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Review

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The Metabolic Pathway of Cardiac Troponins Release: Mechanisms and Diagnostic Role

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Abstract

Modern methods of cardiac troponin determination have enabled early diagnosis of acute myocardial infarction (AMI) and selection of optimal treatment tactics for patients early from admission. It has markedly improved the further prognosis of these patients. Unfortunately, there are a number of problems arising from the use of high-sensitivity cardiac troponins: frequent and unexplained increases in serum troponin levels in a number of pathological conditions not associated with AMI; insufficient study of mechanisms of release and increase, features of circulation and elimination of cardiac troponins; inconsistent data on the influence of several factors (circadian, gender and age characteristics), on cardiac troponin levels. All this may be accompanied by difficulties and errors in differential diagnosis as well as insufficient use of the diagnostic potential of cardiac troponins. In general, these problems are due to our insufficient understanding of the metabolic pathway of cardiac troponins. This review briefly discusses the main stages of the metabolic pathway of cardiac troponins and focuses in detail on the first stage of metabolism (the release of cardiac troponins).

Keywords: Myocardial infarction; Cardiovascular diseases; Diagnostics; Troponin T; Troponin I; Metabolism; Metabolic pathway; Release of cardiac troponins

Introduction

According to current studies, cardiac troponin molecules are detectable in blood serum [1-6] and a number of other body fluids such as urine [7, 8] and oral fluid [9-11] of almost all healthy people. This has been made possible by the development and use of high-sensitivity and ultra-sensitivity assay methods that can detect very low concentrations of cardiac troponins (at a few ng/L or less) in human body fluids [11-14]. This ability to detect low levels of cardiac troponins has improved the early diagnosis of acute myocardial infarction (AMI) by detecting these cardiac markers in the first hours from the onset of the clinical picture of AMI. Thus, due to a number of large and multicenter studies it was possible to validate the early diagnostic algorithms of exclusion/confirmation of AMI with non-ST-segment elevation myocardial infarction (NSTEMI) (0 - 1 h and 0 - 2 h algorithm), which are reflected in the current recommendations of the European Society of Cardiology. The basic principle of these algorithms is based on the assessment of the kinetics of high-sensitivity cardiac troponin levels during the first hour (0 - 1 h algorithm) and during 2 h (0 - 2 h algorithm) (Table 1) [15].

However, there are different optimal and threshold concentrations for each high-sensitivity immunoassay (developed by different manufacturers). As a rule, diagnosis of NSTEMI is excluded when cardiac troponin levels are low or very low on admission to the emergency department and troponin levels do not increase on repeat collection and blood testing after 1 or 2 h. The management tactic for these patients is early discharge and subsequent outpatient or elective treatment if necessary. In cases where cardiac troponin levels are above the accepted limit (for the appropriate high-sensitivity immunoassay and the company) and a repeat blood draw and test shows a significant increase in troponin levels, the likelihood of a diagnosis of NSTEMI is high. The management tactic for these patients is emergency hospitalization as well as performance of other diagnostic methods and evaluation of the results. To confirm this diagnosis, the data of other methods of examination (history and clinical picture, electrocardiography, echocardiography, and coronary angiography) should be additionally taken into account. The need to use other diagnostic methods is determined by the fact that troponin levels may be elevated not only in AMI but also in quite a number of pathologies (e.g., sepsis, acute myocarditis, hypertensive crisis, heart arrhythmias, cardiotoxic effects of some chemotherapeutic agents, etc.) [16-28] and physiological conditions (for example, long, heavy and strenuous exercise and/or psychoemotional stress) [29-33], which affect cardiomyocytes and contribute to troponin release into blood serum by some mechanisms. The mechanisms of cardiomyocyte damage in these conditions differ from the main mechanism which is characteristic of AMI (ischemic necrosis of myocardial cells). Considering this cir-

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Table 1. Early Diagnostic Algorithms for Exclusion/Confirmation of Non-ST-Elevation Myocardial Infarction (NSTEMI) (0 - 1 H Algorithm and 0 - 2 H Algorithm)

1-h NSTEMI diagnostic algorithm					
Troponin immunoassay, company (manufacturer)	**Biomarker concentration that indicates an extremely low probability of an NSTEMI diagnosis, ng/L**	**Biomarker concentration that indicates a low probability of an NSTEMI diagnosis, ng/L**	**Changes in biomarker concentration after 1 h at which a diagnosis of NSTEMI should be excluded, ng/L**	**Biomarker concentration that indicates a high probability of an NSTEMI diagnosis, ng/L**	**Changes in biomarker concentration after 1 h at which a diagnosis of NSTEMI should be confirmed, ng/L**
High-sensitivity cardiac troponin T (Elecsys; Roche)	< 5	< 12	< 3	≥ 52	≥ 5
High-sensitivity cardiac troponin I (Architect; Abbott)	< 4	< 5	< 2	≥ 64	≥ 6
High-sensitivity cardiac troponin I (Centaur; Siemens)	< 3	< 6	< 3	≥ 120	≥ 12
High-sensitivity cardiac troponin I (Access; Beckman Coulter)	< 4	< 5	< 4	≥ 50	≥ 15

2-h NSTEMI diagnostic algorithm					
Troponin immunoassay, company (manufacturer)	**Biomarker concentration that indicates an extremely low probability of an NSTEMI diagnosis, ng/L**	**Biomarker concentration that indicates a low probability of an NSTEMI diagnosis, ng/L**	**Changes in biomarker concentration after 2 h at which a diagnosis of NSTEMI should be excluded, ng/L**	**Biomarker concentration that indicates a high probability of an NSTEMI diagnosis, ng/L**	**Changes in biomarker concentration after 2 h at which a diagnosis of NSTEMI should be confirmed, ng/L**
hs-cTnT (Elecsys; Roche)	< 5	< 14	< 4	≥ 52	≥ 10
hs-cTnI (Architect; Abbott)	< 4	< 6	< 2	≥ 64	≥ 15
hs-cTnI (Centaur; Siemens)	< 3	< 8	< 7	≥ 120	≥ 20
hs-cTnI (Access; Beckman Coulter)	< 4	< 5	< 5	≥ 50	≥ 20

