universal Definition of Myocardial Infarction" (European Society of Cardiology, 2018) [2].

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Modern highly sensitive and ultra-sensitive methods for detecting cardiac troponins detect even significantly minor damage to the heart muscle, increasing the number of patients with elevated troponin concentrations, thereby complicating the interpretation of laboratory results [2]. In clinical practice, it is difficult to interpret the dynamic changes in the concentration of troponins in conditions such as tachycardia/tachyarrhythmias, inflammation of the heart membranes (endocarditis, myocarditis, pericarditis), and thromboembolism of the pulmonary artery (Fig. 2). An increase in troponin levels in these diseases indicates cardiomyocyte damage. In some cases (e.g., with impaired renal filtration due to renal failure, false-positive results), an increase in the serum levels of cardiac troponins is noted even in the absence of cardiomyocyte damage.

In the following paragraphs, we discuss the increase mechanisms and the diagnostic values of troponins in these non-coronarogenic conditions.

MECHANISMS FOR INCREASING THE TROPONIN LEVEL AND THEIR DIAGNOSTIC VALUE

Mechanisms of troponin elimination from the blood

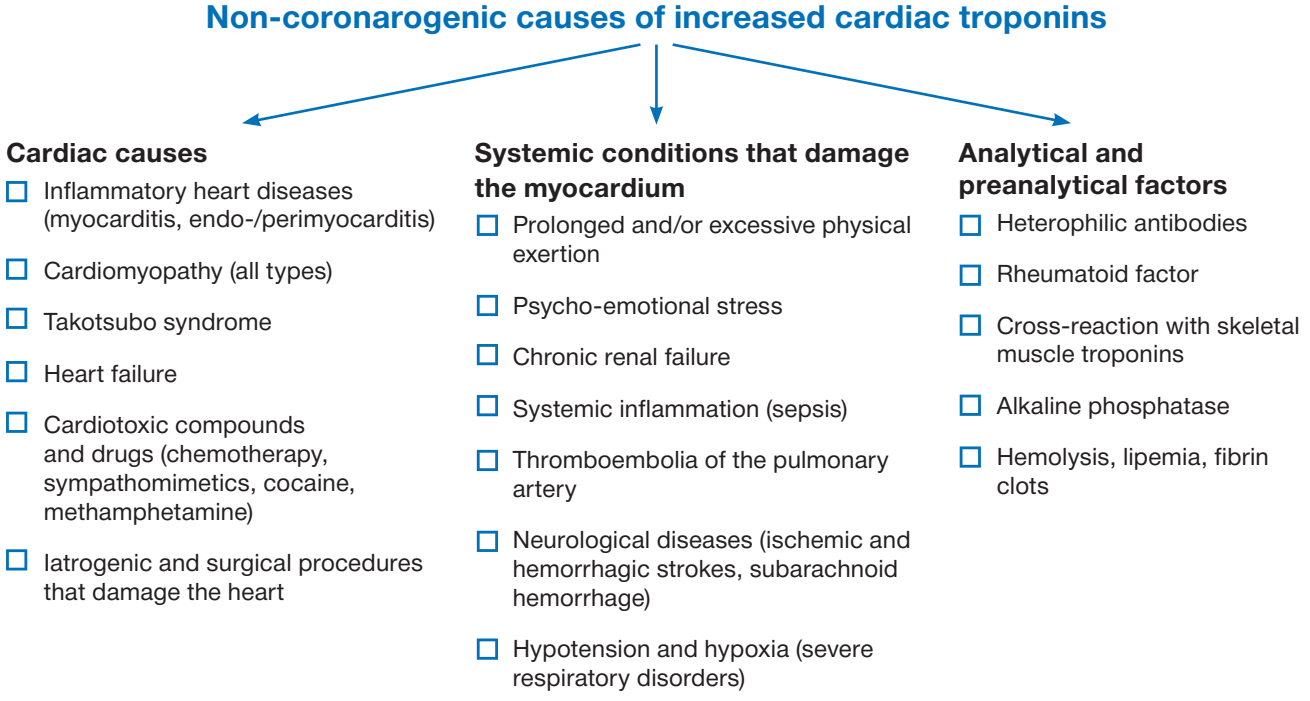
Troponins in renal failure

The blood concentration of cardiac troponins depends not only on the mechanisms of their release from cardiomyocytes but also on the mechanisms of elimination from the blood. To date, the following methods have been established for removing troponins from the bloodstream:

1) Intracellular cleavage by specific proteases (in the cells of the reticuloendothelial system)
2) Renal filtration
3) Extracellular cleavage of troponins under the action of proteases

The processes of intracellular and extracellular cleavage have been studied in several reports. According to the data of the Russian biochemists I. Katrukha et al., the thrombin enzyme specifically cleaves cardiac troponin T

Fig. 2. Non-coronarogenic causes of increased concentration of cardiac troponins



into several peptide fragments [8]. Researchers note the need for further study of the processes of intracellular and extracellular degeneration of troponins to improve immunoassays [8–10].

