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REVIEW ARTICLE

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Mechanisms for Cardiac Troponin Increase in Arterial Hypertension

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Abstract

Despite the fact that cardiac troponins (cTnI and cTnT) are cardiospecific, they can be elevated in many systemic and non-cardiac physiological and pathological conditions. The diagnostic value of cTnI and cTnT significantly depends on the method of their determination. Thus, previously used low- and moderate-sensitivity immunoassays detected only serious myocardial damage and did not determine troponins in patients suffering from certain chronic pathologies. High-sensitivity troponin assays can detect minor damage to cardiac muscle cells in many pathological conditions, and troponin levels have a high predictive value. Among the early pathological conditions requiring the attention of clinicians is arterial hypertension (AH), which is also accompanied by an increase in the levels of hsTn in serum and urine. Currently, mechanisms responsible for increased levels of cardiac troponins in the blood serum and urine in hypertension are not well covered in the scientific literature. This article discusses in detail the presumptive mechanisms that cause increased levels of cTnI and cTnT in AH.(**International Journal of Biomedicine. 2021;11(4):397-402.**)

Key Words: cardiac troponins • cardiovascular disease • arterial hypertension • glomerular filtration rate

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Abbreviations

AH, arterial hypertension; **AMI**, acute myocardial infarction; **CVD**, cardiovascular disease; **cTnT**, cardiac troponin T; **cTnI**, cardiac troponin I; **GFR**, glomerular filtration rate; **hsTn**, high-sensitivity troponin; **MMP2**, matrix metalloproteinase-2; **Tn**, troponin; **TnT**, troponin T.

The cardiac troponin (cTn) complex is a critical regulator of cardiac muscle contraction. cTn is composed of three distinct subunits named according to their functions: a highly conserved Ca^{2+} binding subunit (cTnC); an actomyosin ATPase inhibitory subunit (cTnI), and a tropomyosin binding subunit (cTnT).[1,2] The importance of cTn in the regulation of myocardial function is evidenced by the fact that mutations causing changes in the amino acid sequence in cTnI, cTnT, cTnC are accompanied by significant and life-threatening disorders of the contractile function of the cardiac muscle, and in particular, hereditary cardiomyopathies.[3-5] The amino acid composition of cTnC is similar to the amino acid composition of TnC in skeletal muscle fibers; therefore, this protein is not used as a biomarker of AMI. On the contrary, the amino acid composition of cTnI and cTnT is unique, giving them the necessary specificity, which is very important for use in AMI diagnosis.[6-8] In addition to the specific structure of the protein, the features of determination methods play an important role in laboratory diagnostics, which are constantly being improved and change our understanding of the biology and diagnostic value of many biomarkers, including cTnI and cTnT.[6-10] For example, the methods for determining cTnI and cTnT, originally developed by Cummins and Katus,[11-13] were characterized by low sensitivity and specificity, which was manifested by the relatively late detection of diagnostically

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significant concentrations in AMI patients and a significant number of nonspecific (cross) reactions of anti-cTnI and anti-cTnT antibodies with troponins released from damaged skeletal muscle fibers during rhabdomyolysis and/or exercise.[14-16]

The use of hs-cTn assays showed that the levels of cTnI and cTnT depend on a number of biological factors, including gender, age, and circadian characteristics.[17-20] The gender peculiarities of the levels of cTnI and cTnT are that the serum levels of the latter are significantly higher in men than in women, which is typical for almost all high-sensitivity immunoassays currently used. By analogy with another cardiac-specific enzyme (creatine kinase) and creatinine, a product of protein metabolism, the gender differences in troponin concentrations are due to a higher mass of striated muscles, including cardiac muscles, in males.[6,17] Age-related features of the levels of cTnI and cTnT are characterized by higher levels of troponins in elderly patients than in young patients and, most likely, are associated with the presence of chronic latent comorbid pathologies that cause subclinical lesions of cardiomyocytes.[6,21-23] Circadian features consist in the predominance of morning levels of troponins over evening ones, which is explained by the increased activity of a number of systems of the human body. The increased activity of these systems is an evolutionarily developed adaptive mechanism necessary for a healthy person for the period of wakefulness;[24] however, these systems also have a negative effect on myocardial cells.[25] It should be noted that a number of studies using high-sensitivity immunoassays have shown that cTnI and cTnT can be determined not only in blood serum, but also in urine and saliva,[26-31] and the levels of cTnI and cTnT significantly differ between the patient groups and healthy individuals. In the future, the indicated scientific data will allow the development of new diagnostic approaches. In particular, the idea of creating test strips to determine cTnI and cTnT in non-invasively obtained biological fluids has been proposed.[32]

High-sensitivity methods for determining cTnI and cTnT have demonstrated that cardiomyocytes are extremely sensitive to any kind of damage, and the concentration of cTnI and cTnT can increase in many pathological and physiological conditions (Table 1). Moreover, even in healthy patients, cTnI and cTnT are released from cardiomyocytes, but their concentration, as a rule, does not exceed the 99th percentile.[9] The mechanisms underlying the cTnI and cTnT release from cardiomyocytes and, accordingly, their increase in serum in healthy patients, have not been conclusively established.