NSTEMI: non-ST-segment elevation myocardial infarction; hs-cTn: high-sensitivity cardiac troponin.

cumstance, cardiac troponins cannot be considered as absolute specific biomarkers of AMI but can be considered as absolute specific biomarkers of "myocardial damage". A number of clinical studies also indicate that in most cases serum levels of cardiac troponins are elevated in pathologies which are in no way associated with AMI [34-37]. For example, according to a large study that included 1,573 patients with elevated levels of cardiac troponin T, AMI was confirmed in only 10% of them. The remaining patients (about 90%) with elevated levels of cardiac troponin T were diagnosed with other pathologies that caused cardiomyocyte damage and increased troponin levels by nonischemic mechanisms. Besides, a very interesting finding in this study is that in approximately 30% of patients with elevated serum troponin T levels the exact cause and mechanism of the elevation could not be determined [37]. Thus, elevated cardiac troponin levels may indicate the diagnosis of AMI only if there are any clinical signs of myocardial ischemia whereas without signs of ischemia troponins merely indicate the presence of cardiomyocyte damage [38].

The problems of interpreting the positive results of cardiac troponins are associated with a lack of understanding of the metabolic pathway of cardiac troponins and the factors that will affect the metabolic pathway. In particular, the specific mechanisms of the release of cardiac troponins into the bloodstream have not been studied.

Besides, a number of researchers are actively considering the possibility of using other body fluids (e.g., urine and oral fluid) for diagnosis and further prognosis assessment for patients suffering from cardiovascular diseases or non-cardiac diseases causing myocardial cell damage and cardiac troponin release [7-10, 39-45]. For example, several pilot studies have clearly demonstrated the diagnostic value of high-sensitivity troponins in oral fluid in case of AMI [9, 39-42], in urine in case of diabetes mellitus [7] and in urine in case of arterial hypertension [8]. This may be of great clinical importance, since simple noninvasive and nontraumatic obtaining of urine and oral fluid does not require trained medical personnel during biomaterial acquisition and it also reduces the risk of infection with hemocontact infections such as human immunodeficiency virus (HIV) and viral hepatitis, whereas previously the diagnostic value of cardiac troponins in this noninvasive-derived biomaterial was extremely low or questionable when moderate-sensitivity troponin immunoassays were used [9, 10]. To my understanding, this is due to the fact that the concentration of cardiac troponin molecules in urine and/or oral fluid is relatively low and "not visible" to moderate-sensitivity troponin immunoassays. In other words, the minimum detectable concentration (detection limit) of the moderate-sensitivity immunoassays used was significantly higher than the concentration of cardiac troponin molecules presents in urine and oral fluid. Thus, the diagnostic capabilities and diagnostic value of cardiac troponins in human body fluids have changed significantly due to the increased sensitivity of troponin immunoassays.

In addition to the increased diagnostic capabilities of high-sensitivity cardiac troponins, our understanding of the biology and metabolism of cardiac troponins has changed as troponin immunoassays have improved. For example, moderate-sensitivity troponin immunoassays which have been widely used before the first high-sensitivity immunoassays could not detect cardiac troponin molecules in blood serum and other body fluids in healthy people. Therefore, cardiac troponin molecules were considered as strictly intracellular molecules and the presence of cardiac troponins in blood serum was considered as one of the key pathological criteria to confirm AMI in patients with clinical signs of myocardial ischemia [46-50]. In a number of cases researchers noted that elevated levels could be observed in other severe pathological conditions (septic shock, massive pulmonary embolism, Takotsubo cardiomyopathy, acute myocarditis and others) causing nonischemic myocardial cell damage. As a rule, such patients did not have complex clinical signs of myocardial ischemia (typical pain syndrome in the chest area, ischemic changes according to electrocardiography and echocardiography) which helped doctors in differential diagnosis and in making a correct diagnosis [50-52]. However, affected by the use of high-sensitivity troponin immunoassays cardiac troponin, molecules began to be detected in the blood serum of all healthy individuals [11, 12, 53, 54]. These data allow to consider cardiac troponin molecules as normal myocardial metabolites (provided that their level does not exceed the conventional 99th percentile values which differ significantly in different troponin immunoassays). Besides, affected by the use of high-sensitivity troponin immunoassays the researchers found that blood serum cardiac troponin concentrations were dependent on a number of biological features (gender, age and circadian), the influence of which had never been traced before (when moderately sensitive immunoassays were used) [54-59]. However, the mechanisms of release of cardiac troponin molecules from cardiac myocytes in healthy individuals and the mechanisms of formation of these biological traits are not conclusively studied and require further clarification. Presumed mechanisms of release and formation of these features will be discussed in this manuscript below.

It is worth noting individually that the prevalence of elevated results and the extent of increase in cardiac troponin levels in many systemic and nonischemic pathologies, as well as physiological conditions (physical exercise) is significantly higher with high-sensitivity troponin immunoassays than with moderate-sensitivity detection methods. This is confirmed by a number of comparative studies [60-63]. Thus, when using high-sensitivity immunoassays, differential diagnosis may be difficult, and practitioners should be even more careful when interpreting elevated troponin levels in their patients. The upside of using high-sensitivity troponins in systemic and nonischemic pathologies is the ability to assess the short- and long-term prognosis of patients who suffer from these diseases.

