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REVIEW ARTICLE

An Overview on the Mechanisms of Myocardial Damage in Hypertension and the Diagnostic Contribution of Cardiospecific Troponins T and I

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Abstract:

Hypertension (HT) is one of the most common cardiovascular (CV) pathologies and a key risk factor for the development of CV disease and its complications. There are two main etiopathogenetic types of HT: primary and secondary. As a result of HT, damage to many organs (heart, blood vessels, retina, *etc*.) can occur. These organs are considered the main target organs in HT and assessment of their condition plays an important role for optimal management of patients with HT. Increased levels of cardiospecific troponins T and I, localized in the main type of myocardial cells (cardiomyocytes), may indicate myocardial damage. At the same time, the degree of myocardial damage may correlate with the degree of increase in cardiospecific troponins T and I. In recent studies, cardiospecific troponins T and I have established themselves as early and highly specific criteria for myocardial damage not only in myocardial infarction, but also in many other cardiac (*e.g.*, arrhythmias, endocarditis, myocarditis, takotsubo syndrome, or cardiomyopathy) and extra-cardiac (*e.g.*, renal failure, sepsis, or diabetes mellitus) conditions. Many authors suggest using cardiospecific troponins T and I as prognostic markers for the above pathologies. Thus, the determination of cardiospecific troponins T and I can provide additional diagnostic advantages in the management of patients with pathological conditions that damage the myocardium. The purpose of this article is to systematize information about the pathogenetic mechanisms of myocardial damage in HT and to consider the diagnostic contribution of cardiospecific troponins T and I for the management of patients with HT.

Keywords: Myocardial damage, Mechanisms, Cardiospecific troponins, Troponin T, Troponin I, Prognosis.

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1. INTRODUCTION

To date, cardiospecific troponins T and I are the most valuable indicators for detecting myocardial damage in acute myocardial infarction and a number of non-infarct diseases (myocarditis, Takotsubo syndrome, cardiomyopathy, *etc*.) [1 - 7].

It is important to note that the diagnostic value of cardiospecific troponins T and I depends, first of all, on the method of their determination and, accordingly, will differ significantly in moderately sensitive and highly sensitive methods. With the development of methods for the determination of cardiospecific troponins T and I, there have been significant changes in the understanding of their biochemistry and diagnostic value. For example, immunoassays of the first and second generation [8, 9] could only detect large-focal acute myocardial infarction and had a pronounced drawback in the form of cross-reactions of diagnostic antibodies (antibodies against cardiospecific troponins T and I) with skeletal troponin molecules [10 - 12]. This circumstance, perhaps, played a decisive role in the formation of erroneous hypotheses regarding the extracardiac expression of cardiospecific troponins T and I in skeletal muscle [13 - 15]. Thus, Schmid *et al*. in a recent study did not confirm the existence of the cardiospecific troponins T and I expression in human striated skeletal muscle [16], which was previously reported by others [13 - 15]. At the same time, the study by Schmid *et al*. showed that the problem of cross-reactivity persisted even with the most modern high-sensitivity troponin immunoassays [16].

Despite the absolute cardio specificity, there are many reasons, both physiological and pathological, which are accompanied by an increase in concentrations of cardiospecific troponins T and I in serum [4, 7, 17]. In general, at this point, it is conditionally possible to distinguish three groups of reasons for the increase in cardiospecific troponins T and I in blood serum, which may not be associated with acute myocardial infarction (Table **1**).

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Table 1. Non-infarct causes of increased cardiospecific troponins in serum.

CARDIAC CAUSES	NON-CARDIAC CAUSES	FALSE CAUSES
Atrial fibrillation	**Sepsis**	**Heterophilic antibodies**
Cardiac surgery	**Renal failure**	**Alkaline phosphatase**
Cardiomyopathy	**Diabetes mellitus**	**Rheumatoid factor**
Heart failure	**Chronic obstructive pulmonary disease**	**Cross-reactions (rhabdomyolysis)**
Takotsubo syndrome	**Heavy physical exercise**	**Haemolysis in serum**
The use of cardiotoxic drugs	**Stroke**	**Fibrin clots in serum**
Cardiac amyloidosis	**COVID-19**	**Macrotroponin**

Table 2. Limit of detection and percentage of "Troponin-positive healthy individuals" in troponin immunoassays.

Troponin Immunoassays	Limit of Detection, ng/	Percentage of "troponin-positive individuals", %
Low sensitivity	500-1000	0
Moderate sensitivity	100-500	<50
High-sensitivity 1st generation	50-100	>50
High-sensitivity 2nd generation	10-50	50-95
High-sensitivity 3rd generation	1-10	<95
High-sensitivity 4th generation ("ultrasensitive")	<1	>95

Among the non-infarct causes of increased cardiospecific troponins, it is particularly worth noting false-positive causes that are caused by a number of mechanisms. Thus, fibrin clots (micro-clots) can form due to incomplete blood clotting before centrifugation. Fibrin clots can nonspecifically affect the specific antigen-antibody interaction during the immunochemical determination of analytes, interact with diagnostic (anti-troponin) antibodies, and cause a false increase in serum levels of cardiospecific troponins [4, 7]. Rheumatoid factor (autoantibodies against their own immunoglobulins G) and heterophilic antibodies can cross-bind either with capture or label antibodies that are part of the troponin immunoassay [7]. Hemolysis of blood serum directly affects the optical density, which is directly proportional to the concentration of cardiospecific troponins [12]. Alkaline phosphatase is an enzyme that is often used in immunochemical methods for detecting cardiospecific troponins to enhance the signal. This enzyme is attached to antibodies (label antibodies) and catalyzes the reaction to form a reaction product (colored solution) after the formation of antigen-antibody complexes and the addition of a substrate. The optical density of the solution is directly proportional to the number of antigen-antibody complexes and, accordingly, the concentration of analytes/antigens (cardiospecific troponins). Increased activity of alkaline phosphatase in the blood serum of patients (for example, in diseases of the liver and biliary tract, *etc*.) may falsely amplify the signal [12]. Macrotroponin (macro-complexes of troponin) are formed as a result of binding of autoantibodies with cardiospecific troponins, which leads to a decrease in clearance of cardiospecific troponins and an increase in their serum concentration. In addition, troponin macrocomplexes can affect antigen-antibody interaction during immunoassay [12].

In addition, before the advent of high-sensitive immunoassays, cardiospecific troponins T and I were considered strictly intracellular molecules, the detection of which in blood serum was considered a diagnostic criterion for acute myocardial infarction [18, 19]. With the appearance of the first high-sensitive immunoassays, cardiospecific troponins T and I began to be detected in a significant number (≥50%) of the examined healthy individuals (high-sensitive immunoassays of the 1st generation). The subsequent improvement of highly sensitive immunoassays led to an even more significant increase in sensitivity ("ultrasensitive") and the ability to detect protein molecules of cardiospecific troponins T and I in almost all examined completely healthy patients [20]. Thus, a large number of healthy individuals became "troponin-positive" (Table **2**). High-sensitivity troponin immunoassays also identified biological features of cardiospecific troponins T and I concentrations, including gender, age, and circadian features [21 - 26].

Thanks to modern methods for the determination of cardiospecific troponins T and I, new possibilities have opened up for the use of these biomarkers in clinical practice. In particular, cardiospecific troponins T and I can be used to assess the risk of cardiovascular (CV) or cerebrovascular diseases and complications (stroke, acute and chronic heart failure, acute myocardial infarction, thromboembolic complications, *etc*.) [26, 27], to determine the prognosis of patients with both cardiac and non-cardiac disease (atrial fibrillation, coronary artery disease, pulmonary embolism, strokes, sepsis, diabetes mellitus, chronic renal failure, oncological diseases and others) [6, 28 - 32], monitoring of cardiotoxic chemotherapy [33 - 37], detection of latent forms of coronary artery disease using stress tests (physical or pharmacological stress) followed by blood sampling and determination of troponins [37 - 40], *etc*. Thus, almost any pathological condition that causes myocardial damage can be diagnosed by cardiospecific troponins T and I.