Currently, there are a considerable number of review articles that discuss in detail the mechanisms for increasing cTnI and cTnT in many cardiac (myocarditis, cardiomyopathy, heart failure, arrhythmias)[32-35] and non-cardiac pathologies; (sepsis, exercise, renal failure, cancer, the use of chemotherapeutic drugs)[46-39] however, AH is rarely discussed in this respect. The purpose of this article was to review some hypothetical mechanisms for increasing cTnI and cTnT in human biological fluids.

Mechanisms responsible for increased levels of cTnI and cTnT in AH

Although the molecules of cardiac troponins, taking into account their molecular weight (cTnI-25 kDa, cTnT-37 kDa), are low-molecular-weight proteins; whole molecules cannot pass through the intact membrane of cardiomyocytes. However, like any protein molecules, cTnT and cTnI are extremely sensitive to the action of proteases, which can be activated under certain pathological conditions. According to the results of experimental studies, stretching of the cardiac muscle tissue, oxidative stress, and ischemia of cardiomyocytes lead to the activation of MMP2, which, in turn, cleaves the cTnI molecule into small peptide fragments that can pass through the cardiomyocyte membrane into the extracellular space and, further, into the blood.[40-42] Another intracellular enzyme that can cause the degradation of cTnI is calpain-1, whose activity

Table 1.

Pathological and physiological conditions causing an increase in the levels of cardiac troponins in addition to AMI, according to [8, 19] with changes and additions

The possible causes of elevated serum cTns in addition to AMI		
Myocardial damage in cardiac pathologies	Myocardial damage in non-cardiac and systemic pathological and physiological conditions	False positive cTn elevation
• Inflammatory heart diseases (endocarditis, myocarditis, pericarditis) • Cardiac arrhythmias (atrial fibrillation, supraventricular tachycardia and others) • Cardiomyopathies (all types) and heart failure • Cardiotoxic drugs (chemotherapeutic drugs for the treatment of cancer, adrenomimetics, cocaine, and others) • Cardiac surgery (CABG, catheter ablation, and others)	• Physiological conditions (heavy physical exertion, stressful situations, old age, male gender, morning time interval) • Sepsis • Chronic diseases (chronic renal failure, chronic obstructive pulmonary disease, diabetes mellitus, oncological diseases) • Pulmonary embolism • Disorders of the central nervous system stroke, subarachnoid hemorrhage) • COVID-19	• Heterophilic antibodies • Rheumatoid factor • Biotin • Hemolysis • Fibrin clots in the blood serum • Cross (nonspecific) reactions of diagnostic antibodies with skeletal muscle troponin isoforms

increases with increasing load on the myocardium under experimental conditions.[43] Blocking calpain-1 with a specific inhibitor reduces the degradation of the troponin molecule. [44] Since under conditions of AH the load on the myocardium increases significantly, the fragmentation of troponins and the release of the smaller fragments from cardiomyocytes can be considered very reasonable.

In addition to proteolytic cleavage of troponins, the activated proteases are likely to induce proteolysis and cleavage of protein components of the cardiomyocyte membrane, facilitating the release of cytoplasmic proteins. In cardiomyocytes, approximately 5% of the total troponins are located outside the troponin complex directly in the cytoplasm (cytoplasmic or non-structural fraction). It is believed that the troponin proteins that make up this fraction are released first in pathological and physiological conditions. At the same time, given the relatively small volume of this fraction, the troponin levels in reversible myocardial damage, for example, during heavy physical exertion or stressful situations, do not exceed the 99th percentile by more than 3-5 times.[45-47] Considering the small degree of an increase in cardiac troponins in AH, it can be assumed that the key contributor to the increase is also made by the cytoplasmic fraction of troponins.[48-50]

Along with the intracellular proteolytic cleavage of troponins, the membrane permeability of cardiomyocytes also plays an important role, which can change under a number of physiological and pathological conditions. According to Hessel et al., myocardial overload leads to stretching of the heart muscle and activation of transmembrane glycoprotein receptors called integrins. These proteins function as mechanotransducers, increasing membrane permeability, and activating MMP-2 and calpain-1, which additionally enhance proteolytic degradation of troponins.[51] Thus, the cleavage of troponins into small fragments and an increase in the permeability of the cardiomyocyte membrane create the necessary conditions for the release of the cytoplasmic pool of troponins, which leads to increasing the levels of cardiac troponins in AH.

