journal of clinical practice 2020 Том 11 №3

BIOMARKERS OF ACUTE MYOCARDIAL INFARCTION: DIAGNOSTIC AND PROGNOSTIC VALUE. PART 1

A.M. Chaulin[1, 2], D.V. Duplyakov[1, 2]

[1] Samara Regional Cardiology Dispensary, Samara, Russian Federation

[2] Samara State Medical University, Samara, Russian Federation

The morbidity and mortality rates for acute myocardial infarction (AMI) have been growing rapidly in the recent years, causing a significant socio-economic damage. The cardiospecific biomarkers play an important role in the diagnosis and prediction of AMI. The purpose of this review is to summarize the information about the main existing cardiac biomarkers and their diagnostic and prognostic value for patients with AMI. The currently existing cardiac biomarkers of AMI may be divided into several groups: biomarkers of necrosis and ischemia of cardiomyocytes, neuroendocrine biomarkers, inflammatory biomarkers, as well as a number of new AMI biomarkers, the diagnostic value of which is still poorly understood in AMI. In the first part of the review, we discuss the diagnostic and prognostic value of the biomarkers of myocardial necrosis and ischemia (aspartate aminotransferase; creatine phosphokinase and its isoform MB; cardiac troponins; myoglobin; BB-isoform of glycogen phosphorylase; ischemia-modified albumin; cardiac protein binding fatty acids) and neuroendocrine biomarkers of AMI (natriuretic peptides; adrenomedulline; copeptin, catestatin; components of the renin-angiotensin-aldosterone system).

Keywords: *laboratory diagnostics, acute myocardial infarction, AMI, biomarkers, cardiac troponins, myoglobin, ischemia-modified albumin, glycogen phosphorylase-BB, fatty acid binding protein, natriuretic peptides, adrenomedullin, catestatin, copeptin.*

(***For citation:*** Chaulin AM, Duplyakov DV. Biomarkers of Acute Myocardial Infarction: Diagnostic and Prognostic Value. Part 1. *Journal of Clinical Practice.* 2020;11(3):75–84. doi: 10.17816/clinpract34284)

INTRODUCTION

For the first time the concept of biomarkers of heart damage in acute myocardial infarction (AMI) was described more than half a century ago by A. Karmen et al. [1], who in 1954 reported an increase in aspartate aminotransferase in patients with AMI. In subsequent years, creatine phosphokinase (CPK), or creatine kinase, and lactate dehydrogenase were identified as more sensitive and specific biomarkers for the diagnosis of AMI [2]. However, it soon became clear that neither total CPK and lactate dehydrogenase, much less aspartate aminotransferase, have specificity for ischemic myocardial damage [3, 4]. Further development of methods of protein analysis made it possible to identify isoforms of CPK-MB and lactate dehydrogenase-1, which have a higher specificity for cardiomyocytes [5], but the diagnostic significance of the latter gradually faded into the background with the discovery of cardiac-specific troponin (cTn) [6– eight].

The first methods for determining c-Tn were somewhat inferior in their effectiveness to the enzyme CP-K-MB, which until 2000 was still the “gold standard” for diagnosing AMI. In 2000, experts from the European Society of Cardiology (ESC) and the American College of Cardiology (ACC), based on several large clinical studies, recommended the use of cTnI and cTnT as the main biomarkers of AMI due to their sensitivity and almost absolute cardiac specificity [9–11]. At the same time, according to several studies, cTnI and cTnT do not have absolute cardiospecificity [12, 13]. So, D. Rusakov et al. [12] found the expression of cTnT in the middle membrane of the vena cava and pulmonary veins, and G. Bodor et al. [13] reported on the expression of cTnT both in healthy human skeletal muscle and in muscle samples affected by polymyositis and Duchenne muscular dystrophy.

Today, many cardiac indicators of the state are known that have diagnostic and prognostic value in AMI, but none of them simultaneously meets two key criteria for an ideal AMI biomarker — absolute cardiospecificity and high sensitivity, confirming minor myocardial damage, which makes it possible to make an accurate diagnosis and proceed to adequate treatment in the early stages of acute heart attack. Conventionally, all known cardiomarkers can be divided into several groups (Table 1).