Another promising area for the use of cardiac troponins in clinical practice is monitoring of the condition and assessment of cardiovascular diseases risk and complications in healthy individuals or patients with certain risk factors (e.g., obesity, diabetes mellitus, arterial hypertension, advanced age, etc.). High-sensitivity troponin immunoassays can detect insignificant levels of blood serum cardiac troponins which may indicate subclinical myocardial damage [64-68]. For example, a study by Ucar et al showed that in patients with newly diagnosed arterial hypertension, elevated levels of high-sensitivity troponin T were associated with left ventricular hypertrophy

and geometric parameters that were indicative of unfavorable left ventricular remodeling [66]. McEvoy et al also reported that baseline high-sensitivity troponin T levels were strongly associated with the development of left ventricular hypertrophy and arterial hypertension in the long term (over 6 years of follow-up). This can be used under outpatient treatment to identify those individuals who should be monitored more frequently and/or recommended necessary preventive measures [67]. In addition to that Panteghini et al reported that in patients with arterial hypertension elevated levels of high-sensitivity troponin T are associated with a higher risk of major adverse cardiovascular and cerebrovascular events (MACCE) [68]. Thus, based on the results of a laboratory study, practitioners can identify patients who have a higher risk of developing cardiovascular diseases or the risk of developing complications in patients who have certain risk factors. This area for the potential use of high-sensitivity cardiac troponins has been actively studied recently. In the future, the data obtained will help to develop special algorithms for diagnosis and monitoring of patients using high-sensitivity troponin immunoassays, which can help physicians to initiate the earliest and the best therapeutic and preventive measures that will help improve patients' prognosis. The possibility of using noninvasive-derived body fluids (e.g., urine) which are more convenient to obtain under outpatient treatment adds special advantages to this process. For example, a recent study by Chen et al shows that levels of high-sensitivity troponin I in the urine of diabetic patients can be a useful diagnostic tool for predicting cardiovascular complications. Thus, the researchers found that the concentration of high-sensitivity troponin I of more than 4.1 ng/L in urine is an independent factor for predicting adverse cardiovascular events in individuals with diabetes mellitus [7].

One of the important problems of laboratory methods for the determination of cardiac troponins in clinical practice is lack of standardization [69-71]. This is expressed by the fact that if different immunoassays are used to determine cardiac troponins in body fluids of patients, different results (different concentrations of cardiac troponins) will be obtained. Thus, there are now a large number of different methods for determining cardiac troponins in blood serum and each of these methods produces different absolute values to make it impossible to compare the final results in the same sample. Moreover, serum troponin concentrations may differ by a factor of 2 - 10 or more during the use of different immunoassays [69-74]. This may be due to such factors as analytical characteristics (different sensitivity) and different diagnostic antibodies directed against different antigenic domains and epitopes (areas) of cardiac troponin molecule (anti-cTn). It should also be understood that cardiac troponin molecules in blood serum and probably in other body fluids (urine and oral fluid) are presented as a quite heterogeneous fraction: free whole molecules of troponin I and troponin T, binary complexes (troponin T + troponin I), triple complexes (troponin T + troponin C + troponin I), different fragments of troponin T and troponin I molecules with different sizes and molecular masses and modified forms (due to oxidation and phosphorylation) of the above troponin molecules [75-80]. Moreover, cardiac troponin T genes have several exons that can undergo alternative splicing [81, 82]. So, it is theoretically possible to have more than 100 isoforms of cardiac troponin T that will have different amino acid sequences and consequently their composition may have epitopes that will differ from the standard epitopes targeted by the diagnostic antibodies of the commercial kit [78, 83-86]. This may result in some diagnostic antibodies not interacting with these epitopes in the immunoassay. In some particular cases, such as hereditary cardiomyopathies, mutations in the genes encoding cardiac troponins may occur [86-89]. Thus, changes at the nucleotide sequence level (DNA and mRNA of cardiac troponins) will subsequently be reflected as changes at the amino acid sequence level. From a pathophysiological point of view, such amino acid changes of troponins can lead to disruption of their function (regulation of myocardial contraction and relaxation). This is the pathophysiological basis of cardiomyopathies. From a laboratory point of view, it can also lead to disruption of antigen-antibody interaction (interaction of cardiac troponin molecules and anti-cTn antibodies) during immunoassay. Since the strength of the antigen-antibody interaction is directly proportional to the concentration of cardiac troponins, we can say that there are certain structural changes in troponins (in the region of those epitopes targeted by diagnostic antibodies).

Different troponin molecules and their fragments as well as oxidized and phosphorylated derivatives may have different lifespans (half-lives) and different immune reactivity to diagnostic antibodies. This will have a significant impact on the diagnostic value of cardiac troponins and make an important contribution to the formation of differences in the laboratory examination of the body fluid of the patient [83-86]. In general, it can be noted that different troponin immunoassays in fact detect different troponin molecules in the same patient.

An additional factor that may influence the components of the heterogeneous troponin fraction and consequently the final assay result is the activity of enzymes causing proteolytic cleavage and modification (oxidation, phosphorylation, dephosphorylation) of cardiac troponin molecules and their fragments. For example, a number of studies have reported that phosphorylation of the cardiac troponin T molecule increases with left ventricular hypertrophy and heart failure. From a pathophysiological point of view, this causes a decrease in myocardial contractility; and from the laboratory point of view, it may contribute to underestimation of cardiac troponin concentration, since interaction of phosphorylated troponins with diagnostic antibodies of commercial kits is impaired. Thus, detection of phosphorylated molecules and fragments of cardiac troponins requires special phosphorus-specific anti-cTn antibodies [90, 91]. It is also quite interesting that the phosphorylated troponin T molecule is more sensitive to the proteolytic activity of the calpain enzyme compared to the unphosphorylated troponin T molecule [92]. The activity of proteolytic enzymes targets the peptide bonds connecting the amino acid residues in the structure of cardiac troponin molecules. Disruption of the peptide bonds can lead to the formation of smaller fragments of cardiac troponins which can change their physicochemical properties and affect the diagnostic value and diagnostic capabilities of cardiac troponins. For example, increased activity of those proteolytic enzymes that cause proteolytic degradation of troponin molecules may

lead to changes in the heterogeneous fraction of troponins and decrease the concentration of cardiac troponins in blood serum. Reducing the size of some fragments of cardiac troponin molecules may contribute to their ability to pass into the urine and oral fluid through the renal filter and hematosalivary barrier by filtration. To my understanding, this is a key mechanism explaining the new diagnostic possibilities of cardiac troponin studies in these noninvasive-derived human body fluids.