The involvement of the kidneys in the elimination of cardiac troponins from the bloodstream is controversial. Some researchers contradicted this troponin removal mechanism due to the fact that it was not possible to determine troponins in the urine [11, 12]. Nevertheless, in clinical practice, elevated troponins were often noted in patients with renal failure, which is an indirect evidence of the involvement of the kidneys in the removal of troponins. The most significant evidence of the role of renal filtration in increasing the serum troponin levels is observed in the Chronic Renal Insufficiency Cohort study, which included 2,464 patients with chronic renal failure, but without evident signs of cardiovascular disease. A lower glomerular filtration rate (GFR) was associated with higher troponin T concentrations; hence, in patients with GFR lower than 30 ml/min, troponin levels were 3 times higher than in patients with GFR greater than 60 ml/min. The association between lower GFR values and higher levels of troponin T is partly due to a decrease in renal clearance of troponin T. The holistic protein is a significantly large molecule that passes through the glomerular filter; however, fragments of troponin T are sufficiently small and are considered to be filtered by the kidneys. Nevertheless, in this study, the concentration of troponin T was normal in some patients with low GFR, which indicates that impaired renal clearance is not the only reason for the increase in troponin levels in patients with chronic renal failure [13].

Recently, Croatian researchers P. Pervan et al. provided direct evidence on the important role of the kidney in the removal of troponins. Using a highly sensitive immunoanalyzer Abbott Architect i1000SR (USA), a highly sensitive troponin I (hs-cTnI) was detected in the urine of all patients, and the urinary level of hs-cTnI in normotensive patients was lower (14.95 pg/ml) than that in patients with high blood pressure (26.59 pg/ml) ($p < 0.05$). The authors believe that determining the level of hs-cTnI in the urine can be used in establishing the diagnosis of hypertension and in monitoring hypertension [14].

Another proposed mechanism responsible for the increase in cardiac troponins in chronic renal failure is the “skeletal hypothesis,” which is confirmed by reports of the expression of cardiac isoforms of troponins in the skeletal muscle. In chronic renal failure, skeletal muscle alteration (uremic skeletal myopathy) occurs, followed by reparative regeneration processes in which the cardiac isoforms of troponins are expressed. Some studies revealed that the expression of cardiospecific troponins in the skeletal muscle is normal during the embryonic period. V. Ricchiutti and F. Apple reported the detection of cardiac troponin T mRNA in the skeletal muscle biopsy samples in 50% of patients with chronic renal failure [15]. However, in a study by C. Haller et al., no cardiac isoforms of troponin T were detected in the biopsy samples of the muscles of the anterior abdominal wall in patients with terminal chronic renal failure [16]. Thus, data on the expression of cardiac isoforms in the skeletal muscle in uremic myopathy are contradictory.

It is worth noting that the elimination of troponins also occurs through the histohematological barriers (hematosalivary, hematoliquor). This is observed in several studies in which the cardiac troponins were found in the cerebrospinal fluid and oral fluid [17–19]. In patients with AMI, troponin concentrations in the blood serum were associated with the oral fluid. Ac-

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cording to researchers, the saliva can be used as a biomaterial for the noninvasive diagnosis of AMI [19].