Apoptosis of cardiomyocytes

Apoptosis of cardiomyocytes is initiated by a number of mechanisms that may be associated with the development and progression of AH. According to the results of a study by Cheng et al.,[52] stretching the heart muscle increases oxidative stress and the expression of the Fas protein, which is one of the key inducers for programmed cell death. Another mechanism causing increased apoptosis of cardiomyocytes is the action of the adrenergic system, an increase in the activity of which is very characteristic for AH. Experimental studies have shown that the effect of beta-adrenergic receptor agonists (norepinephrine and isoproterenol) on cardiomyocytes is that they trigger intracellular apoptotic signals by cAMP-dependent and NF2-dependent mechanisms.[53-55] Programmed death of cardiomyocytes can lead to very significant increases in cTn levels, as demonstrated in a recent experimental study by Weil et al.[56] In that experiment, the researchers initiated apoptosis in the porcine myocardium by short-term overloading of the left ventricle with pressure. At the same time, after 30 minutes the levels of troponins already exceeded the upper limit of the norm, and after 1 and 24 hours the concentrations of TnT reached relatively high values (856±956 ng/l and 1.462±1.691 ng/l, respectively). At the same time, the researchers did not reveal any histological signs of cardiomyocyte necrosis, which indicates that the mechanism for apoptosis of myocardial cells was responsible for the increase in serum troponin levels.[56]

Features of cTn elimination through the glomerular filter: Influencing factors and possibilities of non-invasive diagnostics

In addition to the mechanisms for the release of troponin into the systemic circulation following myocardial cell injury, the mechanisms for troponin elimination from blood play an important role. Thus, in patients with no signs of CVD, but with signs of chronic renal failure, elevated troponin levels are often observed.[57,58] Moreover, in patients with a lower GFR, troponin levels are higher than in patients with a higher GFR. [58] However, direct evidence for the elimination of troponins through the glomerular filter, in particular studies confirming the presence of troponins in urine, has been lacking for a long time. In some studies, urinary troponin levels were detected only in isolated cases, and therefore this mechanism for troponin elimination was considered questionable.[59] Troponin molecules were considered relatively large and, according to some authors, could not pass through the glomerular filter.[59] However, several recent studies have shown the presence of troponin molecules in urine in patients with CVD. For example, in a study by Pervan et al.,[26] hsTnI was found in morning urine in patients with AH and normotensive individuals. However, in hypertensive patients, the mean hsTnI value was higher than in those with normal blood pressure. Since AH enhances GFR, it is probably this mechanism that determines the results obtained. Levels of troponins in urine are relatively low, which explains why moderate-sensitivity assays did not detect these concentrations. It should be noted that in the study by Pervan et al.,[26] a high-sensitivity troponin assay was used to determine hsTnI in urine. In a study by Chen et al.,[27] the authors observed significantly higher levels of urine hsTnI in patients with diabetes mellitus than in those without subsequent incident cardiovascular events. The multivariate logistic regression analysis using different models consistently showed that urine hsTnI >4.10 pg/mL was an independent factor predictive of incident cardiovascular events.

A possible explanation for how troponin molecules penetrate the glomerular filter is the proteolytic cleavage processes under the influence of a number of intra- and extracellular proteinases, most likely, splitting into small fragments that can penetrate into urine and saliva.[26-28,60] However, the processes of proteolytic cleavage of troponins inside cells and in blood serum are extremely poorly understood. Although researchers report several dozen fragments of various molecular weights and sizes, all the enzymes that are responsible for the cleavage of troponins and the formation of such a significant number of fragments are unknown.[61-63] At the same time, the results of the study by Katrukha et al. [61] suggest that the 29-kDa fragment of cTnT in AMI serum samples mainly appears due to the cleavage by thrombin during serum sample preparation. It is noteworthy

that under conditions of hypertension, thrombin is activated,[64] and, accordingly, the processes of proteolytic cleavage of troponins into small fragments are enhanced, and an increase in GFR promotes the elimination of formed small fragments through the glomerular filter into the urine. The identification of all factors influencing the proteolytic degradation of troponin molecules is essential for understanding this process and improving laboratory diagnostics, including the use of urine as a non-invasive biomaterial. The mechanisms described above for increasing the levels of cTnT and cTnI in human biological fluids in AH are summarized in Figure 1.

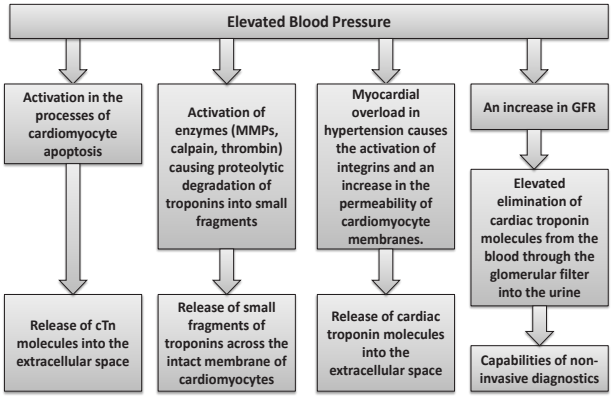

Fig. 1. *Mechanisms responsible for increased levels of cardiac troponins in AH.*

In conclusion, the increase in the levels of cardiac troponins in AH is based on the following mechanisms: activation of proteolytic cleavage of troponin molecules inside cardiomyocytes, the increased permeability of cardiomyocyte membranes, and the increased apoptotic processes, as well as the effect of AH on the filtration of troponin fragments through the glomerular filter into the urine. Measurement of urinary hsTn, collected easily and non-invasively, can be an acceptable biomarker with a high diagnostic value.

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