Elimination of cardiac troponin molecules plays an important role in the laboratory diagnosis of cardiovascular disease including AMI and this metabolic feature should be considered in the differential diagnosis. Elimination of cardiac troponin molecules is accomplished in several ways, which are summarized in Table 2.

Metabolic Pathway of Cardiac Troponins

Many metabolic features of troponins briefly discussed above are extremely understudied nowadays and their role in laboratory diagnosis and differential diagnosis of cardiovascular diseases requires clarification, generalization, and separate discussion of current knowledge on cardiac troponin metabolism which is the subject of the present article.

Given the abundance of possible metabolic mechanisms and factors influencing cardiac troponin levels as well as their potential clinical significance (Table 2), one should note high relevance of further studies of troponin protein metabolism. To my understanding, this will optimize algorithms for early AMI diagnosis, improve the differential diagnosis of AMI and a number of cardiovascular diseases, reduce the risks of misdiagnoses, expand diagnostic capabilities of troponins in clinical practice and particularly develop algorithms for assessing the risk of cardiovascular diseases in healthy individuals, assess the prognosis of patients suffering from diseases causing myocardial damage and validate methods for noninvasive diagnosis of cardiovascular diseases including AMI.

Stage of Biosynthesis and Release of Cardiac Troponin Molecules From Cardiac Myocytes Into the Bloodstream

After the first high-sensitivity troponin immunoassays were developed in 2007 - 2010 and cardiac troponin concentrations were detected in a significant number of healthy individuals, many researchers asked: how are cardiac troponin molecules released from intact myocardial cells into the blood serum? Researchers consider the following as possible (hypothetical) mechanisms: 1) apoptosis of cardiomyocytes; 2) myocardial cell regeneration and renewal; 3) increased permeability of cell membranes; 4) release of troponins by vesicular transport; 5) enhanced proteolytic degradation of troponin molecules inside the cell [93-101]. Besides, some of these mechanisms, such as apoptosis, can cause reversible and irreversible (under prolonged and/or excessive action of a damaging factor) myocardial cell damage.

Significance of cardiomyocyte apoptosis in release of cardiac troponins

As a result of activation of apoptosis processes in cells, the activity of caspase enzymes increases. It can cleave (damage) DNA and protein structures of the cell but unlike necrosis, apoptosis preserves the integrity of the cell membrane for relatively long time [95, 96, 102-105]. Modern methods for detecting apoptosis are light, electron and fluorescent microscopy, flow cytometry, immunohistochemistry as well as the TUNEL method which is generally considered to be the most sensitive (early) and valuable criterion for detecting cell apoptosis. TUNEL method allows to visualize cell nuclei containing fragmented (influenced by caspases) DNA [106-108]. This method is actively used by researchers to study the causes and mechanisms of cardiomyocyte apoptosis. A recent study by Weil et al investigated the effect of short-term ischemia on cardiomyocyte apoptosis in laboratory animals. The researchers simulated short-term ischemia (duration of ischemia was approximately 10 min) using balloon occlusion of the left anterior descending artery of the pig heart. The researchers used coronarography to prove complete occlusion and restored normal coronary blood flow by deflating the balloon after 10-min ischemia. Then myocardial histological examination was performed in one half of these animals, and cardiac troponin I levels were examined in the other half over a 24-h period (first sampling was performed 10 min after reperfusion and last sampling was performed 24 h after reperfusion). Histological examination of animal myocardium showed no signs of ischemic necrosis due to short duration of ischemia. However, compared to the nonischemic myocardial areas, the number of cardiomyocytes in apoptosis (TUNEL-positive cardiomyocytes) increased significantly (six-fold) in the focus of myocardium that underwent short-term ischemia. It is quite remarkable that troponin I levels began to rise as early as 10 min after reperfusion, and 30 min later cardiac troponin I levels reached the upper limit of normal range (38 ng/L). After that they continued to increase smoothly and reached extremely high values (1,021 ± 574 ng/L) in 24 h after reperfusion [108]. This experimental work is of great value because it clearly demonstrates several key points: 1) Short-term cardiomyocyte ischemia triggers apoptosis processes, but does not cause cell necrosis; 2) Apoptosis plays a significant role in the release of cardiac troponin molecules from myocardium into blood serum; 3) cardiac troponin levels in apoptosis begin to increase within the first minutes after reperfusion (in contrast to the atherothrombotic type of AMI when troponin molecules remain "blocked" in the ischemic zone and their time of penetration into the systemic bloodstream may significantly depend on the nature of reperfusion therapy and the phenomenon of "washout"); 4) Cardiac troponin levels in apoptosis can reach very high values, as in AMI. However, it is worth noting the limitation of this study: relatively short interval of myocardium study after reperfusion (24 h), and the results of this study cannot establish the reversibility of cardiomyocyte damage in ischemia-induced apoptosis.