Troponins in tachycardia/ tachyarrhythmias

In clinical practice, an increase in the serum levels of cardiac troponins is sometimes noted in patients with supraventricular tachyarrhythmia (SVT). The most possible mechanism responsible for the elevation of troponins in SVT is considered to be shortening of diastole [20]. In accordance with the anatomical features, the blood supply to the heart is implemented in diastole. During systole, the aortic valve leaflets occupy the aortic sinuses and thus close the coronary ostia. During diastole, the aortic valve closes, which leads to the opening of the coronary ostia into which blood it enters. Thus, a decrease in diastole leads to an imbalance between the demand and delivery of oxygen. According to M. Zellweger et al.'s study, four clinical cases of increased troponin I have been described in patients with SVT. The heart rate was 170–250 beats/min, and the duration was 1.5–22 h. Coronary heart disease was ruled out based on the results of stress echocardiography and coronarography. An increase in creatine phosphokinase activity was also observed. The degree of increase in troponin I and creatine phosphokinase levels did not depend on the heart rate and duration of tachycardia [21]. T. Bakshi et al. found an increase in troponin I level not associated with coronary heart disease in 21 patients. The presence of lesion in the coronary arteries is ruled out according to the result of coronary angiography. Simultaneously, in 6 patients, tachycardia was the cause of troponin increase (SVT in 4 patients and ventricular tachycardia in 2 patients). In 5 patients, the causes of increased troponin I levels were physical activity, pericarditis, and heart failure. In 10 patients, the cause of troponin I elevation was not established [22].

In a larger study of 104 patients with SVT, elevated troponin I levels were reported in 48% of patients [23]. N. Ben Yedder et al. conducted a retrospective study involving 73 patients with SVT and without signs of coronary heart disease. Troponin T level increased in 24 patients (32.9%). The maximum heart rate was significantly higher in patients with elevated troponin T levels than that in patients with troponin-negative results (190.8 versus 170.3 beats/min, respectively, $p = 0.008$). Additionally, an association was revealed between the maximum heart rate during SVT and the level of troponin T increase ($r = 0.637$, $p = 0.001$) [24].

Since several patients with SVT experience the symptoms of chest pain, they are often mistakenly diagnosed with AMI, and inappropriate treatment in the form of antiplatelet and thrombolytic drugs is prescribed. Only coronary angiography rules out the signs of coronary artery lesion in patients with SVT [24, 25]. According to F. Xue et al.'s study, 2 cases are described when AMI was mistakenly diagnosed in patients with SVT. In both patients, upon admission with complaints of chest pain, troponin I level increased (0.09 and 0.16 ng/ml, respectively, with a norm of 0.08). A few hours after hospitalization, there was an even more significant increase in the concentration of troponin I level (to 0.52 and 2.28, respectively). As a result, AMI was mistakenly diagnosed in patients, and appropriate treatment was prescribed. Within a few days after hospitalization, patients underwent coronarography, which did not reveal any signs of coronary artery obstruction [25].

Troponins in myocarditis, endocarditis, and pericarditis

The main mechanism for increasing cardiomarkers in myocarditis, in particular troponins, is associated with the direct cytotoxic effect of infectious agents (viruses, bacteria), toxins, and autoantibodies on cardiomyocytes. Concentrations of cardiac troponins in myocarditis and their sensitivity and specificity vary widely. According to several studies, troponins, determined using moderately sensitive methods for the diagnosis of myocarditis, had a sensitivity of 34%–71% and a specificity of 86%–94% [26–28].

Due to the high mortality rates of newborn infants and children from myocarditis (average rates, 75% and 25%, respectively), timely diagnosis and therapy adequate to treat the severity of disease are of utmost importance [29]. The clinical presentation of childhood myocarditis is often asymptomatic or paucisymptomatic under the guise of other diseases, most often acute respiratory viral infections. The search for biomarkers for the early diagnosis of myocarditis and assessment of prognosis is considered a priority. A large retrospective analysis of medical records by Y. Chang et al., which included 94 pediatric patients with acute myocarditis, revealed that fatal cases were significantly more common in children with increased levels of cardiac troponin I, a creatine kinase-MB isoform. Simultaneously, increased concentrations of these biomarkers were associated with arrhythmia, hypotension, acidosis, and a decreased left ventricular ejection fraction. The vast majority of patients died within the first 72 h. In the multivariate analysis, significantly high cTnI levels (> 45 ng/ml) and a decrease in the left ventricular ejection fraction (< 42%) were associated with a high risk of death, specifically in the first 24 h. According to the authors, for patients with high cTnI concentrations, more intensive therapy is reasonable [30].