One of the significant causes of elevated cardiospecific troponins T and I, which deserves special attention, is hypertension (HT). According to the modern classification, there are two main etiopathogenetic types of HT: primary and secondary. HT can damage many organs (heart, blood vessels,

retina, kidneys, brain, *etc*.). These organs are considered the main target organs in HT and assessment of their condition plays an important role for optimal management of patients with HT. Among all the target organs in HT, the most important and frequently affected tissue is the myocardium. This can be detected using high-sensitivity methods for determining cardiospecific troponins T and I [41 - 44].

The purpose of this article is to evaluate information about the pathogenetic mechanisms of myocardial damage in HT and to substantiate the diagnostic contribution of cardiospecific troponins T and I for the management of patients with HT.

HT has a huge impact on quality of life, risk of morbidity, and mortality rates worldwide [41]. HT is the cause of about 54% of strokes and 47% of coronary artery disease cases each year [42]. As a result, in 2013, HT was recognized as the number one risk factor associated with mortality in the world population [43]. Moreover, the prevalence of HT in the population may be much higher than is currently believed. Many patients with high blood pressure, as a rule, may not be aware, which raises particular concerns. Thus, according to a study, 2% of people from the general healthy population (n=1097, age: 16-92, males: 49%) had blood pressure >180/110 mmHg and did not know about it [41].

2. CARDIOSPECIFIC TROPONINS T AND I IN HT: EVIDENCE FROM CLINICAL STUDIES

In most cases, elevated cardiospecific troponins T and I levels are not always indicative of acute myocardial infarction [44 - 46]. For example, a study [44] retrospectively analysed the main reasons for the increase in cardiospecific troponin T in patients (n=1573) who were admitted to the emergency department with complaints of chest pain. Of these, only 175 patients had an acute myocardial infarction, while in 1389 individuals, the reasons for the increase in cardiospecific troponin T were not associated with acute myocardial infarction. The most significant reasons for the increase in cardiospecific troponin T were heart failure, renal failure, diabetes mellitus, stroke, HT, and others. The authors also reported that, in 30% of cases, the cause of the cardiospecific troponin T increase remained unknown. It can be assumed that some of these cases were due to false positive results and subclinical myocardial injuries in other pathologies [44, 46].

In recent studies, HT is also mentioned as a significant non-infarct cause of increased serum levels of cardiospecific troponins T and I [47, 48].

Harvell *et al*., while conducting an analysis of the reasons for the increase in cardiospecific troponin I, found that HT ranks 4th among the reasons for an increase in cardiospecific troponin I (after acute myocardial infarction, infectious and renal diseases) [49]. Afonso *et al*. in their retrospective analysis, which included 576 patients with HT, found that cardiospecific troponin I was increased in 32% of them with an average peak level of 4.06 ± 14.6 ng/ml. The authors also found that compared with the patients with normal cardiospecific troponin I levels, patients with increased cardiospecific troponin I concentrations were older, had a lower left ventricular ejection fraction, a higher heart rate, and a higher prevalence of diabetes mellitus and pulmonary oedema [50].

According to different studies, the degree of increase in the level of cardiospecific troponins and troponin-positive patients with HT may differ significantly. This probably depends on the sensitivity of the methods used for determining cardiospecific troponins, the degree of increase in blood pressure and the presence of concomitant diseases among the participants. Thus, Acosta *et al*., found that only 15% of patients with HT had an increase in cardiospecific troponin T concentration above the upper reference level or the 99th percentile (>15 ng/L) [51]. Elevated cardiospecific troponins in HT predict long-term adverse CV outcomes [52 - 54]. So, according to Patanshetty *et al*. major adverse cardiac or cerebrovascular events (MACCE) (combination of myocardial infarction, unstable angina, hypertensive crisis, pulmonary oedema, stroke, or transient ischaemic attack) developed during the 2-year follow-up period much more often in those HT patients who had an elevated cardiospecific troponin I level (71%), compared with patients who had a cardiospecific troponin I level within normal limits (38%) ($p<0.01$). In addition, patients with elevated cardiospecific troponin I levels were also more likely to have obstructive coronary artery disease (odds ratio = 8.97; 95% confidence interval = 1.4-55.9; $p<0.01$) [52]. In another retrospective cohort study [53], which included 929 patients with HT, an increased level of cardiospecific troponin I was recorded in about a third of patients. At the same time, patients with elevated cardiospecific troponin I levels more often developed adverse events such as acute myocardial infarction (66% *vs* 34%; odds ratio = 4.74; confidence interval = 2.74-8.20 $p<0.001$) and pulmonary oedema (50 *vs* 30%; odds ratio = 2.31; confidence interval = 1.24-4.30, $p=0.007$). Even after adjusting for relevant covariates (gender, race, history of diabetes mellitus, coronary heart disease and heart failure), the predictive value of cardiospecific troponin I in the detection adverse events remained significant [53]. According to Omondi *et al*., the prevalence of elevated cardiospecific troponin T levels in HT patients is quite low, amounting to only 7%. During the mean follow-up periods of 6 months and 1 year, mortality in the group of patients with elevated cardiospecific troponin T levels was 27% and 32%, respectively, while in the group of patients with normal cardiospecific troponin T concentrations it was only 5 and 8%, respectively. According to statistical analysis, compared with patients with normal cardiospecific troponin T levels, patients with HT and elevated cardiospecific troponin T have a higher risk of death within 6 months (odds ratio = 6.4; confidence interval = 2.1-19.2) and within 1 year (odds ratio = 3.7; confidence interval = 1.4-9.8) ($p<0.01$) [54].

Chronic subclinical myocardial damage detected by high-sensitivity troponin immunoassays may precede the development of HT in the general population [55 - 57]. According to a large study by McEvoy *et al*., which included 6516 healthy people, baseline cardiospecific troponin T concentrations in serum were associated with the risk of developing HT and left ventricular hypertrophy within 6 years [56]. Thus, a laboratory blood test for cardiospecific troponin T can be a useful tool for outpatient monitoring of blood pressure and identifying those patients who should apply measures to prevent HT. In patients with already diagnosed HT, the cardiospecific troponin T level is associated with both left

ventricular hypertrophy and a deterioration in the geometric parameters of the left ventricle [46, 51]. The major results of clinical studies are presented in the summary (Table **3**).

Thus, cardiospecific troponins T and I, determined using high-sensitivity immunoassays, often increase before the development of HT, and have an important prognostic value in HT, making it possible to identify those patients who need more thorough examination and treatment in order to prevent the development of adverse consequences.

The release of cardiospecific troponins T and I from the myocardium indicates damage to contractile cells, which leads to a gradual deterioration of myocardial function, a decrease in the quality of life of patients, and a deterioration in long-term outcomes. Therefore, patients with elevated cardiac-specific troponins are usually more ill, to begin with.

Table 3. The results of clinical studies devoted to the diagnostic contribution of cardiospecific troponins T and I in hypertension.