Table 1

The main laboratory biomarkers of acute myocardial infarction with diagnostic and prognostic value

AIM biomarkers	Laboratory AIM biomarkers	Accepted abbreviations for AMI biomarkers
I. Biomarkers of necrosis and ischemia of cardiomyocytes	Aspartate aminotransferase Creatine phosphokinase Creatine phosphokinase MB isoform Lactate dehydrogenase-1 Cardiac troponins T and I Myoglobin Glycogen phosphorylase BB-isoform Ischemia-modified albumin Heart-type fatty acid binding protein	AST CPK CPK-MB LDH-1 cTnI, cTnT Mb GPBB IMA hFABP
II. Neuroendocrine biomarkers	Natriuretic peptides Adrenomedullin Catestatin Copeptin Components of the renin-angiotensin-aldosterone system (aldosterone, renin, angiotensin II)	BNP/NT-proBNP ADM CST - PAAC / RAAS
III. Inflammatory biomarkers	C-reactive protein Interleukin-6 Tumor necrosis factor Myeloperoxidase Matrix metalloproteinases Soluble form of CD40 ligand Procalcitonin Placental growth factor	CRP IL6 TNF MPO MMPs sCD40L PCT PGF
IV. Other emerging cardiac biomarkers	Microribonucleic acids Stimulating growth factor expressed by gene 2 Growth differentiation factor 15 Galectin-3 Proprotein convertase of subtilisin-keksin type 9	microRNA ST2 GDF-15 - PCSK9

Note. AIM — acute myocardial infarction.

MAIN LABORATORY BIOMARKERS OF ACUTE MYOCARDIAL INFARCTION

I. Biomarkers of necrosis and ischemia of cardiomyocytes

Cardiac troponins (cTnI, cTnT, cTnC)

Troponin proteins are important for the interaction of actin and myosin, and for the regulation of muscle tissue contractile function in response to cytosolic calcium and troponin phosphorylation. The troponin complex is located together with tropomyosin on the actin filament. The heart-specific isoforms cTnI and cTnT exist in myocardial tissue, while cTnC is also expressed in skeletal muscle, which makes it unsuitable for use as a biomarker of AMI [14–16].

To diagnose myocardial infarction, in accordance with the third universal definition of myocardial infarction, the following laboratory criterion is used: detection of an increase in more than the 99th percentile (upper control limit) and / or a regular dynamics of a decrease in the level of cTn in serum; in addition, cTn levels should be measured with a coefficient of variation ≤ 10% [17, 18]. Advances in technology and the development of highly sensitive assays (hs-cTn) have improved the identification of myocardial injury with the ability to detect elevated troponin levels within the first hours after the onset of symptoms of cardiac ischemia [18–21].

Although elevated serum cTn levels reflect myocardial injury, the mechanistic basis for this observation remains unclear. In addition to spontaneous AMI after acute coronary occlusion and rupture of atherosclerotic plaques, cardiac muscle necrosis may be secondary to

https://doi.org/10.17816/clinpract34284

journal of clinical practice 2020 Том 11 №3

ischemia resulting from increased oxygen demand or decreased oxygen delivery due to coronary embolism, coronary artery spasm, arrhythmia, hypertension, severe anemia and respiratory disorders. Therefore, cTn levels can increase not only in ischemic heart disease and myocardial infarction, but also in other noncardiac disorders (Fig. 1) [11, 22–25]. One of the important factors contributing to the increase in the concentration of cTn in the blood is the rate of their elimination, including renal filtration. Indeed, cTn levels are elevated in patients with renal insufficiency without symptoms of acute coronary syndrome, although they are at increased risk of heart failure. Another study reported that in 50% of patients with renal failure and high cTn levels, coronary arteries were not stenotic on coronary angiography [26], implying that cTn is chronically elevated in this population.

Highly sensitive methods of determination are capable of registering minor and reversible myocardial damage that occurs in some physiological, as well as at the initial stages of a number of pathological conditions [11, 24], which significantly expands the possibilities of their use. In addition, information on the circadian rhythms of hs-cTnT concentration is very interesting: morning values exceed evening values [27, 28]. Researchers have linked the circadian rhythms of hs-cTnT concentration to those of the neuroendocrine system and hemostasis. Thus, higher morning hs-cTnT values coincide with increased morning activity of the sympathoadrenal system, including the adrenal glands and the coagulation system, which seem to promote the release of more cTn molecules from cardiomyocytes in the morning [27, 28]. Nevertheless, information on the circadian rhythms of hs-cTnT concentration and the mechanisms underlying their formation is still limited and further studies are required to clarify their effect on diagnostic algorithms for AMI.