Highly sensitive troponins have advantages over moderately sensitive troponins and a number of other biomarkers and methods for diagnosing myocarditis. Thus, in a study by C. Ukena et al., the concentrations of hs-cTnT, copeptin, and N-terminal precursor of natriuretic hormone (NT-proBNP) were measured in patients with suspected myocarditis (n = 70). Based on endomyocardial biopsy data ("gold standard"), all patients admitted were divided into 3 groups: (a) acute myocarditis, (b) chronic myocarditis, and (c) absence of an inflammatory process in the myocardium. The highest mean concentrations and the range of hs-cTnT concentrations (262.9 [61.4–884.2] pg/ml) were noted in patients with acute myocarditis, and they exceeded the hs-cTnT values both in patients with chronic myocarditis (20.4 [15.6–20.4] pg/ml, $p < 0.0001$) and in patients without myocardial inflammation (19.5 [13.8–50.7] pg/ml, $p < 0.0001$). At that, the levels of copeptin and NT-proBNP did not significantly differ between these groups and, accordingly, were ineffective in the diagnosis of myocarditis [31].

The pathogenetic significance of viral persistence in the myocardium is not fully understood. Scientists using the polymerase chain reaction method investigated the viral genome (enteroviruses [Coxsackie], parvovirus B19, adenovirus, herpes viruses [Epstein-Barr]) in patients with suspected myocarditis. It is noteworthy that the levels of hs-cTnT were significantly higher ($p = 0.042$) in patients with a detected viral genome (37.4 [21.9–163.6] pg/ml) than those in patients with no viral nucleic particles (20 [14–44.4] pg/ml) [31]. This, most likely, indicates the toxic effect of virions on myocardial cells, which cannot be detected by endomyocar-

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dial biopsy, specifically with low activity of the inflammatory process.

In some studies, the serum concentrations of cardiac troponins in several patients with myocarditis did not increase, posing the following important question for researchers: Why are highly sensitive troponins (90%–100%) in ischemic myocardial damage (AMI) show significantly lower efficacy for the diagnosis of inflammatory damage to cardiomyocytes (myocarditis)? This is due to several factors. First, the analytical characteristics of troponin immunoassays are significantly different, and in the blood serum of the same patient, troponin concentrations when using different immunochemical test systems will differ significantly. This is due to the fact that in the test systems of different manufacturers, there may be antibodies to different epitopes (antigenic determinants) of the troponin molecule, and the cardiac troponin molecules themselves are in the blood as a heterogeneous fraction (fragments of troponin molecules, free molecules, oligomeric complexes). Moreover, each can circulate in oxidized or phosphorylated form [32]. According to another assumption, autoantibodies to cardiac troponins play a role in a false-negative decrease in serum levels of troponins in myocarditis. According to A. Matsumori et al., in the blood of patients with myocarditis, the titer of autoantibodies to troponins significantly increases [33]. Autoantibodies to troponins are essential in the pathophysiology of damage to cardiomyocytes and, in addition, are sources of analytical interference in the determination of troponins, binding epitopes of circulating troponin molecules, which makes them inaccessible to diagnostic antibodies that comprise the test system [34].

Endocardial and epicardial cells do not contain cardiac troponins, but endocarditis and pericarditis are often accompanied by an increase in their serum levels, which is probably due to the involvement of myocardial tissue in the inflammatory process. Hence, R. Tsenovoy et al. recorded an increase in troponin levels above the normal values (> 0.4 ng/ml) in 57% of patients with infectious endocarditis. It is noteworthy that among the troponin-positive patients, nosocomial mortality or valve replacement surgery was observed more frequently (51 versus 15%, respectively, $p < 0.005$) [35]. According to another retrospective study, troponin I level was elevated in 65% of patients with infectious endocarditis. Elevated troponin I levels were also associated with a poor prognosis (combination of adverse events), namely, death, myocardial abscess, and lesion of the central nervous system ($p < 0.001$) [36].

According to the study by M. Imazio et al., troponin I level exceeded the upper reference limit (1.5 ng/ml) in 38 (32%) of the 118 patients with acute viral or idiopathic pericarditis. In some patients, the kinetics of serum troponin levels in pericarditis corresponded to the kinetics of troponins in heart attack. An increase in the concentration of creatine kinase-MB and anomalies of regional contractility of the left ventricular wall according to echocardiography were also noted. These aspects led to incorrect preliminary diagnoses at the admission stage. Overestimated troponin I level in patients with acute pericarditis was significantly associated with younger age ($p < 0.001$), male sex ($p = 0.007$), ST segment elevation ($p < 0.001$), and the presence of effusion in the pericardial cavity ($p = 0.007$). Simultaneously, in this study, positive cTnI was not associated with a poor prognosis in acute pericarditis [37], in contrast to the studies described above on the prognostic value of cardiac troponins in myocarditis and endocarditis.