S.No.	Brief Description of the Experimental Group of Patients	Diagnostic Contribution of Cardiospecific Troponins	References
1	Patients with non-coronary pathologies (elevated concentrations of cardiospecific troponin T, which is not associated with acute myocardial infarction), n=1398	HT is one of the main reasons for an increase in the concentration of cardiospecific troponin T (in about 10% of patients).	Lindner *et al*. [44]
2	Patients with non-cardiac causes of chest pain, n=572	HT is one of the significant predictors of an increase in the concentration of cardiospecific troponin T. In addition, patients with an increased concentration of troponin T had an increased risk of death (odds ratio: 3.0; 95% confidence interval, 0.8-10.6; p=0.02).	Irfan *et al*. [45]
3	Patients with non-infarct increased concentration of cardiospecific troponin I, n=458	HT is one of the frequent causes of increased concentration of cardiospecific troponin I (8% of patients).	Harvell *et al*. [49]
4	Patients with HT, n=567	Elevated levels of cardiospecific troponin I were observed in 186 (32%) hypertensive patients; the mean peak level of troponin I = 4.06 ± 14.6 ng/ml.	Afonso *et al*. [50]
5	Patients with HT, n=467	Increased concentration of cardiospecific troponin I was observed in 15% of patients. Elevated troponin levels were associated with an increased risk of chronic heart failure (odds ratio: 4.28, confidence interval 2.21-8.25) and coronary artery disease (odds ratio: 2.08, confidence interval 1.28-3.36).	Acosta *et al*. [51]
6	Patients with HT, n=236	Increased concentration of cardiospecific troponin I was observed in 56 (24%) hypertensive patients. In addition, in patients with HT, elevated cTnI confers a significantly greater risk of long-term MACCE (composite of myocardial infarction, unstable angina, hypertensive crisis, pulmonary oedema, stroke or transient ischemic attack), and is a strong predictor of obstructive coronary artery disease (odds ratio: 8.97; 95% confidence interval: 1.4-55.9; p<0.01).	Pattanshetty *et al*. [52]
7	Patients with HT, n=929	289 (31%) patients with HT had an increased concentration of cardiospecific troponin I. Patients with HT and elevated concentrations of cardiospecific troponin I are at higher risk of long-term cardiac events, including myocardial infarction (odds ratio: 4.74; confidence interval 2.74-8.20 p<0.001) and pulmonary oedema (odds ratio: 2.31; confidence interval: 1.24-4.30, p= 0.007).	Talha Ayub *et al*. [53]
8	Patients with HT, n=457	A total number of 34 (7%) patients had elevated levels of cardiospecific troponin T. When compared to patients with normal cardiospecific troponin T levels, patients presenting with HC and elevated cardiospecific troponin T have higher odds of mortality at 6 months (odds ratio: 6.4; 95% confidence interval: 2.1-19.2 and at 1 year (odds ratio: 3.7; 95% confidence interval: 1.4-9.8).	Omondi *et al*. [54]
9	Healthy individuals without signs of HT and cardiovascular pathologies, n=6516	Cardiospecific troponin T (>5 ng/l) was associated with incident HT (odds ratio: 1.29; 95% confidence interval: 1.14-1.47) and risk of left ventricular hypertrophy odds ratio: 5.19; 95% confidence interval: 1.49-18.08).	McEvoy *et al*. [56]
10	Patients with newly diagnosed hypertension, n=306	The highest cardiospecific troponin T values were observed in the concentric hypertrophy group compared with the control, normal geometry, concentric remodelling, and eccentric hypertrophy groups (p<0.05, for all). Also, hs-cTnT values of the eccentric hypertrophy group were higher than the control, normal geometry and concentric remodelling groups (p< 0.05, for all). So, cardiospecific troponin T level is related not only to left ventricular hypertrophy, but also to left ventricle geometry in patients with HT. In addition, cardiospecific troponin T levels may mediate poorer left ventricle geometric patterns of the left ventricle in hypertensive patients.	Uçar *et al*. [57]

Abbreviations: HT, hypertension; MACCE, major adverse cardiac or cerebrovascular events; hs-cTnT, high-sensitivity cardiac troponin T

3. MYOCARDIAL DAMAGE AND MECHANISMS RESPONSIBLE FOR THE INCREASE IN SERUM CARDIOSPECIFIC TROPONINS T AND I IN HT

The mechanisms of myocardial damage and/or increased levels of cardiospecific troponins in HT have not been established. I suggest that the following mechanisms may potentially underlie myocardial damage and/or an increase in cardiospecific troponins T and I in HT:

1. increased membrane permeability due to myocardial overload;

2. ntensification of the processes of proteolytic degradation of cardiospecific troponin molecules inside cardiomyocytes and extracellularly caused by an increase in blood pressure;

3. myocardial hypertrophy caused by increased blood pressure;

4. intensification of the apoptosis processes due to stretching of the myocardium and excessive activation of the adrenergic system;

5. the effect of increased blood pressure on the elimination of troponins by filtration processes in the kidneys [46];

3.1. Influence of Blood Pressure on the Increase in Membrane Permeability of Cardiomyocytes and the Release of Cardiospecific Molecules

The permeability of the cell membrane of cardiomyocytes is an important factor in determining the possibility of the release of intracellular protein molecules (cardio markers) into the extracellular fluid and further into the blood. In the cytoplasm of cardiomyocytes, in addition to the structural pool of troponins, which is an important component of the troponin complex that regulates the processes of contraction and relaxation of cardiac muscle tissue, there is a non-structural (unbound) troponin pool, which is approximately 6-8% for cardiospecific troponin T and 3-4% for cardiospecific troponin I of the total mass of troponin proteins in the cell and does not participate in myocardial contraction [58, 59]. Some believe that the cardiospecific troponin T and cardiospecific troponin I molecules that make up this non-structural fraction can be freely released in completely healthy patients, providing a normal (<99^{th} percentile) baseline serum concentration. With minor and reversible myocardial injuries, which, for example, can be observed during psychoemotional stress [60] and prolonged/heavy sports loads [61], the degree of increase in cardiospecific troponin T and cardiospecific troponin I, as a rule, is insignificant (does not exceed 99 percentile by >3-5 times), in contrast to irreversible damage myocardial tissue, for example, in myocardial infarction.

Presumably, integrins, transmembrane glycoprotein receptors that bind the extracellular matrix with the intracellular cytoskeleton, play an important role in the regulation of myocardial stretching, membrane permeability, and the regulation proteolytic degradation of troponins within cardiomyocytes. According to Hessel *et al*., myocardial overload leads to the stretching and activation of integrins, which function as mechanotransducers [62]. According to the researchers, the stimulation of integrins activates matrix metalloproteinase-2 and calpain-1, leading to proteolytic cleavage of troponin I, as well as an increase in the release of an unbound pool of cardiospecific troponins due to an increase in membrane permeability [62].

3.2. Influence of Blood Pressure on the Processes of Proteolytic Degradation of Cardiospecific Troponins Inside Cardiomyocytes and in the Blood

One of the possible mechanisms for the release of cardiospecific troponins T and I in HT without lethal damage (destruction of the cell membrane) of the cardiomyocyte is the processes of proteolytic degradation of cardiospecific troponin molecules into such small fragments that, presumably, can pass through the intact cell membrane. Thus, it has been shown that mechanical stretching of cardiomyocytes caused by pressure and/or volume overload triggers a cascade of intracellular signals that lead to an increase in the level of intracellular calcium, an increase in the formation of intracellular nitric oxide, and the subsequent activation of intracellular proteinases (matrix metalloproteinase-2, matrix metalloproteinase-14) [63 - 65], which, in their turn, are capable of cleaving the cardiospecific troponin I molecule inside the cell into smaller fragments [66, 67], facilitating their release outside.

In addition to matrix metalloproteinase-2 and matrix metalloproteinase-14, the enzyme calpain-1 may be responsible for the proteolytic degradation of cardiospecific troponin I inside the cell. In an experimental study on isolated rat hearts (Langendorff model), an increase in preload caused pronounced calpain-mediated proteolysis of the cardiospecific troponin I molecule, regardless of myocardial ischemia. Inhibition of calpain-1 activity by a specific synthetic blocker and elimination of the increased preload prevented the degradation of the cardiospecific troponin molecule [64 - 67].

Hypothetically, the concentration of cardiospecific troponins T and I in HT may change due to the cleavage processes of the cardiospecific troponin T and cardiospecific troponin I molecules. Thus, in an experimental study by [68], thrombin, a procoagulant enzyme, causes proteolytic degradation of the full-length cardiospecific troponin T molecule into two small parts (fragments). At the same time, in patients with HT, there is an increased activity of platelets, markers of the coagulation system, including thrombin [69, 70], which can potentially affect the processes of proteolytic degradation of cardiospecific troponin molecules.