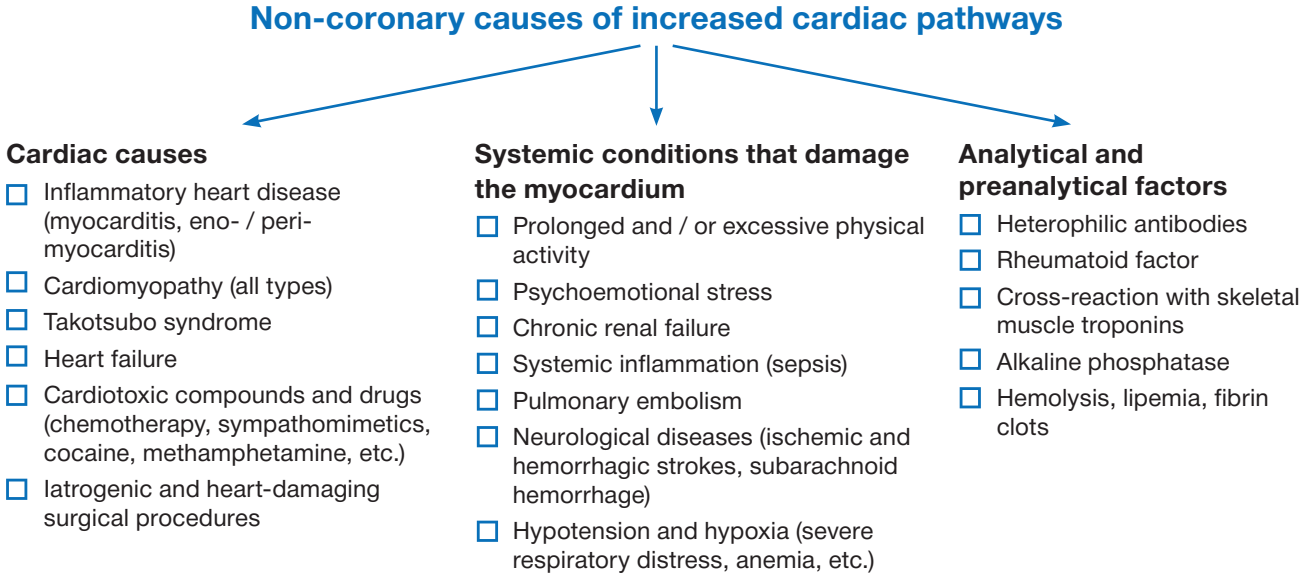
High cTn levels are useful for diagnostic purposes and are also an independent prognostic marker, as evidenced by several clinical trials and meta-analyzes [29, 30]. The cTn level can inform clinical decisions about whether to take more aggressive or conservative treatment for acute coronary syndrome, since abnormal cTn levels can identify the subgroups of patients who benefit most from early invasive therapy [31].

With the development of highly sensitive methods for determining cTn, the possibility of non-invasive diagnostics of cardiovascular diseases also appeared [10, 32–34]. Thus, P. Pervan et al. [32] in their study concluded that urinary hs-cTn levels can be used in the diagnosis and monitoring of arterial hypertension. Other studies reported the possibility of determining cTn in the oral fluid in order to determine the severity of coronary heart disease [33] and diagnose AMI [34].

Myoglobin, Mb

Myoglobin is a low molecular weight cytoplasmic heme protein that is the most sensitive generally accepted biomarker for AMI. Due to its low molecular weight, myoglobin leaves cardiomycytes much faster and can be detected in the blood 1 hour after myocardial injury, reaches a peak within 4–12 hours, and then returns to its initial level within 24 hours [35]. However, myoglobin has a lower specificity for cardiac necrosis than cTnI and cTnT, and myoglobin levels can be increased in noncardiac disorders such as skeletal

Fig. 1. The main reasons (with the exception of acute myocardial infarction) of increased cardiac troponins [11]



muscle disease or injury, as well as in chronic kidney disease [36, 37].

Despite the lack of cardiac specificity, the combination of myoglobin with cTnI or cTnT significantly improved the ability to identify individuals with an increased risk of mortality from AMI compared to each of these biomarkers separately [38, 39].