Troponins in systemic inflammation (sepsis)

Cardiospecific troponins increase significantly often with systemic inflammation, and the mechanisms for their increase vary. One of them is myocardial ischemia, which occurs due to an imbalance between the cardiomyocytes' need for oxygen and its delivery in case of intact coronary arteries. The imbalance is caused by several pathophysiological pathways, the most significant of which are fever, hypotension, respiratory failure (respiratory hypoxia), acid-base and water-electrolyte balance disorders, and microcirculation disorders, which leads to a decrease in hemoperfusion of all organs, including myocardium. Thus, in case of fever and hypotension, tachycardia increases, under which cardiomyocytes require more oxygen and metabolic substrates (glucose, fatty acids). However, their delivery through the coronary arteries decreases. Acid-based disorders, in turn, are accompanied by a disruption in the functioning of enzymes that provide myocardial energy processes. Increased glycolysis in the myocardium leads to additional production of lactate, the progression of acidosis, hypoxia, and metabolic disorders, thereby closing the vicious pathogenetic circle. Under such conditions, reversible or irreversible damage (death) to myocardial cells occurs, which leads to the release of troponins [38, 39].

It is believed that the leading role in the alteration of cardiomyocytes in sepsis is played by inflammatory mediators, namely, tumor necrosis factor alpha (TNF-α), interleukins (ILs) 1 and 6, and bacterial exo- and endotoxins, which have direct cytotoxic action. This is confirmed by an experimental study by A. Kumar et al. The administration of serum obtained from patients with sepsis and containing inflammatory mediators (TNF-α, IL-1) reduced the amplitude and rate of contraction of cardiac myocytes [40]. Additional mechanisms for increasing cardiac troponin levels in patients with sepsis can be myocardial vascular microthrombosis and increased apoptosis of cardiomyocytes. Additionally, it should be considered that severe sepsis and septic shock are often accompanied by multisystemic disorders, including renal failure, in which the elimination of troponins from the blood decreases. This is evidenced by J. Wilhelm et al.'s study, who noted a correlation between hs-TnT and serum creatinine ($r = 0.554$; $p < 0.001$) [41]. Considering the above, it is evident that the mechanisms of increasing cardiac troponin levels in sepsis vary, and their complex contribution is possible with the predominance of some specific mechanisms in a particular situation (the cause of sepsis, severity).

Troponins are valuable prognostic markers for sepsis. Thus, a large meta-analysis by F. Bessiere et al., which was combined with 13 original works with 1,227 patients with sepsis, revealed that an increased level of troponin was significantly associated with an increased risk of death (odds ratio [OR], 1.91; confidence interval [CI], 1.62–2.24) [38].

Several studies have measured highly sensitive troponins in patients with sepsis [41, 42]. H. Rosjo et al. analyzed the concentration of cTnT and hs-cTnT in 207 patients with sepsis, and 166 (80%) patients of them had a concentration of hs-cTnT above the 99th percentile, whereas levels of moderately sensitive troponin (cTnT) only increased in 86 (42%) patients. An association was noted between hs-cTnT levels and disease severity (according to SAPS II, $r = 0.27$, $p < 0.001$), multisystemic dysfunction (according to SOFA, $r = 0.30$, $p < 0.001$), and creatinine concentration ($r = 0.32$, $p < 0.001$). The median level of hs-cTnT was higher in

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the group of deceased patients than that in the group of survivors (0.054 [0.022–0.227] versus 0.035 [0.015–0.111] μg/L, $p = 0.047$), whereas moderately sensitive troponin T levels did not significantly differ in these groups ($p = 0.14$). Concentrations of hs-cTnT in patients with septic shock were significantly higher than those in patients without shock (0.044 [0.024–0.171] versus 0.033 [0.012–0.103] μg/L, $p = 0.03$), whereas cTnT levels did not differ in patients with shock and without shock [42]. Considering this, it can be concluded that hs-cTnT is significantly better for assessing the severity and survival rate of patients with sepsis than cTnT. However, due to such a frequent increase in hs-cTnT, difficulties may arise in the differential diagnosis.