The processes of cardiospecific troponin cleavage intra- [63 - 67] and extracellularly [68] lead to a change in the composition and availability of some antigenic determinants, which can be targeted by diagnostic antibodies, which will lead to a change in the concentration of cardiospecific troponin T and cardiospecific troponin I in the blood. This circumstance, perhaps, is the main factor providing the difference in the levels of cardiospecific troponins obtained in the study of the same serum by different test systems. Moreover, the splitting of full-size troponin molecules into smaller fragments will help the latter to pass through the renal and hematosalvarial filter into urine and oral fluid in much larger quantities [71 - 74]. At the same time, on the one hand, the diagnostic value of troponins in blood serum may decrease, since they will be

eliminated more quickly from the blood, and on the other hand, new diagnostic possibilities appear by using biological fluids obtained in a non-invasive way.

3.3. Myocardial Volume Overload and Hypertrophy

HT is accompanied by myocardial overload and its gradual hypertrophy, which correlates with the concentration of cardiospecific troponins in serum [55 - 57, 75]. In several clinical studies, it has been found that higher levels of cardiospecific troponin T, measured with a highly sensitive immunoassay, well below the detection range of standard assays, are associated with cardiac structural abnormalities, including left ventricular hypertrophy (both left ventricular wall thickening and dilation) and left ventricular systolic dysfunction [55 - 57, 75]. These associations were consistent in subgroups of patients who did not suffer from CV diseases and/or had a low risk of developing CV diseases [55].

McEvoy and colleagues studied the possibility of using cardiospecific troponin T to identify individuals at risk of HT and left ventricle hypertrophy. The researchers found that elevated levels of cardiospecific troponin T (>5 ng/L) were associated with the risk of HT (odds ratio: 1.29; 95% confidence interval: 1.14-1.47). In addition, the baseline level of cardiospecific troponin T was also strongly associated with incident left ventricular hypertrophy by electrocardiography over 6 years (adjusted odds ratio: 5.19; 95% confidence interval: 1.49-18.08] for troponin T ≥14 *vs*. <5 ng/l) [56]. In another study, Uçar *et al*. investigated a possible association between cardiospecific troponin T and left ventricle geometric patterns in newly diagnosed hypertensive patients (n=306). According to the echocardiographic examination, four different geometric patterns were determined in all patients with HT by the left ventricle mass index and relative wall thickness. It was found that the highest values of cardiospecific troponin T were observed in the group with concentric hypertrophy compared with the control group, groups with normal geometry, concentric remodelling and eccentric hypertrophy ($p<0.05$ for all). Multivariate regression analysis showed that troponin T was independently associated with left ventricle geometry, as well as left ventricle mass index. Thus, troponin T levels may mediate poorer left ventricle geometric patterns in patients with HT [57].

In addition, in healthy men, the levels of cardiospecific troponins T and I are higher than in women [76 - 79], which was also reflected in the determination of the 99th percentile levels (taken as the upper normal level) in almost all currently known high-sensitivity immunoassays [78]. Higher levels of cardiospecific troponins T and I and creatine kinase in men, according to researchers, are associated with greater myocardial mass [76, 77].

3.4. Stretching of the Myocardial Wall, Adrenergic System, and Apoptosis

HT contributes to myocardial overload, causing the stretching of its walls, which in turn intensifies apoptosis. An experimental study showed that myocardial stretching is closely related to the activation of the processes of programmed cell death due to increased oxidative stress (generation of reactive oxygen species) and expression of the Fas protein [80]. Another mechanism that intensifies the processes of apoptosis in HT is the action of the adrenergic system [81 - 86]. In experiments on isolated cultured cardiomyocytes *in vitro*, it was shown that stimulation of beta-adrenergic receptors with norepinephrine [83, 84] and isoproterenol [85] induces apoptosis by cAMP-dependent and NF2-dependent mechanisms, respectively [83 - 85]. Apoptosis, in turn, can lead to a significant increase in cardiospecific troponin levels, even in the absence of cardiomyocyte necrosis [84, 85]. In addition to these data, short-term left ventricular pressure overload simulated in laboratory pigs by intravenous administration of phenylephrine resulted in increased apoptosis, but without signs of necrosis. At the same time, the level of cardiospecific troponin T exceeded the value of the 99th percentile within 30 min; after 1 h the troponin concentration was 856 ± 956 ng/l, and after 24 h the troponin level rose to 1.462 ± 1.691 ng/l [86]. Such a sharp dynamics of an increase in the concentration of cardio markers, which differs from the dynamics of an increase in the levels of biomarkers in acute myocardial infarction, may be due to the absence of blockage of coronary blood flow, which causes the molecules of cardiospecific troponins to enter the general bloodstream faster, in contrast to the persistent occlusion characteristic of acute myocardial infarction.

3.5. Influence of Blood Pressure on Filtration Processes in the Kidneys

Since the concentration of cardiospecific troponin molecules in blood serum is determined not only by the degree of release from cardiomyocytes but also by the degree of their elimination from the bloodstream, the functional state of the kidneys will play an important role in the laboratory diagnostics of CV diseases [87 - 89]. Although chronic renal failure is one of the common causes of an increase in the concentration of cardiospecific troponins not associated with acute myocardial infarction [90], and a lower glomerular filtration rate is associated with higher levels of cardiospecific troponin T [91], cardiospecific troponin molecules were not detected in the urine of each patient, and the diagnostic value in this biological fluid was extremely doubtful [71]. However, with the development of immunochemical methods with increased sensitivity, there have been changes in ideas about the biological value of cardiospecific troponins in urine. In particular, in the study by Pervan *et al*., cardiospecific troponin I was found in the morning urine portion of all 20 examined patients. It is noteworthy that in patients with HT, the mean levels of cardiospecific troponin I were higher compared with healthy individuals (26 *vs* 14 pg/ml, $p=0.045$) [72]. Since blood pressure is one of the key factors that influence glomerular filtration rate, the higher blood pressure characteristic of HT probably intensifies the elimination of cardiospecific troponins from the blood through the renal filter.

4. OPTIONS TO STUDY CARDIOSPECIFIC TROPONINS IN HT IN BIOLOGICAL FLUIDS OBTAINED BY A NON-INVASIVE WAY

As an alternative diagnostic approach for a number of CV diseases, including acute myocardial infarction, heart failure,

and HT, it is possible to use human biological fluids obtained non-invasively [72 - 74, 92 - 100]. In particular, studies have shown that the salivary and urinary levels of cardiospecific troponin I [93 - 95] and brain natriuretic peptide [96, 97] in coronary artery disease or myocardial infarction and heart failure is higher than in healthy patients, respectively. Considering the fact that the cardiospecific troponin I level in the morning urine of hypertensive patients is significantly higher than in the urine of normotensive patients, and antihypertensive drugs lead to a decrease in urinary cardiospecific troponin I concentrations, cardiospecific troponin I measurement is a promising new tool for the diagnostics and monitoring of patients with HT [72]. It has been shown that cardiospecific troponin I values >4.1 pg/ml in morning urine in patients with diabetes are associated with the development of short-term adverse cardiovascular events [98]. Moreover, for such purposes on an outpatient basis, urine examination is more convenient and non-invasive than blood examination [98]. The study of cardiospecific troponin concentration in urine can also be used in pregnant women to detect preeclampsia and assess the severity of myocardial injuries. Researchers propose the development of indicator test strips for the detection of cardiospecific troponins T and I in urine and saliva [99 - 101].

The specific mechanisms by which the cardiospecific troponin T and cardiospecific troponin I molecules pass through the glomerular filter are not conclusively known. Integral protein molecules of cardiospecific troponins are rather large compounds for unimpeded passage through the constituent components of the renal and hematosalvarial barriers. At the same time, troponin molecules are prone to proteolytic degradation, both inside the cardiomyocyte and extracellularly, leading to the formation of many fragments with a lower molecular weight which, apparently, can freely pass through the pores of the glomerular and hematosalvarial barriers [98 - 101]. Further clarification of these mechanisms of proteolytic degradation and elimination, as well as the establishment of factors influencing these processes, is an important task and the subject of further research.