The literature also describes a lot of situations when cardiomyocyte apoptosis occurs by other mechanisms (not related to short-term myocardial ischemia): with an increase in left

Table 2. Metabolic Pathway of Cardiac Troponins

Main stages of metabolic pathway of cardiac troponins	Brief description of the stage and factors that affect metabolic pathway of cardiac troponins	Main clinical and diagnostic significance of metabolic pathway of cardiac troponins
The stage of biosynthesis and release of cardiac troponin molecules from cardiac myocytes into the bloodstream	Cardiac troponin molecules are mainly synthesized in cardiomyocytes and can be released into blood serum both under physiological conditions (physical and psychoemotional stress) and during pathological processes (e.g., myocarditis, sepsis, hypertensive crisis, pulmonary embolism, Takotsubo syndrome and a number of others). The main mechanisms of release of cardiac troponin molecules into the bloodstream are: 1) cardiomyocyte necrosis; 2) cardiomyocyte apoptosis; 3) cardiac myocyte regeneration and renewal processes; 4) increased cell membrane permeability; 5) release of troponins via vesicular transport; 6) increased proteolytic degradation of troponin molecules within cardiac myocytes and release of reduced fragments even through the intact cell membrane. The first one is the key mechanism which is characteristic of AMI, while the others may be characteristic of physiological conditions and of reversible and irreversible cardiomyocyte damage in nonischemic and systemic pathologies (e.g., myocarditis, sepsis, arterial hypertension, and others). Using high-sensitivity immunoassays, it has also been found that the degree of release of troponin molecules from cells into the bloodstream depends on several biological factors: 1) gender (males have a higher degree of release); 2) circadian (more molecules are released from myocytes in the morning than in the evening and night); and 3) age-related (older patients have more molecules released from myocardial cells than younger patients).	Troponin concentration in blood serum has a direct correlation with the degree of release of troponin molecules from myocardium into the bloodstream. The extent of release of troponin molecules from the myocardium may depend on the type and severity of the pathological process or physical load (under physiological conditions). Gender peculiarities have an important clinical significance in modern diagnostic algorithms which are used in some algorithms of early diagnosis of AMI. Circadian and age-specific features are not yet reflected in the current clinical guidelines and diagnostic algorithms due to little study. However, as further research and new data become available, there is a probability of validating their clinical significance and subsequent introduction into practical medicine.
The stage of cardiac troponin molecules circulation in blood serum	The molecules circulating in blood serum can be affected by a number of enzymes belonging to the groups of proteases, kinases (phosphorylases), phosphatases, and oxidases. The activity of these enzymes may change under physiological and pathological conditions as well as medication. The study of specific factors influencing enzyme activity is a very interesting and extensive research area.	Concentration of cardiac troponins in blood serum may depend on the activity of a number of enzymes (proteases, kinases (phosphorylases), phosphatases and oxidases) that cleave and modify cardiac troponin molecules, leading to changes in the antigen-antibody interaction in immunochemical assays. The clinical significance of this step in troponin metabolism lies in the potential to obtain. Further studies are needed to identify specific enzymes and their specific influence on troponin molecules.
The stage of cardiac troponin molecules elimination from blood serum	Elimination of cardiac troponin molecules from blood serum can be accomplished by the following mechanisms: 1) elimination of molecules through hematotissue barriers (glomerular, heme-salivary, heme-placental, heme-encephalic, and others) into other body fluids (urine, oral fluid, amniotic fluid, pericardial fluid, cerebrospinal fluid); 2) uptake of cardiac troponin molecules by cells of reticuloendothelial system (mononuclear phagocyte system) (macrophages) and intracellular cleavage into amino acids within these cells; 3) cleavage of troponin molecules in bloodstream as a result of proteolytic enzymes (for example, thrombin enzyme).	Troponin concentration in blood serum has inverse dependence on elimination rate. Thus, when the rate/extent of elimination of cardiac troponin molecules from the bloodstream decreases, there will be an increase levels of cardiac troponins in blood serum. A very typical clinical example is the accumulation of cardiac troponin molecules and their increased blood serum concentrations in patients with chronic kidney failure without obvious signs of cardiovascular disease. Besides, depressed kidney function and decreased glomerular filtration rate may be observed in a number of other severe systemic diseases, which are often accompanied by a marked decrease in blood pressure (e.g., severe sepsis) or pathologies that cause damage to the renal vessels and renal glomeruli (e.g., diabetes mellitus). The clinical role of the other mechanisms of cardiac troponin elimination needs further research and clarification.

AMI: acute myocardial infarction.

ventricular myocardial preload; with myocardial tissue stretching and increased neurohumoral stimulation through beta-adrenoreceptors [109-117].

According to the results of the experimental study, when left ventricular myocardial preload increases, there is an increase in apoptosis and blood serum cardiac troponin I level. Laboratory animals were injected intravenously with phenylephrine (injection rate = 300 µg of medication per minute) for 1 h to increase end-diastolic pressure. After the experimental simulation, histological examination of the medications was performed in one half of the animals and blood for cardiac troponin I determination was taken from the other half of the animals. On histological examination of myocardium, the number of cardiomyocytes in a state of apoptosis was significantly higher ($P < 0.01$) in animals of the experimental group (31.3 ± 11.9 cardiomyocytes/cm^2) compared with the control group (4.6 ± 3.7 cardiomyocytes/cm^2). Twenty-four hours after the experimental simulation, the number of cardiomyocytes undergoing apoptosis decreased to 6.2 ± 5.6 myocytes/cm^2 and did not significantly differ ($P = 0.46$) from the indicators in the control group. No signs of cardiomyocyte necrosis were observed at the indicated time intervals. At the same time, 30 min after the increase in end-diastolic pressure, serum troponin I levels exceeded the upper limit of normal range and after 1 h cardiac troponin I levels reached very high values (856 ± 956 ng/L) [118]. Overall, the results of this study regarding the important role of apoptosis in the release of cardiac molecules add to the data described above.