Troponins in neurogenic pathologies (ischemic stroke and subarachnoid and intracerebral hemorrhage)

Several studies reported an increase in cardiac troponin levels in strokes and subarachnoid hemorrhages. J. Jensen et al. revealed an increase in troponin T levels in 25 (10%) of the 244 patients with ischemic stroke. Patients with increased levels of troponin T had a significantly higher risk (3.39 times) of death based on a 19-month follow-up period than patients with decreased levels of troponin T [43]. R. Sandhu et al. studied the association between cardiac troponin I levels and nosocomial mortality in patients with ischemic stroke and intracerebral and subarachnoid hemorrhage. Patients with ischemic stroke and increased levels of troponin I died more often than patients with ischemic stroke and normal troponin I levels (65 versus 4%, $p < 0.001$). Fatal cases in patients with intracerebral hemorrhage and elevated troponin I levels were significantly more common than those in patients with intracerebral hemorrhage and normal troponin I concentrations (64 versus 24%, $p < 0.005$). With subarachnoid hemorrhage, nosocomial mortality was higher (40%) in patients with elevated levels of troponin I than that in patients (11%) with normal levels of inhibitory subunit ($p < 0.005$). Thus, the researchers concluded that in patients with these neurogenic pathologies, elevated levels of troponin I determine the prognosis [44].

According to a large systematic review that included 15 studies (2,901 patients with stroke), 18.1% of participants had elevated troponin levels. The prevalence in individual studies ranged from 0% to 35%, most likely due to the different exclusion criteria and different test systems for determining troponin and threshold values. Additionally, troponin-positive patients were more likely to have ischemic changes on the electrocardiogram (OR, 3.0; 95% CI, 1.5–6.2) and an increased risk of death (OR, 2.9; 95% CI, 1.7–4.8) compared with patients with low troponin levels [45].

The mechanisms for increasing cardiac troponins in strokes and subarachnoid hemorrhages have not been fully established. It has been suggested that elevated serum troponin levels in acute stroke are due to myocardial damage caused by sympathoadrenal activation. To test this hypothesis, M. Barber et al. conducted a study in which the concentration of troponin I and adrenaline in the blood serum were determined in patients with acute ischemic stroke ($n = 222$). Moreover, 20% of patients showed an increase in troponin I level above the reference limit (> 0.2 μg/L). Troponin-positive patients had higher levels of adrenaline than troponin-negative patients (on average 0.27 versus 0.17 nmol/L, $p = 0.0002$), and their electrocardiograms were more likely to have signs of ischemia resembling AMI. Thus, the authors concluded that the activation of the sympathoadrenal system in acute

stroke is an important factor in myocardial injury [46].

The frequency of strokes increases markedly after AMI, specifically in the early stages. The severity of ischemic brain injury and the localization of stroke affect the prognosis of patients. In stroke survivors, cardiovascular diseases represent a major cause of long-term death [47]. Some researchers believe that the main mechanism for increasing troponins in stroke is myocardial ischemia [48]. However, according to other studies, this mechanism cannot fully explain the increase in troponins in stroke. Thus, blood circulation disorders according to myocardial perfusion scintigraphy were not more frequent or pronounced in patients with stroke and elevated troponins when compared with those patients with acute stroke whose troponin concentration was normal. Other researchers believe that the main mechanisms for increasing the troponin levels in stroke are renal and heart failure [49].

In strokes and subarachnoid hemorrhages, systolic dysfunction of the left ventricle is noted. In patients with subarachnoid hemorrhages and impaired wall movement, there were no perfusion defects during myocardial scintigraphy and no abnormalities were noted on coronarography. Disorders of the wall motion were reversible [50, 51]. Systolic dysfunction of the left ventricle in patients with subarachnoid hemorrhages is associated with normal myocardial perfusion and abnormal sympathetic innervation. These results can be explained by the excessive release of norepinephrine from the sympathetic terminations of the myocardium, which can damage both cardiomyocytes and the nerve endings themselves [51].

Atrial fibrillation is considered the main cause of ischemic stroke. According to I. Beaulieu-Boire et al., elevated levels of troponin I are predictors of atrial fibrillation in patients with acute ischemic stroke or transient ischemic attacks. In troponin-positive patients, 24-hour monitoring of Holter electrocardiogram showed fibrillation more often than in individuals with normal troponin levels (34.7 versus 9.7%, $p = 0.004$) [52].

Constantly elevated serum levels of highly sensitive troponins, exceeding the 99th percentile, may indicate chronic myocardial injury. L. Ryden et al. studied the association between chronic myocardial injury and stroke. Chronic myocardial damage (hs-TnT > 14 ng/L) was reported in 7.9% of patients out of the 19,640 patients. In patients with chronic myocardial injury (hs-TnT > 14 ng/L), the risk of stroke is 4 times higher than that in individuals with an hs-TnT concentration of less than 5 ng/L [53].