5. FUTURE DIRECTIONS OF FUNDAMENTAL (EXPERIMENTAL) AND CLINICAL STUDIES

The study of the mechanisms of myocardial damage and the diagnostic contribution of cardiospecific troponins T and I in HT is a relatively young research area of cardiology. The development of this direction is closely related to an increase in the sensitivity of methods for determining cardiospecific troponins, which made it possible to detect minor subclinical myocardial damage in the early stages of the development of CV pathologies. Despite the progress made in understanding the mechanisms of myocardial damage and the diagnostic contribution of cardiospecific troponins T and I in HT, further research is needed. Future research directions in this area can be conditionally divided into two groups: 1) fundamental research (on laboratory animals and cell cultures) to clarify the mechanisms of myocardial damage and the mechanisms of release of cardiospecific troponins from the myocardium in HT. In particular, it is necessary to clarify the specific role of each of the proposed mechanisms: membrane permeability, apoptosis, hypertrophy, proteolytic degradation, *etc*. 2) clinical studies to confirm the prognostic value of cardiospecific troponins T and I in patients with HT; associations of cardiospecific troponins levels with other risk factors for HT, electrocardiography and echocardiography data, and the possibility of using cardiospecific troponins levels to assess the risk of HT development and progression. The use of cardiospecific troponins T and I can likely improve the current methods of assessing CV risk in a number of pathologies, including HT [102].

CONCLUSION

HT is one of the most significant causes of myocardial damage and increased serum levels of cardiospecific troponins T and I are not associated with acute myocardial infarction. Determination of high-sensitive cardiospecific troponins in blood serum in HT has a high predictive value, making it possible to identify patients with a higher risk of CV diseases and a number of dangerous complications (acute myocardial infarction, acute and chronic heart failure, pulmonary oedema, stroke, *etc*.). In addition, cardiospecific troponins (>5 ng/l) are associated with left ventricular hypertrophy and the risk of HT in healthy individuals (without signs of CV disease) in the long term. The mechanisms underlying the increase in serum cardiospecific troponins T and I in HT are diverse and include: 1) increased membrane permeability due to myocardial overload; 2) intensification of the processes of proteolytic degradation of cardiospecific troponin molecules inside cardiomyocytes and extracellularly caused by an increase in blood pressure; 3) myocardial hypertrophy caused by increased blood pressure; 4) intensification of the apoptosis processes due to stretching of the myocardium and excessive activation of the adrenergic system; 5) the effect of increased blood pressure on the elimination of troponins by filtration processes in the kidneys. The study of high-sensitivity cardiospecific troponins T and I in biological fluids obtained in a non-invasive way, in particular, in urine, is of considerable interest for the diagnostics and monitoring of HT.

Despite the progress made in understanding the mechanisms of myocardial damage and the diagnostic contribution of cardiospecific troponins T and I in HT, further (fundamental and clinical) research is needed. This is necessary to clarify the specific role of the mechanisms of myocardial damage and the release of troponins from cardiomyocytes and to clarify the diagnostic contribution of cardiospecific troponins T and I in hypertensive patients.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The author declares no conflict of interest financial or otherwise.

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REFERENCES

[1] Thygesen K, Alpert JS, Jaffe AS, *et al.* Fourth universal definition of myocardial infarction (2018). J Am Coll Cardiol 2018; 72(18): 2231-64.
[http://dx.doi.org/10.1016/j.jacc.2018.08.1038] [PMID: 30153967]

[2] Chaulin A. Cardiac troponins: Contemporary biological data and new methods of determination. Vasc Health Risk Manag 2021; 17: 299-316.
[http://dx.doi.org/10.2147/VHRM.S300002] [PMID: 34113117]

[3] Garg P, Morris P, Fazlanie AL, *et al.* Cardiac biomarkers of acute coronary syndrome: from history to high-sensitivity cardiac troponin. Intern Emerg Med 2017; 12(2): 147-55.
[http://dx.doi.org/10.1007/s11739-017-1612-1] [PMID: 28188579]

[4] Chaulin A. Elevation mechanisms and diagnostic consideration of cardiac troponins under conditions not associated with myocardial infarction. Part 1. Life 2021; 11(9): 914.
[http://dx.doi.org/10.3390/life11090914] [PMID: 34575063]

[5] Imazio M, Klingel K, Kindermann I, *et al.* COVID-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart 2020; 106(15): 1127-31.
[http://dx.doi.org/10.1136/heartjnl-2020-317186] [PMID: 32499236]

[6] Nallet O, Gouffran G, Lavie Badie Y. Troponin elevation in the absence of acute coronary syndrome. Ann Cardiol Angeiol 2016; 65(5): 340-5.
[http://dx.doi.org/10.1016/j.ancard.2016.09.006]

[7] Chaulin AM. Elevation mechanisms and diagnostic consideration of cardiac troponins under conditions not associated with myocardial infarction. Part 2. Life (Basel) 2021; 11(11): 1175.
[http://dx.doi.org/10.3390/life11111175] [PMID: 34833051]

[8] Collinson PO. Troponin T or troponin I or CK-MB (or none?). Eur Heart J 1998; 19: N16-24.

[9] Vasatova M, Pudil R, Horacek JM, Buchler T. Current applications of cardiac troponin T for the diagnosis of myocardial damage. Adv Clin Chem 2013; 61: 33-65.
[http://dx.doi.org/10.1016/B978-0-12-407680-8.00002-6] [PMID: 24015599]

[10] Viallon A, Marjollet O, Berger C, *et al.* Troponin I values during rhabdomyolysis in elderly patients admitted to the emergency department. Presse Med 2006; 35(11 Pt 1): 1632-8.
[http://dx.doi.org/10.1016/S0755-4982(06)74871-0]

[11] Punukollu G, Gowda RM, Khan IA, *et al.* Elevated serum cardiac troponin I in rhabdomyolysis. Int J Cardiol 2004; 96(1): 35-40.
[http://dx.doi.org/10.1016/j.ijcard.2003.04.053] [PMID: 15203259]

[12] Chaulin AM. False-positive causes in serum cardiac troponin levels. J Clin Med Res 2022; 14(2): 80-7.
[http://dx.doi.org/10.14740/jocmr4664] [PMID: 35317362]

[13] Apple FS, Ricchiuti V, Voss EM, *et al.* Expression of cardiac troponin T isoforms in skeletal muscle of renal disease patients will not cause false-positive serum results by the second generation cardiac troponin T assay. Eur Heart J 1998; 19: N30-3.

[14] Ricchiuti V, Apple FS. RNA expression of cardiac troponin T isoforms in diseased human skeletal muscle. Clin Chem 1999; 45(12): 2129-35.
[http://dx.doi.org/10.1093/clinchem/45.12.2129] [PMID: 10585344]

[15] Messner B, Baum H, Fischer P, Quasthoff S, Neumeier D. Expression of messenger RNA of the cardiac isoforms of troponin T and I in myopathic skeletal muscle. Am J Clin Pathol 2000; 114(4): 544-9.
[http://dx.doi.org/10.1309/8KCL-UQRF-6EEL-36XK] [PMID: 11026100]

[16] Schmid J, Liesinger L, Birner-Gruenberger R, *et al.* Elevated cardiac troponin t in patients with skeletal myopathies. J Am Coll Cardiol 2018; 71(14): 1540-9.
[http://dx.doi.org/10.1016/j.jacc.2018.01.070] [PMID: 29622161]

[17] Chaulin AM. On the effect of heterophilic antibodies on serum levels of cardiac troponins: A brief descriptive review. Life 2022; 12(8): 1114.
[http://dx.doi.org/10.3390/life12081114] [PMID: 35892916]

[18] Vasile VC, Jaffe AS. High-sensitivity cardiac troponin for the diagnosis of patients with acute coronary syndromes. Curr Cardiol Rep 2017; 19(10): 92.
[http://dx.doi.org/10.1007/s11886-017-0904-4] [PMID: 28840515]

[19] Chaulin AM, Abashina OE, Duplyakov DV. High-sensitivity cardiac troponins: Detection and central analytical characteristics. Cardiovasc Ther Prev 2021; 20(2): 2590.
[http://dx.doi.org/10.15829/1728-8800-2021-2590]