Cheng et al described the mechanisms of cardiomyocyte apoptosis during myocardial stretch (distension) [109]. Ventricular myocardial distension is noted at physiological conditions (long and strenuous exercise) and at a number of pathologies (arterial hypertension, pulmonary embolism, chronic obstructive pulmonary disease, heart failure, etc.). Therefore, one can assume an important role of apoptosis in release of cardiac troponin molecules from myocardium at these conditions. The extent of troponin release appears to depend on the strength and duration and the damaging factor. For example, in physical exercise, arterial hypertension and nonmassive pulmonary embolism, there is less stress on the ventricular myocardium. That is expressed by a relatively small increase in serum levels of cardiac troponins. Whereas in massive pulmonary embolism there is a sharp right ventricular myocardial overload which leads to a much more significant increase in cardiac troponin concentrations [119-121].

The effect of neurohumoral (adrenergic system) on apoptosis processes was found in a study conducted by Singh et al. The opposite effects on apoptotic processes depending on the stimulation of β-adrenoreceptors were also noted: the stimulation of β1-adrenoreceptors increases apoptosis while the stimulation of β2-adrenoreceptors inhibits apoptosis [111, 112, 117]. Density of β-adrenoreceptor types changes in elderly patients. Particularly, the density of β2-adrenoreceptors decreases. This may lead to a decrease in the inhibitory effect on apoptosis and a relative increase in the activity of apoptosis mediated through β1-adrenoreceptors [113-115]. Thus, apoptosis may play a role in the release of cardiac troponin molecules from the myocardium in elderly patients. Several clinical studies using high-sensitivity troponin immunoassays have revealed age-related features of serum troponin levels, according to which cardiac troponin concentrations are higher in elderly people than in young people.

So, given the above data, there is every reason to suggest an important role of apoptosis in myocardial cell damage and increased serum levels of cardiac troponins in pulmonary embolism, arterial hypertension, heart failure, as well as prolonged and/or excessive exercise in the elderly too. Further studies are needed to confirm and clarify the specific role of apoptosis in the release of cardiac troponin molecules from cardiac myocytes.

Myocardial cell regeneration and renewal

Using labeled radioisotopes (14C) embedded in the DNA of myocardial cells, some researchers have been able to reveal cardiomyocyte renewal (regeneration) and the fact that intensity of renewal decreases with age. Thus, 1% of cardiomyocytes are renewed in a person aged 25 or less per year, while in a person aged 75 it is 0.45%. According to the authors, about half of human cardiomyocytes are renewed during the whole life [122]. It is assumed that the process of cardiomyocyte renewal is associated with the release of cardiac troponin molecules from the cytoplasm of cardiomyocytes into the bloodstream, but it is still unknown how it occurs [122-128]. It is conceivable that troponin molecules would be released from progressively naturally aging and dying cardiomyocytes. This mechanism may explain the presence of normal (less than the 99th percentile) serum levels of cardiac troponins determined by high-sensitivity immunoassays in all healthy individuals. However, it is worth noting that the data on the presence of cardiac muscle tissue regeneration are contradictory and denied by a number of authors [129-131]. Therefore, additional studies are needed to validate this mechanism of troponin release.

Increased permeability of the cell membrane of cardiac myocytes

An increase in the permeability of a membrane of any human cell is associated with the release of cytoplasmic contents and particularly various molecules that can be used as specific biomarkers of certain diseases. Increased permeability of the cell membrane of cardiomyocytes may develop as a result of two main mechanisms: 1) Damage of cell membranes by proteolytic enzymes, the activity of which may increase already in short-term myocardial ischemia; 2) As a result of myocardial tissue distension.

Short-term myocardial ischemia can occur in such conditions as strenuous exercise, psycho-emotional stress, sepsis (as a result of increased myocardial oxygen demand) and ischemic heart disease (due to reduced oxygen delivery to cardiac myocytes). At the same time, the extent of cardiac troponins increase by this mechanism will depend on the strength of the physiological/pathological process. Thus, in minor or reversible (short-term) ischemia that develops during physical

exercise and psychoemotional stress, the extent of troponin increase is less significant than in sepsis or AMI. This is probably associated with the release of only cytoplasmic (free) fraction of cardiac troponins (troponin proteins that are freely localized in cell cytoplasm) from cardiomyocytes. The amount of this fraction of cardiac troponins is relatively small (about 3.5% of the total intracellular content of cardiac troponins), so the extent of increase in these conditions will also be small. However, if the ischemia is more prolonged and severe (such as in severe sepsis or AMI), the activity of proteolytic enzymes will be greater, leading to the cleavage of the structural fraction of troponins (proteins that are part of the troponin-tropomyosin complex) and consequently to a greater release of troponin molecules from cardiomyocytes.

The second mechanism of cardiac troponins release is associated with an increase in myocardial load and distension. Researchers have established the relationship between myocardial overload and increased levels of cardiac troponins [132-135]. There is some similarity with the release of natriuretic peptides from the myocardium during myocardial distension which occurs during distension and overload of the heart muscle such as in heart failure. The extent of release of cardiac troponin and natriuretic peptide molecules from cardiomyocytes in heart failure depends on the extent of distension and the stage of the pathological process. Therefore, patient prognosis is assessed by the level of these biomarkers [10]. The specific molecular mechanisms by which cardiac troponins are released from the myocardium during overload and distension are unknown. Some researchers believe that integrin molecules play one of the major roles in this mechanism. These are transmembrane glycoproteins that bind intracellular and extracellular space. Activation of these proteins is associated with myocardial distension. In their study, Hessel et al demonstrated that activation of integrins leads to increased levels of cardiac troponin I. At the same time, troponin release was not associated with ischemic and necrotic changes in the myocardium, because lactate and lactate dehydrogenase levels were normal and the histological pattern of myocardium in microscopy did not differ from controls [135].