Troponins in pulmonary artery thromboembolia

Pulmonary artery thromboembolia is a common cause of elevation of troponin levels. Moreover, approximately 50% of patients experience “coronary-like” pain, which causes difficulties and errors in differential diagnosis [54]. The main mechanism of troponin release from cardiomyocytes in pulmonary artery thromboembolia (PATE) has not been conclusively established. Acute deformities of the right ventricle in response to increased pulmonary artery resistance can lead to increased troponin levels in PATE. Thus, T. Meyer et al. noted that 62.5% of patients with dilated right ventricle had elevated levels of troponin I, whereas 28.6% of troponin-positive patients had normal diameter of the right ventricle. Elevated troponin was significantly associated with dilatation of the right ventricle ($p = 0.009$). Additionally, patients with increased troponin I levels had a significantly larger number of segmental defects during lung scanning using ventilation perfusion scintigraphy compared to

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troponin-negative patients (p = 0.0002) [55].

Another explanation for elevated troponin levels in PATE may be hypoxemia due to the mismatch between perfusion and ventilation. In some patients who died from massive PATE, autopsy revealed isolated right ventricle infarction with intact coronary arteries [56].

A study [57] showed that the kinetics of troponin T release in myocardial infarction and PATE is significantly different. Thus, peak troponin T concentrations were lower than with AMI. Troponin T circulated at elevated concentrations with PATE for a significantly shorter time (30–40 h) than with AMI (more than 120 h). Based on these data, the researchers suggested that the mechanism of myocardial injury and the release of troponins in PATE patients differ from that in AMI patients [57].

Some researchers believe that the mechanism of troponin release in PATE depends on its severity. In mild PATE, troponins are released from the cytosolic pool, whereas in moderate to massive PATE, irreversible ischemia and death of cardiomyocytes occur. According to E. Giannitsis et al., an increase in cardiac troponins depends on the volume of injury to the pulmonary vasculature. With massive PATE, troponin is increased in 50% of patients; with submassive PATE, it is approximately in 35% of cases; and with non-massive PATE, it practically does not occur. Inpatient mortality, cardiogenic shock, and the need for resuscitation were more common in patients with elevated cTnT compared to patients with decreased cTnT. Troponin-positive patients more often required inotropic support and artificial pulmonary ventilation [58].

According to large-scale meta-analysis by C. Becattini et al. (20 studies, 1,985 patients), elevated troponin levels were significantly associated with mortality in the short term (at hospital or within the next 30 days) (OR, 5.24; 95% CI, 3.28–8.38), death as a result of PATE (OR, 9.44; 95% CI, 4.14–21.49), and with unfavorable outcomes (OR, 7.03; 95% CI, 2.42–20.43) [59].

In another meta-analysis (9 studies, 1,366 normotensive patients with acute symptomatic PATE), elevated troponin levels in patients increased the probability of death in the short term by 4.26 times [60].

J. Kim et al. suggest using the ratio of D-dimers and troponin I for the differential diagnoses of PATE and AMI. The authors conducted a retrospective study that included 771 patients with myocardial infarction and 233 patients with acute PATE. An increase in D-dimers was recorded in approximately half (49.5%) of patients with myocardial infarction, and the concentration of cTnI increased in 38.6% of PATE patients. The threshold values for the differentiation of PATE and myocardial infarction were 1.12 mg/L for D-dimer (sensitivity, 81.1%; specificity, 70.2%) and 0.72 ng/ml for cTnI (sensitivity, 80.6%; specificity, 78.9%). When using the ratio of D-dimers/cTnI greater than 1.82 in the differential diagnosis of PATE from myocardial infarction, the sensitivity and specificity were significantly higher than the diagnostic value of individual markers and amounted to 93.3% and 86.6%, respectively. Using this ratio, an invasive study such as coronarography can be avoided [61].

False-positive troponins

In some cases, elevated troponin concentrations cannot be explained, despite even a thorough clinical examination. Such cases are called false-positive and are most often associated with such factors as heterophilic antibodies, rheumatoid factor, alkaline phosphatase, and cross-reactions with skeletal muscle troponins [62–65].