[20] Garcia-Osuna A, Gaze D, Grau-Agramunt M, *et al.* Ultrasensitive quantification of cardiac troponin I by a Single Molecule Counting method: Analytical validation and biological features. Clin Chim Acta 2018; 486: 224-31.
[http://dx.doi.org/10.1016/j.cca.2018.08.015] [PMID: 30110608]

[21] Haeckel R. The influence of age and other biological variables on the estimation of reference limits of cardiac troponin T. Clinical Chemistry and Laboratory Medicine (CCLM) 2018; 56(5): 685-7.
[http://dx.doi.org/10.1515/cclm-2017-1082] [PMID: 29257753]

[22] Chaulin AM, Duplyakov DV. On the potential effect of circadian rhythms of cardiac troponins on the diagnosis of acute myocardial infarction. Signa Vitae 2021.
[http://dx.doi.org/10.22514/sv.2021.050]

[23] Bohn MK, Higgins V, Kavsak P, Hoffman B, Adeli K. High-sensitivity generation 5 cardiac troponin T sex- and age-specific 99th percentiles in the CALIPER cohort of healthy children and adolescents. Clin Chem 2019; 65(4): 589-91.
[http://dx.doi.org/10.1373/clinchem.2018.299156] [PMID: 30737206]

[24] Chaulin AM, Duplyakova PD, Duplyakov DV. Circadian rhythms of cardiac troponins: mechanisms and clinical significance. Russ J Cardiol 2020; 25(3S): 4061.
[http://dx.doi.org/10.15829/1560-4071-2020-4061]

[25] Sigurdardottir FD, Lyngbakken MN, Holmen OL, *et al.* Relative prognostic value of cardiac troponin i and c-reactive protein in the general population (from the Nord-Trøndelag Health [HUNT] Study). Am J Cardiol 2018; 121(8): 949-55.
[http://dx.doi.org/10.1016/j.amjcard.2018.01.004] [PMID: 29496193]

[26] Clerico A, Padoan A, Zaninotto M, Passino C, Plebani M. Clinical relevance of biological variation of cardiac troponins. Clin Chem Lab Med 2021; 59(4): 641-52.
[http://dx.doi.org/10.1515/cclm-2020-1433] [PMID: 33554558]

[27] Willeit P, Welsh P, Evans JDW, *et al.* High-sensitivity cardiac troponin concentration and risk of first-ever cardiovascular outcomes in 154,052 participants. J Am Coll Cardiol 2017; 70(5): 558-68.
[http://dx.doi.org/10.1016/j.jacc.2017.05.062] [PMID: 28750699]

[28] Chaulin A, Duplyakov D. MicroRNAs in atrial fibrillation: Pathophysiological aspects and potential biomarkers. Int J Biom 2020; 10(3): 198-205.
[http://dx.doi.org/10.21103/Article10(3)_RA3]

[29] Ukena C, Kindermann M, Mahfoud F, *et al.* Diagnostic and prognostic validity of different biomarkers in patients with suspected myocarditis. Clin Res Cardiol 2014; 103(9): 743-51.
[http://dx.doi.org/10.1007/s00392-014-0709-z] [PMID: 24781421]

[30] Sheyin O, Davies O, Duan W, Perez X. The prognostic significance of troponin elevation in patients with sepsis: A meta-analysis. Heart Lung 2015; 44(1): 75-81.
[http://dx.doi.org/10.1016/j.hrtlng.2014.10.002] [PMID: 25453390]

[31] Ali SA, Kazmi S, Jalal-Ud-Din M, Qasim MI, Jadoon ZG. Frequency of elevated troponin T in patients of hronic renal failure without clinically suspected acute myocardial infarction. J Ayub Med Coll Abbottabad 2019; 31(3): 364-7.
[PMID: 31535507]

[32] Shah KS, Maisel AS, Fonarow GC. Troponin in heart failure. Heart Fail Clin 2018; 14(1): 57-64.
[http://dx.doi.org/10.1016/j.hfc.2017.08.007] [PMID: 29153201]

[33] Chaulin AM, Abashina OE, Duplyakov DV. Pathophysiological mechanisms of cardiotoxicity in chemotherapeutic agents. Russ Open Med J 2020; 9(3): e0305.
[http://dx.doi.org/10.15275/rusomj.2020.0305]

[34] Ananthan K, Lyon AR. The role of biomarkers in cardio-oncology. J Cardiovasc Transl Res 2020; 13(3): 431-50.
[http://dx.doi.org/10.1007/s12265-020-10042-3] [PMID: 32642841]

[35] Chaulin AM, Duplyakov DV. Arrhythmogenic effects of doxorubicin. Complex Issues of Cardiovascular Diseases 2020; 9(3): 69-80.
[http://dx.doi.org/10.17802/2306-1278-2020-9-3-69-80]

[36] Sorodoc V, Sirbu O, Lionte C, *et al.* The value of troponin as a biomarker of chemotherapy-induced cardiotoxicity. Life 2022; 12(8): 1183.
[http://dx.doi.org/10.3390/life12081183] [PMID: 36013362]

[37] Chaulin AM, Duplyakov DV. Cardioprotective strategies for doxorubicin-induced cardiotoxicity: Present and future. Ration Pharmacother Cardiol 2022; 18(1): 103-12.
[http://dx.doi.org/10.20996/1819-6446-2022-02-11]

[38] Samaha E, Brown J, Brown F, *et al.* High-sensitivity cardiac troponin

T increases after stress echocardiography. Clin Biochem 2019; 63: 18-23.
[http://dx.doi.org/10.1016/j.clinbiochem.2018.11.013] [PMID: 30502318]

[39] Donnellan E, Phelan D. Biomarkers of cardiac stress and injury in athletes: What do they mean? Curr Heart Fail Rep 2018; 15(2): 116-22.
[http://dx.doi.org/10.1007/s11897-018-0385-9] [PMID: 29520707]

[40] Chaulin A, Dupliakov D. Physical activity and cardiac markers: PART 1. *Human. Sport.* Medicine 2022; 22(2): 15-28.
[http://dx.doi.org/10.14529/hsm220202]

[41] Caligiuri SPB, Austria JA, Pierce GN. Alarming prevalence of emergency hypertension levels in the general public identified by a hypertension awareness campaign. Am J Hypertens 2017; 30(3): hpw136.
[http://dx.doi.org/10.1093/ajh/hpw136] [PMID: 28057629]

[42] Lawes CMM, Hoorn SV, Rodgers A. Global burden of blood-pressure-related disease, 2001. Lancet 2008; 371(9623): 1513-8.
[http://dx.doi.org/10.1016/S0140-6736(08)60655-8] [PMID: 18456100]

[43] World Health Organization. A Global Brief on Hypertension: Silent Killer, Global Public Health Crisis. In: WHO/DCO/WHD/2013. 2nd ed.. Geneva, Switzerland: World Health Organization 2013.

[44] Lindner G, Pfortmueller CA, Braun CT, Exadaktylos AK. Non-acute myocardial infarction-related causes of elevated high-sensitive troponin T in the emergency room: A cross-sectional analysis. Intern Emerg Med 2014; 9(3): 335-9.
[http://dx.doi.org/10.1007/s11739-013-1030-y] [PMID: 24326466]

[45] Irfan A, Twerenbold R, Reiter M, *et al.* Determinants of high-sensitivity troponin T among patients with a noncardiac cause of chest pain. Am J Med 2012; 125(5): 491-498.e1.
[http://dx.doi.org/10.1016/j.amjmed.2011.10.031] [PMID: 22482847]

[46] Chaulin A. Clinical and diagnostic value of highly sensitive cardiac troponins in arterial hypertension. Vasc Health Risk Manag 2021; 17: 431-43.
[http://dx.doi.org/10.2147/VHRM.S315376] [PMID: 34366667]

[47] Long B, Long DA, Tannenbaum L, Koyfman A. An emergency medicine approach to troponin elevation due to causes other than occlusion myocardial infarction. Am J Emerg Med 2020; 38(5): 998-1006.
[http://dx.doi.org/10.1016/j.ajem.2019.12.007] [PMID: 31864875]

