The Open Cardiovascular Medicine Journal

Content list available at: https://opencardiovascularmedicinejournal.com

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.

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

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

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

<table>
<thead>
<tr>
<th>Troponin Immunoassays</th>
<th>Limit of Detection, ng/l</th>
<th>Percentage of “troponin-positive individuals”, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low sensitivity</td>
<td>500-1000</td>
<td>≤1</td>
</tr>
<tr>
<td>Moderate sensitivity</td>
<td>100-500</td>
<td>&lt;50</td>
</tr>
<tr>
<td>High-sensitivity 1st generation</td>
<td>50-100</td>
<td>&gt;50</td>
</tr>
<tr>
<td>High-sensitivity 2nd generation</td>
<td>10-50</td>
<td>50-95</td>
</tr>
<tr>
<td>High-sensitivity 3rd generation</td>
<td>1-10</td>
<td>&lt;95</td>
</tr>
<tr>
<td>High-sensitivity 4th generation (“ultrasensitive”)</td>
<td>&lt;1</td>
<td>&gt;95</td>
</tr>
</tbody>
</table>

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 number of antigen-antibody complexes and, accordingly, the concentration of analytes/antigens (cardiospecific troponins). Increased activity of alkaline phosphatase in the blood of patients (for example, in diseases of the liver and biliary tract, etc.) may falsely amplify the signal [12]. Macrotrroponin (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,
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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=0.001) [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 of 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.

<table>
<thead>
<tr>
<th>S.No.</th>
<th>Brief Description of the Experimental Group of Patients</th>
<th>Diagnostic Contribution of Cardiospecific Troponins</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patients with non-coronary pathologies (elevated concentrations of cardiospecific troponin T, which is not associated with acute myocardial infarction), n=1398</td>
<td>HT is one of the main reasons for an increase in the concentration of cardiospecific troponin T (in about 10% of patients).</td>
<td>Lindner et al. [44]</td>
</tr>
<tr>
<td>2</td>
<td>Patients with non-cardiac causes of chest pain, n=572</td>
<td>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).</td>
<td>Irfan et al. [45]</td>
</tr>
<tr>
<td>3</td>
<td>Patients with non-infarct increased concentration of cardiospecific troponin I, n=458</td>
<td>HT is one of the frequent causes of increased concentration of cardiospecific troponin I (8% of patients).</td>
<td>Harvell et al. [49]</td>
</tr>
<tr>
<td>4</td>
<td>Patients with HT, n=567</td>
<td>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.</td>
<td>Afonso et al. [50]</td>
</tr>
<tr>
<td>5</td>
<td>Patients with HT, n=467</td>
<td>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).</td>
<td>Acosta et al. [51]</td>
</tr>
<tr>
<td>6</td>
<td>Patients with HT, n=236</td>
<td>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&lt;0.01).</td>
<td>Pattanshetty et al. [52]</td>
</tr>
<tr>
<td>7</td>
<td>Patients with HT, n=929</td>
<td>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 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&lt;0.01).</td>
<td>Talha Ayub et al. [53]</td>
</tr>
<tr>
<td>8</td>
<td>Patients with HT, n=457</td>
<td>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).</td>
<td>Omondi et al. [54]</td>
</tr>
<tr>
<td>9</td>
<td>Healthy individuals without signs of HT and cardiovascular pathologies, n=6516</td>
<td>Cardiospecific troponin T (&gt;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).</td>
<td>McEvoy et al. [56]</td>
</tr>
<tr>
<td>10</td>
<td>Patients with newly diagnosed hypertension, n=306</td>
<td>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&lt;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.</td>
<td>Uçar et al. [57]</td>
</tr>
</tbody>
</table>

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 TROPNINS 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. 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 [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 (<99th 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 dilatation) 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 immunochromic 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 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, future 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

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The author declares no conflict of interest financial or otherwise.
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