Myoglobin is excreted mainly through the kidneys, and renal failure is considered a predictor of poor outcomes, including an increased risk of mortality, in patients with AMI [40]. Thus, it is assumed that myoglobin predicts mortality by identifying patients with renal failure.

Glycogen phosphorylase BB isoenzyme, GPBB

Glycogen phosphorylase (GP) is an intracellular enzyme that regulates carbohydrate metabolism by mobilizing glycogen. GP catalyzes the first stage of glycogenolysis (the breakdown of glycogen), as a result of which the monosaccharide glucose-1-phosphate is cleaved from this polysaccharide. There are three different GP isoenzymes: GPMM (present in skeletal muscle), GPLL (in the liver), and GPBB (in the brain and cardiac muscle) [41]. During myocardial ischemia, the GPBB enzyme is activated and enhances the breakdown of glycogen. GPBB is released into the bloodstream 2–4 h after ischemic myocardial injury [42, 43]. Early release of GPBB into the blood is a common result of a combination of increased glycogenolysis and increased cell membrane permeability, which is typical of myocardial ischemia and necrosis [41, 44]. In a study by N. Singh et al. [44] found that GPBB was the most sensitive and specific biomarker for detecting AMI compared with myoglobin and CPK-MB in the first 3–4 hours after the onset of chest pain. Thus, GPBB can be used as an additional biomarker for the early diagnosis of AMI.

Ischemia-modified albumin, IMA

In acute ischemia, the N-terminus of albumin is changed (modified), as a result of which its binding capacity decreases: the resulting protein is called ischemic-modified albumin [45].

The advantage of this biomarker over cTn is that positive IMA levels appear within minutes after ischemia and remain elevated for several hours, even before myocardial necrosis develops [46]. Consequently, a negative IMA result in the initial assessment of the patient's condition indicates a low risk of developing adverse events, which provides significant cost savings [47]. In patients with suspected acute coronary syndrome, diagnostic accuracy at admission increased when IMA was used in conjunction with cTnT data and electrocardiography [48]. In fact, IMA in combination with cTnT results is a more sensitive marker for predicting adverse cardiac events than cTnT alone, although the specificity and sensitivity of IMA is too low to be useful for clinical decision making when used as an independent indicator [49].

Heart-type fatty acid binding protein, hFABP

Heart-type fatty acid binding protein (hFABP) is a small cytoplasmic protein present in cardiomyocytes, which in some of its biochemical characteristics is similar to myoglobin: due to its low molecular weight and cytoplasmic localization, it is also rapidly released and is involved in the circulation after myocardial injury [50]. L. Agnello et al. [51] found that early diagnosis of AMI can be based on the measurement of the level of hFABP in the blood. Nevertheless, in a clinical study, hs-cTn was superior to hFABP in sensitivity. In addition, hFABP is not a myocardial specific indicator, since it is expressed in skeletal muscle and kidney [52]. Thus, the diagnostic value of hFABP remains controversial.

The prognostic value of hFABP in patients with suspected acute coronary syndrome has been studied in several studies [53–55]. A high level of hFABP during 1 year of follow-up was the best predictor of adverse cardiovascular events among the markers of necrosis (hFABP, cTnI, and CPK-MB) in patients with myocardial infarction without ST segment elevation [53]. Sequential (serial) measurements of hFABP during admission and discharge provided valuable information about adverse cardiac events in patients with chronic heart failure: for example, patients with persistently elevated levels of hFABP had the highest incidence of adverse cardiac events, including sudden cardiac death and hospital readmissions [54]. However, hFABP was not accepted as a standard biomarker of acute coronary syndrome due to the fact that it is much inferior in specificity to cTn [55].

II. Neuroendocrine biomarkers of acute myocardial infarction

Natriuretic peptides (BNP / NT-proBNP)

Brain natriuretic peptide, or Natriuretic peptide type B (BNP), is a hormone secreted by cardiomyocytes in the ventricles of the heart in response to cardiac stress and ventricular dysfunction. After its synthesis, the proBNP precursor is cleaved into the active BNP hormone, which performs a number of functions in the human body, and the inactive NT-proBNP fragment

https://doi.org/10.17816/clinpract34284

journal of clinical practice 2020 Том 11 №3

(N-terminal prohormone of brain natriuretic peptide). BNP functions include vasodilation, sodium and water excretion (natriuresis), and inhibition of the renin-angiotensin-aldosterone system [56].