[48] Masri W, Le Guillou E, Hamdi E, *et al.* Troponin elevation in other conditions than acute coronary syndromes. Ann Biol Clin 2017; 75(4): 411-9.
[http://dx.doi.org/10.1684/abc.2017.1262] [PMID: 28751286]

[49] Harvell B, Henrie N, Ernst AA, *et al.* The meaning of elevated troponin I levels: Not always acute coronary syndromes. Am J Emerg Med 2016; 34(2): 145-8.
[http://dx.doi.org/10.1016/j.ajem.2015.09.037] [PMID: 26508391]

[50] Afonso L, Bandaru H, Rathod A, *et al.* Prevalence, determinants, and clinical significance of cardiac troponin-I elevation in individuals admitted for a hypertensive emergency. J Clin Hypertens 2011; 13(8): 551-6.
[http://dx.doi.org/10.1111/j.1751-7176.2011.00476.x] [PMID: 21806764]

[51] Acosta G, Amro A, Aguilar R, *et al.* Clinical determinants of myocardial injury, detectable and serial troponin levels among patients with hypertensive crisis. Cureus 2020; 12(1): e6787.
[http://dx.doi.org/10.7759/cureus.6787] [PMID: 32140347]

[52] Pattanshetty DJ, Bhat PK, Aneja A, Pillai DP. Elevated troponin predicts long-term adverse cardiovascular outcomes in hypertensive crisis. J Hypertens 2012; 30(12): 2410-5.
[http://dx.doi.org/10.1097/HJH.0b013e3283599b4f] [PMID: 22990357]

[53] Talha Ayub M, Torres C, Del Cid J, *et al.* The prognostic significance of highly sensitive cardiac troponin i elevation in patients presenting with hypertensive crisis. Circulation 2019; 140: A16333.

[54] Omondi A, Spinetto PV, Kargoli F, *et al.* Prevalence and prognostic significance of cardiac troponin-T elevation in patients admitted with hypertensive crises. J Am Coll Cardiol 2017; 69(11): 1803.
[http://dx.doi.org/10.1016/S0735-1097(17)35192-6]

[55] de Lemos JA, Drazner MH, Omland T, *et al.* Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population. JAMA 2010; 304(22): 2503-12.
[http://dx.doi.org/10.1001/jama.2010.1768] [PMID: 21139111]

[56] McEvoy JW, Chen Y, Nambi V, *et al.* High-sensitivity cardiac troponin T and risk of hypertension. Circulation 2015; 132(9): 825-33.
[http://dx.doi.org/10.1161/CIRCULATIONAHA.114.014364] [PMID: 26152706]

[57] Uçar H, Gür M, Kivrak A, *et al.* High-sensitivity cardiac troponin T levels in newly diagnosed hypertensive patients with different left ventricle geometry. Blood Press 2014; 23(4): 240-7.
[http://dx.doi.org/10.3109/08037051.2013.840429] [PMID: 24059745]

[58] Bleier J, Vorderwinkler KP, Falkensammer J, *et al.* Different intracellular compartmentations of cardiac troponins and myosin heavy chains: A causal connection to their different early release after myocardial damage. Clin Chem 1998; 44(9): 1912-8.
[http://dx.doi.org/10.1093/clinchem/44.9.1912] [PMID: 9732976]

[59] Chaulin AM. Cardiac troponins: Current information on the main analytical characteristics of determination methods and new diagnostic possibilities. Medwave 2021; 21(11): e002132.
[http://dx.doi.org/10.5867/medwave.2021.11.002132] [PMID: 34890387]

[60] Lazzarino AI, Hamer M, Gaze D, Collinson P, Steptoe A. The association between cortisol response to mental stress and high-sensitivity cardiac troponin T plasma concentration in healthy adults. J Am Coll Cardiol 2013; 62(18): 1694-701.
[http://dx.doi.org/10.1016/j.jacc.2013.05.070] [PMID: 23810896]

[61] Richardson AJ, Leckie T, Watkins ER, *et al.* Post marathon cardiac troponin T is associated with relative exercise intensity. J Sci Med Sport 2018; 21(9): 880-4.
[http://dx.doi.org/10.1016/j.jsams.2018.02.005] [PMID: 29588114]

[62] Hessel MHM, Atsma DE, van der Valk EJM, Bax WH, Schalij MJ, van der Laarse A. Release of cardiac troponin I from viable cardiomyocytes is mediated by integrin stimulation. Pflugers Arch 2008; 455(6): 979-86.
[http://dx.doi.org/10.1007/s00424-007-0354-8] [PMID: 17909848]

[63] Kandasamy AD, Chow AK, Ali MAM, Schulz R. Matrix metalloproteinase-2 and myocardial oxidative stress injury: Beyond the matrix. Cardiovasc Res 2010; 85(3): 413-23.
[http://dx.doi.org/10.1093/cvr/cvp268] [PMID: 19656780]

[64] Wang W, Schulze CJ, Suarez-Pinzon WL, Dyck JRB, Sawicki G, Schulz R. Intracellular action of matrix metalloproteinase-2 accounts for acute myocardial ischemia and reperfusion injury. Circulation 2002; 106(12): 1543-9.
[http://dx.doi.org/10.1161/01.CIR.0000028818.33488.7B] [PMID: 12234962]

[65] van der Wees CGC, Bax WH, van der Valk EJM, van der Laarse A. Integrin stimulation induces calcium signalling in rat cardiomyocytes by a NO-dependent mechanism. Pflugers Arch 2006; 451(4): 588-95.
[http://dx.doi.org/10.1007/s00424-005-1402-x] [PMID: 16284742]

[66] Feng J, Schaus BJ, Fallavollita JA, Lee TC, Canty JM Jr. Preload induces troponin I degradation independently of myocardial ischemia. Circulation 2001; 103(16): 2035-7.
[http://dx.doi.org/10.1161/01.CIR.103.16.2035] [PMID: 11319190]

[67] Maekawa A, Lee JK, Nagaya T, *et al.* Overexpression of calpastatin by gene transfer prevents troponin I degradation and ameliorates contractile dysfunction in rat hearts subjected to ischemia/reperfusion. J Mol Cell Cardiol 2003; 35(10): 1277-84.
[http://dx.doi.org/10.1016/S0022-2828(03)00238-4] [PMID: 14519437]

[68] Katrukha IA, Kogan AE, Vylegzhanina AV, *et al.* Thrombin-mediated degradation of human cardiac troponin T. Clin Chem 2017; 63(6): 1094-100.
[http://dx.doi.org/10.1373/clinchem.2016.266635] [PMID: 28428352]

[69] Derhaschnig U, Testori C, Riedmueller E, Aschauer S, Wolzt M, Jilma B. Hypertensive emergencies are associated with elevated markers of inflammation, coagulation, platelet activation and fibrinolysis. J Hum Hypertens 2013; 27(6): 368-73.
[http://dx.doi.org/10.1038/jhh.2012.53] [PMID: 23254594]

[70] van den Born BJH, Löwenberg EC, van der Hoeven NV, *et al.* Endothelial dysfunction, platelet activation, thrombogenesis and fibrinolysis in patients with hypertensive crisis. J Hypertens 2011; 29(5): 922-7.
[http://dx.doi.org/10.1097/HJH.0b013e328345023d] [PMID: 21372741]

[71] Ziebig R, Lun A, Hocher B, *et al.* Renal elimination of troponin T and troponin I. Clin Chem 2003; 49(7): 1191-3.
[http://dx.doi.org/10.1373/49.7.1191] [PMID: 12816921]

[72] Pervan P, Svaguša T, Prkačin I, Savuk A, Bakos M, Perkov S. Urine high sensitive Troponin I measuring in patients with hypertension. Signa Vitae 2017; 13(Suppl. 3): 62-4.
[http://dx.doi.org/10.22514/SV133.062017.13]

[73] Maruta T, Li T, Morrissey J, *et al.* 252: Urinary Cardiac Troponin I is Detectable in Patients with Myocardial Injury Using a High-Sensitive Immunoassay. Crit Care Med 2012; 40: 1-328. [http://dx.doi.org/10.1097/01.ccm.0000424470.26633.42]