Troponin release from cardiomyocytes by vesicular transport

This possible mechanism of release of cardiac troponin molecules from cells has been described in experimental studies performed *in vitro* on isolated hepatocytes and cardiomyocytes of laboratory animals. The researchers found that membrane vesicles are formed on the surface of hepatocytes and cardiomyocytes. When cardiomyocyte ischemia is induced, the number of membrane vesicles increases considerably [101]. It is assumed that these vesicles contain cytoplasmic proteins including molecules of cytoplasmic fraction of cardiac troponins. Thus, a small amount of the cytoplasmic fraction may be released into blood serum via a vesicular mechanism and the extent of molecule release increases with increasing ischemia which agrees well with the concept of a biphasic increase in cardiac troponin levels observed during the development of AMI. So, the first peak of troponin concentration in AMI is associated with the release of the entire cytoplasmic fraction of cardiac troponins, while the second peak of concentration is associated with the subsequent slower processes of cardiomyocyte cell membrane disruption and proteolytic cleavage of the structural fraction of troponins which are the part of the sarcomere. In the same physiological and some pathological conditions in which the damaging factor is removed (e.g., cessation of physical activity), only the cytoplasmic fraction of troponins is released as a result of vesicular transport. Therefore, the extent of increase in lower serum levels is much less significant and the duration of circulation of increased levels is shorter accordingly.

Troponin molecules proteolytic degradation processes

The size of a molecule is one of the key factors determining its capability to pass through the cell membrane. Thus, many low molecular mass compounds are much more intensively transported across the cell membrane. This is confirmed by the fact that the concentration of smaller protein molecules (e.g., myoglobin) increases considerably earlier in blood serum during the development of AMI, while the levels of larger protein molecules (e.g., lactate dehydrogenase) increase considerably later [136, 137]. Activity of intracellular proteolytic enzymes is the additional factor that can affect the rate and extent of release of a particular cardiac marker protein molecule. These enzymes cause the cleavage of cardiac marker molecules into smaller fragments which can probably enable the latter to pass even through the intact cell membrane. The activity of certain proteolytic enzymes can be influenced by a number of factors such as increased myocardial load, changes in the acidity (pH) of intracellular environment intake of medications that can block or activate these enzymes and a number of other factors. For example, in the experiment by Feng et al it was found that increased left ventricular myocardial preload increases activation of the intracellular enzyme calpain which enhances proteolytic cleavage of cardiac troponin I. This can lead to an increase in its concentration in blood serum. In this experiment, increased activation of calpain and increased cleavage of troponin I were not associated with myocardial ischemia. This was confirmed by normal lactate levels. After elimination of experimentally induced myocardial overload, the researchers noted a decrease in calpain activity, a decrease in troponin I degradation and normalization of left ventricular functional activity. Similar changes were also noted with calpeptin administration which is a specific inhibitor of calpain [102]. In addition to the role of this mechanism in the release of troponin I molecules from the myocardium an important pathophysiological significance can be noted. Since troponin I plays an important role in the regulation of myocardial contraction and relaxation, the cleavage (damage) of this protein by calpain can further impair myocardial function. This would contribute to the pathogenesis of heart failure. Thus, calpain can be considered as a target for the development of therapeutic agents that could potentially have important clinical significance.

Another interesting mechanism by which the proteolytic cleavage activity of cardiac troponins is enhanced involves changes in the acidity (pH) of the intracellular environment

[138, 139]. Cardiac muscle cells together with liver and kidney cells maintain the acid-base balance of the human body. Their important function is the utilization of lactate which is a product of anaerobic metabolism of other cells such as red blood cells, myosymplasts of skeletal muscle tissue, etc. During normal metabolism, lactate enters hepatocytes as well as myocardial and renal cells, where by the enzyme lactate dehydrogenase it is converted to pyruvate which can then be converted to glucose (Cori cycle) by gluconeogenesis. Some pyruvate can be converted into acetyl coenzyme A which will be further metabolized in mitochondria in the tricarboxylic acid cycle (Krebs cycle) [139, 140]. However, this pathway (aerobic pathway) depends on oxygen and its functioning may be impaired under conditions of myocardial ischemia. As a result of myocardial ischemia, Krebs cycle functioning is impaired and myocardial cells will be forced to switch to anaerobic metabolism. This process will be accompanied by increased lactate formation [140-142]. Thus, under conditions of cardiomyocyte ischemia, acid-base equilibrium will be considerably disturbed. Accumulation of lactate in myocardial cells will lead to acidosis of intracellular environment which is a trigger mechanism for activation of several proteolytic enzymes (e.g., matrix metalloproteinases) and apoptotic enzymes (e.g., caspases), which can cleave cardiac troponin molecules and contribute to release of reduced troponin fragments from cell into blood serum. It should also be noted that with marked activation of proteolytic and apoptotic enzymes, in addition to cleavage of troponin molecules there is likely to be cleavage of protein molecules that are part of the cell membrane. Due to this fact membrane permeability will increase and further contribute to the release of cardiac troponins. Thus, the mechanism of proteolytic cleavage of troponins is closely related to the mechanism of increased membrane permeability. The severity of pathological processes will be related to the activity of these two mechanisms and consequently to the extent of increase in cardiac troponin levels. For example, during physical exercise and psycho-emotional stress the extent of increase in cardiac troponin levels is relatively small which suggests small-scale (subclinical) and reversible damage to cardiomyocytes without further consequences significant for the morphology and function of the heart muscle. The data of magnetic resonance imaging with contrasting gadolinium preparations also testify to it. Thus, no signs of necrosis and cardiosclerosis were detected in athletes [143]. Nevertheless, regular (constant) myocardial damage as even a result of physiological factors (physical loads, stressful situations) can be dangerous for human health as noted in the works of several researchers [29, 144-147]. When using high-sensitivity troponins, the possibility of cardiac troponins elevation in these physiological conditions should be taken into account and should be clarified in patients while taking the history in order to reduce the risk of AMI overdiagnosis [148].