The levels of cardiac natriuretic peptides, especially BNP and NT-proBNP, are elevated after acute coronary syndrome [57]. It was also found that increased BNP levels in patients with AMI are associated with the size of the necrosis zone [58]. Although BNP / NT-proBNP levels are elevated in patients with acute coronary syndrome, they cannot be used as diagnostic markers because they are also elevated in other conditions that have similar symptoms to AMI, such as heart failure and pulmonary embolism. Due to the partial clearance (removal) of BNP and NT-proBNP by renal excretion, patients with renal insufficiency also have high levels of BNP and NT-proBNP [59].

Several studies have demonstrated the high predictive value of BNP and NT-proBNP in AMI patients. Plasma NT-proBNP, measured 2–4 days after the development of AMI, independently predicted left ventricular function and one-year patient survival [60]. Elevated BNP levels upon initial admission of patients with ST-segment elevation myocardial infarction were associated with impaired reperfusion after fibrinolysis and a higher 30-day mortality rate. After adjustment for cTnI, BNP remained independently associated with patient mortality, and the likelihood of developing heart failure and the risk of death of patients increased with higher baseline BNP concentrations [61].

There are reports that BNP and NT-proBNP are better at predicting cardiovascular events than risk assessments on the TIMI (Thrombolysis in Myocardial Infarction) or GRACE (Global Registry of Acute Coronary Events) scales. The predictive value of NT-proBNP was independent, and the combination of NT-proBNP and the TIMI or GRACE scale did not significantly improve the prediction of the risk of death in the short term [62, 63].

BNP and NT-proBNP are excellent predictive biomarkers of adverse events after AMI, but there is still no consensus on whether they can be equally reliably used to select early treatment tactics for patients in order to improve the prognosis of survival, by analogy with how they demonstrate their role in diagnosis and treatment of heart failure [61, 62].

Adrenomedullin, ADM

Adrenomedullin is a regulatory peptide (hormone) that is elevated in the serum of patients with cardiovascular disease. It weakens the development of myocardial infarction during acute myocardial injury and can potentially affect the pathological process both in the acute phase of AMI and as a result of remodeling [64, 65]. Elevated adrenomedullin levels are indicative of cardiac remodeling and may improve risk stratification in patients with heart failure and AMI [65, 66].

Catestatin, CST

Cathestatin is an important peptide that regulates the functioning of the cardiovascular system. Catestatin is an antagonist of catecholamines (dopamine and norepinephrine), exhibiting antihypertensive, antiapoptotic, cardioprotective, and hypoglycemic properties [67]. According to studies [68, 69], in patients with AMI, the levels of cathestatin are higher than in the control group. Catastatin concentrations positively correlate with ventricular remodeling [68] and catecholamine levels and, according to the authors, exhibit protective properties in the postinfarction period [69]. Cathestatin is currently a relatively poorly studied biomarker.

Copeptin

Copeptin, a small glycopeptide consisting of 39 amino acids, is a C-terminal fragment of preprovasopressin, which is secreted in equimolar amounts with antidiuretic hormone (ADH, vasopressin) into the bloodstream after being cleaved in the neurohypophysis. Thus, copeptin is a surrogate biomarker of ADH, and its serum levels reflect the production of ADH by the neurohypophysis [70–72]. The production and secretion of ADH and copeptin is similar to the production of insulin and C-peptide by pancreatic endocrinocytes [73]. In the bloodstream, ADH is unstable and is mainly associated with platelets, while copeptin, on the contrary, is a stable biomarker, which makes it suitable for diagnostic purposes [70–73]. In a recent study by K. Kim et al. [74] showed that a multimarker strategy using copeptin and hs-cTnI was not inferior to serial hs-cTnI measurements in the diagnosis of AMI. Both the sensitivity and the negative predictive value of the multimarker strategy were 100%. At the same time, the diagnostic efficacy of Copeptin alone in AMI was limited. The specificity and positive predictive value of the multimarker strategy were lower than with serial hs-cTnI measurement [74]. According to J. Jeong et al. [75], the diagnostic efficiency of copeptin in the early diagnosis of AMI is higher than that of cTnI. The combination of copeptin and cTnI also has better diagnostic efficacy compared to the combination of CPK-MB and cTnI in the early diagnosis of AMI [75]. M. Budnik et al. [76] concluded that the copeptin/NT-proBNP ratio

can be used in the differential diagnosis of AMI and takotsubo syndrome, a pathological condition similar in clinical symptoms to AMI, which is almost always accompanied by an increase in serum cTn concentration. Thus, the study of copeptin in patients with suspected AMI has some advantages over cTn. Further research is needed to clarify these capabilities.