[74] Mirzaii-Dizgah I, Riahi E. Salivary high-sensitivity cardiac troponin T levels in patients with acute myocardial infarction. Oral Dis 2013; 19(2): 180-4. [http://dx.doi.org/10.1111/j.1601-0825.2012.01968.x] [PMID: 22834943]

[75] Shah ASV, Chin CWL, Vassiliou V, *et al.* Left ventricular hypertrophy with strain and aortic stenosis. Circulation 2014; 130(18): 1607-16. [http://dx.doi.org/10.1161/CIRCULATIONAHA.114.011085] [PMID: 25170097]

[76] Chaulin AM. Gender specificities of cardiac troponin serum levels: From formation mechanisms to the diagnostic role in case of acute coronary syndrome. Life 2023; 13(2): 267. [http://dx.doi.org/10.3390/life13020267] [PMID: 36836623]

[77] Gore MO, Seliger SL, deFilippi CR, *et al.* Age- and sex-dependent upper reference limits for the high-sensitivity cardiac troponin T assay. J Am Coll Cardiol 2014; 63(14): 1441-8. [http://dx.doi.org/10.1016/j.jacc.2013.12.032] [PMID: 24530665]

[78] URL. Available from: https://www.ifcc.org/media/478231/high-sensitivity-cardiac-troponin-i-and-t-assay-analytical-characteristics-designated-by-manufacturer-v122019.pdf

[79] Chaulin A. Gender Characteristics of the Levels of Cardiac Troponins in Blood Serum and the Importance of Using Information About them in the Tactics of Diagnosis of Acute Coronary Syndrome (Literature Review). Laboratory Diagnostics. Eastern Europe. 2022.

[80] Cheng W, Li B, Kajstura J, *et al.* Stretch-induced programmed myocyte cell death. J Clin Invest 1995; 96(5): 2247-59. [http://dx.doi.org/10.1172/JCI118280] [PMID: 7593611]

[81] Chaulin AM, Sergeev AK. The role of fine particles (PM 2.5) in the genesis of atherosclerosis and myocardial damage: Emphasis on clinical and epidemiological data, and pathophysiological mechanisms. Cardiol Res 2022; 13(5): 268-82. [http://dx.doi.org/10.14740/cr1366] [PMID: 36405225]

[82] Chauin A. The main causes and mechanisms of increase in cardiac troponin concentrations other than acute myocardial infarction (Part 1): Physical exertion, inflammatory heart disease, pulmonary embolism, renal failure, sepsis. Vasc Health Risk Manag 2021; 17: 601-17. [http://dx.doi.org/10.2147/VHRM.S327661] [PMID: 34584417]

[83] Singh K, Communal C, Sawyer DB, Colucci WS. Adrenergic regulation of myocardial apoptosis. Cardiovasc Res 2000; 45(3): 713-9. [http://dx.doi.org/10.1016/S0008-6363(99)00370-3] [PMID: 10728393]

[84] Singh K, Xiao L, Remondino A, Sawyer DB, Colucci WS. Adrenergic regulation of cardiac myocyte apoptosis. J Cell Physiol 2001; 189(3): 257-65. [http://dx.doi.org/10.1002/jcp.10024] [PMID: 11748583]

[85] Dalal S, Connelly B, Singh M, Singh K. NF2 signaling pathway plays a pro-apoptotic role in β-adrenergic receptor stimulated cardiac myocyte apoptosis. PLoS One 2018; 13(4): e0196626. [http://dx.doi.org/10.1371/journal.pone.0196626] [PMID: 29709009]

[86] Weil BR, Suzuki G, Young RF, Iyer V, Canty JM Jr. Canty JMJr. Troponin release and reversible left ventricular dysfunction after transient pressure overload. J Am Coll Cardiol 2018; 71(25): 2906-16. [http://dx.doi.org/10.1016/j.jacc.2018.04.029] [PMID: 29929614]

[87] Chaulin A, Duplyakov D. Analytical review of modern information on the physiological and pathochemical mechanisms of the release of cardiospecific proteins from muscle tissue, methodology and technologies of their research, interpretation of the results. Laboratory Diagnostics. Eastern Europe. 2022.

[88] Chaulin AM. Main analytical characteristics of laboratory methods for the determination of cardiac troponins: A review from the historical and modern points of view. Orv Hetil 2022; 163(1): 12-20.

[89] Chaulin AM. Metabolic pathway of cardiospecific troponins: From fundamental aspects to diagnostic role (Comprehensive Review). Front Mol Biosci 2022; 9: 841277. [http://dx.doi.org/10.3389/fmolb.2022.841277] [PMID: 35517866]

[90] Di Lullo L, Barbera V, Santoboni A, *et al.* Troponins and chronic kidney disease. G Ital Nefrol 2015; 32(4): gin/32.4.1.

[91] Dubin RF, Li Y, He J, *et al.* Predictors of high sensitivity cardiac troponin T in chronic kidney disease patients: A cross-sectional study in the chronic renal insufficiency cohort (CRIC). BMC Nephrol 2013; 14(1): 229. [http://dx.doi.org/10.1186/1471-2369-14-229] [PMID: 24148285]

[92] Michailovich CA. Diagnostic role and methods of detection of cardiac troponins: An opinion from historical and current points of view. Curr Cardiol Rev 2023; 19(1): e100622205865. [http://dx.doi.org/10.2174/1573403X18666220610164946] [PMID: 35702796]

[93] Chaulin AM, Duplyakova PD, Bikbaeva GR, *et al.* Concentration of high-sensitivity cardiac troponin I in the oral fluid in patients with acute myocardial infarction: A pilot study. Russ J Cardiol 2020; 25(12): 3814. [http://dx.doi.org/10.15829/1560-4071-2020-3814]

[94] Chaulin AM, Karslyan LS, Bazyuk EV, *et al.* Clinical and diagnostic value of cardiac markers in human biological fluids. Kardiologiia 2019; 59(11): 66-75. [http://dx.doi.org/10.18087/cardio.2019.11.n414]

[95] Bunin VA, Kozlov KL, Linkova NS, Paltseva EM. An increase in troponin-I concentration in the saliva of patients with coronary heart disease correlates with the stage of disease development. Complex Issues of Cardiovascular Diseases 2017; 6(S4): 13-4.

[96] Chaulin AM, Duplyakov DV. Increased natriuretic peptides not associated with heart failure. Russ J Cardiol 2020; 25: 4140. [http://dx.doi.org/10.15829/1560-4071-2020-4140]

[97] Joharimoghadam A, Tajdini M, Bozorgi A. Salivary B-type natriuretic peptide: A new method for heart failure diagnosis and follow-up. Kardiol Pol 2017; 75(1): 71-7. [http://dx.doi.org/10.5603/KP.a2016.0097] [PMID: 27296284]

[98] Chen JY, Lee SY, Li YH, Lin CY, Shieh MD, Ciou DS. Urine high-sensitivity troponin I predict incident cardiovascular events in patients with diabetes mellitus. J Clin Med 2020; 9(12): 3917. [http://dx.doi.org/10.3390/jcm9123917] [PMID: 33276667]

[99] Chaulin AM. Cardiac troponins metabolism: From biochemical mechanisms to clinical practice (Literature Review). Int J Mol Sci 2021; 22(20): 10928. [http://dx.doi.org/10.3390/ijms222010928] [PMID: 34681585]

[100] Potkonjak AM, Sabolović Rudman S, Nikolac Gabaj N, *et al.* Urinary troponin concentration as a marker of cardiac damage in pregnancies complicated with preeclampsia. Med Hypotheses 2020; 144: 110252. [http://dx.doi.org/10.1016/j.mehy.2020.110252] [PMID: 33254557]

[101] Chaulin A. Biology of cardiac troponins: Emphasis on metabolism. Biology 2022; 11(3): 429. [http://dx.doi.org/10.3390/biology11030429] [PMID: 35336802]

[102] Williams B, Mancia G, Spiering W, *et al.* 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J 2018; 39(33): 3021-104. [http://dx.doi.org/10.1093/eurheartj/ehy339] [PMID: 30165516]