Extracardiac expression of cardiac troponin molecules and troponin release from skeletal muscle tissues

Extracardiac expression is worth noting as another possible but most controversial mechanism of increased cardiac troponin levels. According to this mechanism, there is a possibility of expression of cardiac troponin molecules in skeletal muscle tissue in case of chronic kidney failure and a number of hereditary myopathies. Thus, several independent research groups have used polymerase chain reaction and Western blotting to detect cardiac troponin T protein molecules and cardiac troponin T informational (matrix) RNA in the skeletal muscle of patients suffering from end-stage chronic kidney failure [149]. However, it has not yet been scientifically proven that cardiac troponin T molecules expressed in skeletal muscle can be released into the bloodstream in amounts sufficient for their detection by troponin immunoassays. Two research groups led by Messner et al [150] and Jaffe et al [151] found evidence of cardiac troponin T expression in the skeletal muscles of patients who suffered from various myopathies (Duchenne muscular dystrophy, sarcoglycanopathy, facioscapulohumeral muscular dystrophy and other hereditary myopathies). The researchers found no evidence of cardiovascular diseases but noted elevated serum levels of cardiac troponins in these patients [150, 151]. This suggests that cardiac troponins expressed in skeletal muscle can be released into blood serum and cause elevated cardiac troponin concentrations in blood serum. Thus, to avoid diagnostic errors, practitioners and researchers should take into account the possibility of extracardiac expression of cardiac troponin T and nonspecific increases of concentration in some inherited skeletal muscle pathologies. However, other investigators in their manuscript have not confirmed the presence of cardiac troponin expression in skeletal muscles in case of hereditary myopathies and believe that elevated cardiac troponin levels in skeletal muscle diseases are only due to false-positive reactions [152] – the interactions of anti-cTn antibodies with skeletal troponin molecules released from myosymplasts during their alteration.

In general, the possible mechanisms of cardiac troponin release are presented in Table 3 [4, 15, 95, 96, 101, 102, 108-111, 122-124, 132-135, 149-153].

Conclusions

On the basis of this review, I can conclude about the important role of cardiac troponin metabolism in the diagnosis of cardiovascular diseases including AMI; differential diagnosis of cardiovascular diseases and several extracardiac diseases that cause an increase in cardiac troponin levels or affect the circulation and elimination of cardiac troponins from the bloodstream. However, it should be noted that existing data on cardiac troponin metabolism are extremely scarce and further research is required. There is a need to focus on studying the specific mechanisms of cardiac troponin release and to establish their exact role in troponin release in certain diseases and physiological conditions. So, today, the only established mechanism for increasing cardiac troponins in humans is myocardial necrosis. All other mechanisms are hypothetical and very difficult to prove in humans. So, hypothetically, there are seven other potentially possible mechanisms for the release of troponin molecules from the myocardium. These mechanisms

Table 3. Possible Mechanisms of Cardiac Troponin Release From Myocytes

Mechanism of cardiac troponin release	Brief description of the mechanism	Literature source
Cardiomyocyte necrosis	Cell necrosis is accompanied by destruction of the cell membrane. This will contribute to the release of all cytoplasmic components from the cell into the blood serum	[4, 15]
Myocardial cell apoptosis	Cardiomyocyte apoptosis develops as a result of several factors (short-term myocardial ischemia, myocardial distension, increased activity of neurohumoral (sympathoadrenal) system) and may be accompanied by a significant increase in cardiac troponin levels. Small-scale apoptotic processes are possible in healthy people as a result of excessive activity of several factors (physical exercise, psycho-emotional stresses)	[95, 96, 108-111]
Myocardial cell regeneration and renewal	According to some researchers, a small part of cardiomyocytes can be renewed (replaced). Gradual death of senescent cardiomyocytes may result in the release of small amounts of cardiac troponin molecules into blood serum. This explains the normal levels of high-sensitivity troponins (less than the 99th percentile) in all healthy individuals.	[96, 122-124]
Increased permeability of the cell membrane of cardiac myocytes	The extent of cell membrane permeability is an important factor that determines whether intracellular molecules can be released from the cell to the outside. Cell membrane permeability is influenced by the following factors: 1) Myocardial ischemia which causes activation of proteolytic enzymes that can damage the plasma membrane; 2) Proteolytic enzyme activity which depends on the severity of the pathological process or the nature of the physiological factor; 3) Increased loading and distension of cardiac muscle tissue.	[10, 132-135]
Troponin release from cardiomyocytes by vesicular transport	According to this mechanism, cardiac troponin molecules can escape outside the cells as part of membrane vesicles. The activity of vesicular transport depends on the degree of ischemia: vesicular transport of troponins increases with ischemia induction. Only the cytoplasmic fraction of troponins can be released as part of vesicles in physiological conditions. This explains the small extent of troponins increase in blood serum.	[101]
Troponin molecules proteolytic degradation processes	The size of the molecule is considered as a factor influencing its capability to be released through the cell membrane; smaller molecules are released earlier and faster compared to larger molecules. A number of proteolytic enzymes (calpain, matrix metalloproteinases) can be activated under certain physiological and pathological conditions and catalyze the degradation of cardiac troponin molecules into small fragments that will contribute to their passage through the plasma membrane. This mechanism may be combined with a mechanism of increasing membrane permeability, especially when the degree and severity of the damaging factor (e.g., ischemia, myocardial stress) is significant.	[102]
Extracardiac expression of cardiac troponin molecules and troponin release from skeletal muscle tissues	This mechanism is quite controversial and requires further research for validation. According to several authors, cardiac troponin molecules can be expressed in skeletal muscle of patients under certain conditions (kidney failure, inherited myopathies) and then released from skeletal muscle, causing increased cardiac troponin levels in blood serum.	[149-152]

can cause an increase in serum levels of cardiac troponins in patients suffering from various pathologies that negatively affect myocardial cells. Fundamental research is needed to study and validate these mechanisms of cardiac troponin release and to establish their specific diagnostic role.

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Conflict of Interest

The author declares the absence of a conflict of interest.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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