Renin-angiotensin-aldosterone system, RAAS

Renin-angiotensin-aldosterone system (RAAS) is a hormonal system that regulates blood pressure and fluid balance in the human body. The main components of the RAAS used as biomarkers of cardiovascular diseases are renin, angiotensin II, and aldosterone [77]. RAAS is activated after AMI, leading to increased blood volume and vasoconstriction. Aldosterone contributes to a wide range of harmful cardiovascular effects during AMI, including acute endothelial dysfunction, increased oxidative stress, cardiac myocyte necrosis, and increased myocardial hypertrophy and fibrosis [78, 79].

With the exception of BNP, the aforementioned neuroendocrine markers are not yet used in clinical practice for diagnosis or prognosis. Nevertheless, studies have shown that treatment of patients with AMI with inhibitors of the neuroendocrine system, in particular with RAAS inhibitors, reduced morbidity and mortality. For example, mortality and heart failure rates in patients with acute coronary syndrome decreased with the administration of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and aldosterone inhibitors [79, 80]. Given this information, higher levels of these compounds in AMI may indirectly indicate a poor prognosis.

CONCLUSION

An ideal biomarker for AMI should be sensitive and specific in the early period of disease development and have a high predictive value that could help clinicians choose the most optimal treatment strategy. To date, there is no ideal AMI biomarker that would have all the characteristics at the same time. So far, the most valuable diagnostic and prognostic markers of AMI are cTnT and cTnI, which are determined by highly and moderately sensitive methods. Markers such as CP-K-MB, GPBB, myoglobin, and hFABP, which are highly sensitive, have low specificity in the diagnosis of AMI, and therefore cannot be used as the main biomarkers. Albumin, modified by ischemia, is notable for the fact that its blood levels increase in the first minutes of ischemia, even before the development of myocardial necrosis, but it is also not specific enough to be used as an independent indicator. Neuroendocrine laboratory parameters (natriuretic peptides, adrenomedullin, cathestatin, copeptin, components of the renin-angiotensin-aldosterone system) can be used as prognostic biomarkers of AMI. In addition, copeptin is practically not inferior to cTn in the early diagnosis of AMI. The combination of copeptin and cTn has proven itself well in the early diagnosis of AMI in current research. In addition to this, the ratio of copeptin/natriuretic peptides has shown high efficiency for the complex differential diagnosis of two closely related pathological conditions — AMI and takotsubo syndrome.

ADDITIONAL INFORMATION

Funding source. The search and analytical work was carried out at the personal savings of the team of authors.

Competing interests. The authors declare no conflict of interest which should be reported.

AUTHOR CONTRIBUTIONS

A.M. Chaulin — obtaining and analyzing literature data, writing an article, editing an article, approving the final version for publication, full responsibility for the content; D.V. Duplyakov — editing the article, approving the final version for publication, full responsibility for the content. The authors read and approved the final version prior to publication.