Heterophilic antibodies are generated by B lymphocytes in response to exposure to an-

tigens, such as contact with animal antigens (mice, rabbits), blood transfusion, vaccination, and the use of monoclonal antibodies in the treatment of cancer. In a systematic literary analysis, G. Lippi et al. described 16 original works that demonstrate the effect of heterophilic antibodies on the concentration of cardiac troponins. The frequency of interference varies from 0.1% to 3.0% and is almost unpredictable; it can affect both troponin I and troponin T test systems of any manufacturer [62]. The mechanism of a false increase in troponins under the action of heterophilic antibodies is due to their ability to cross-interact with the diagnostic antibodies that make up the immunoassay. The false-positive result of the determination of troponin should be considered. Although troponin plays an important role in the diagnosis of AMI, it should not be the only criterion for establishing this diagnosis. In a clinical case, a significant overstatement of troponin I (Beckman Access, USA) was reported in a patient who was admitted with chest pain (41 ng/ml at a norm of 0.5). With a thorough clinical examination, clinicians ruled out AMI in the patient and suggested a false-positive result. The negative values of troponin I, measured on several other commercial kits (Abbott, Bayer, Roche), also supported this assumption. Subsequently, in the laboratory of manufacturers of Beckman Coulter (USA), the fact of influence on the result of the analysis of heterophilic antibodies was finally established. After the addition of a blocking reagent of heterophilic antibodies, the concentration of troponin I decreased to normal values [63].

In patients with autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus), the main cause of false-increased troponins is the rheumatoid factor. According to A. Al-Awadhi et al., in 5 out of the 50 patients with seropositive rheumatoid arthritis, the concentration of troponin I exceeded 0.1 ng/ml (diagnostic threshold for AMI), whereas in no patient with seronegative rheumatoid arthritis, the concentration of troponin I exceeded the reference limit. Univariate regression analysis showed an association between the concentrations of troponin I and rheumatoid factor ($r = 0.35$, $p < 0.02$) [64].

Immunoassays using alkaline phosphatase as a component of the immunochemical reaction are affected by endogenous alkaline phosphatase [65]. The effect of alkaline phosphatase on troponin concentration was first reported by A. Dasgupta et al. With an activity of alkaline phosphatase of 46 U/L, the concentration of troponin I in the serum sample was 0.5 ng/ml. The researchers subsequently added alkaline phosphatase solutions to the serum to increase the activity of this enzyme and evaluate the effect on troponin concentration. With an activity of alkaline phosphatase of 129 U/L, the concentration of troponin I increased to 4.3 ng/ml. A further increase in alkaline phosphatase activity to 222.913 U/L was also accompanied by an increase in troponin I concentration to 9.4 and 40.1 ng/ml, respectively [66]. Other test systems, which do not use alkaline phosphatase as a component of the immunochemical reaction, are not affected by this effect. In a recent study, R. Marinheiro et al. also revealed that the cause of the false-positive result of troponin I in a patient was alkaline phosphatase [67].

Cross-reactions of commercial (diagnostic) antibodies to cardiac troponins with skeletal isoforms of troponins were considered a frequent phenomenon for the very first immunoassays of generations 1 and 2, which are currently practically not used in clinical practice. Recently, a group of Austrian researchers led by J. Schmid reported an increase in highly sensitive troponins T and I in patients

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with skeletal myopathies. Hs-cTnT was found to be increased in 68.9% of patients with myopathies, and hs-cTnI was increased in 4.1% of patients. Hs-cTnT values were closely associated with creatine kinase and myoglobin (r = 0.679 and 0.786, respectively, $p < 0.001$). The expression of cardiac isoforms of troponins in skeletal muscles, which was reported in some studies, was not revealed by these scientists. According to the authors, the most probable cause of the increase in hs-cTnT and hs-cTnT was a cross-reaction [68].

CONCLUSION

In patients with non-coronarogenic diseases (renal failure, myocarditis, endocarditis, sepsis, stroke, subarachnoid hemorrhage, thromboembolia of the pulmonary artery), cardiac troponin level increases significantly often, which should be taken into consideration in clinical practice when conducting differential diagnosis. If the result is interpreted incorrectly, harm may be inflicted to the patient in the form of incorrect treatment and its consequences. Cardiac troponins with these non-coronarogenic pathologies are valuable prognostic biomarkers. The specific mechanisms for increasing troponins have not been fully established, which requires further study. Special attention should also be paid to false-positive causes of increased cardiac troponins. The elimination of mechanisms leading to false-positive results is the subject of further studies.

CONTRIBUTION OF AUTHORS

A.M. Chaulin received and analyzed the literature data, wrote the article, edited the article, approved the final version for publication, and was fully responsible for the content; L.S. Karslyan and D.V. Duplyakov were involved in editing of the article and approval of the final version for publication and was fully responsible for the content of the manuscript.

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