REFERENCES

1. Karmen A, Wroblewski F, Ladue JS. Transaminase activity in human blood. *J Clin Invest*. 1955;34(1):126–131. doi: 10.1172/JCI103055.
2. Wroblewski F, Ladue JS. Lactic dehydrogenase activity in blood. *Proc Soc Exp Biol Med*. 1955;90(1):210–213. doi: 10.3181/00379727-90-21985.
3. Dolci A, Panteghini M. The exciting story of cardiac biomarkers: from retrospective detection to gold diagnostic standard for acute myocardial infarction and more. *Clin Chim Acta*. 2006;369(2):179–187. doi: 10.1016/j.cca.2006.02.042.
4. Ladenson JH. A personal history of markers of myocyte injury [myocardial infarction]. *Clin Chim Acta*. 2007;381(1):3–8. doi: 10.1016/j.cca.2007.02.039.
5. Nowakowski JF. Use of cardiac enzymes in the evaluation of acute chest pain. *Ann Emerg Med*. 1986;15(3):354–360. doi: 10.1016/s0196-0644(86)80584-4.
6. Troponin T and myocardial damage. *Lancet*. 1991;338(8758):23–24. doi: 10.1016/0140-6736(91)90011-D.
7. Mair P, Mair J, Koller J, et al. Cardiac troponin T in the diagnosis of heart contusion. *Lancet*. 1991;338(8768):693. doi: 10.1016/0140-6736(91)91266-w.
8. Katus HA, Remppis A, Looser S, et al. Enzyme linked immuno assay of cardiac troponin T for the detection of acute myocardial infarction in patients. *J Mol Cell Cardiol*. 1989;21(12):1349–1353. doi: 10.1016/0022-2828(89)90680-9.
9. Myocardial infarction redefined – a consensus document of The Joint European Society of Cardiology/American College of Cardiology Committee for the redefinition of myocardial infarction. *Eur Heart J*. 2000;21(18):1502–1513. doi: 10.1053/euhj.2000.2305.

https://doi.org/10.17816/clinpract34284

journal of clinical practice 2020 Том 11 №3

10. Chaulin AM, Karslyan LS, Grigoriyeva EV, et al. Clinical and diagnostic value of cardiac markers in human biological fluids. *Kardiologiia*. 2019;59(11):66–75. (In Russ). doi: 10.18087/cardio.2019.11.n414.

11. Chaulin AM, Karslyan LS, Duplyakov DV. Non-coronarogenic causes of increased cardiac troponins in clinical practice. *Journal of Clinical Practice.* 2020;10(4):81–93. (In Russ). doi: 10.17816/clinpract16309.

12. Rusakov DYu, Vologdina NN, Tulayeva ON. The development of striated cardiac muscle tissue in the walls of the caval and pulmonary veins. *Journal of Anatomy and Histopathology*. 2015;4(3):105. (In Russ).

13. Bodor GS, Survant L, Voss EM, et al. Cardiac troponin T composition in normal and regenerating human skeletal muscle. *Clin Chem*. 1997;43(3):476–484. doi: 10.1093/clinchem/43.3.476.

14. Sacks DB. Acute coronary ischemia: troponin I and T. *Vasc Med*. 1999;4(4):253–256. doi: 10.1177/1358836X9900400408.

15. Chaulin AM, Grigoryeva YuV. Main aspects of biochemistry, physiology of cardiac troponins. *Bulletin of Science and Practice*. 2020;6(5):105–112. (In Russ). doi: 10.33619/2414-2948/54/13.

16. Duplyakov DV, Chaulin AM. Mutations of heart troponines, associated with cardiomyopathies. *Cardiology: News, Opinions, Training.* 2019;7(3):8–17. (In Russ). doi: 10.24411/2309-1908-2019-13001.

17. Morrow DA, Cannon CP, Jesse RL, et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical characteristics and utilization of biochemical markers in acute coronary syndromes. *Clin Chem*. 2007;53(4):552–574. doi: 10.1373/clinchem.2006.084194.

18. Apple FS, Collinson PO; for the IFCC Task Force on Clinical Applications of Cardiac Biomarkers. Analytical characteristics of high-sensitivity cardiac troponin assays. *Clin Chem*. 2012;58(1):54–61. doi: 10.1373/clinchem.2011.165795.

19. Chenevier-Gobeaux C, Bonnefoy-Cudraz É, Charpentier S, et al. High-sensitivity cardiac troponin assays: answers to frequently asked questions [published correction appears in Arch Cardiovasc Dis. 2015;108(5):331–332]. *Arch Cardiovasc Dis*. 2015;108(2):132–149. doi: 10.1016/j.acvd.2014.11.001.

20. Conrad MJ, Jarolim P. Cardiac troponins and high-sensitivity cardiac troponin assays. *Clin Lab Med*. 2014;34(1):59–73. doi: 10.1016/j.cll.2013.11.008.

21. Body R. Acute coronary syndromes diagnosis, version 2.0: Tomorrow's approach to diagnosing acute coronary syndromes? *Turk J Emerg Med*. 2018;18(3):94–99. doi: 10.1016/j.tjem.2018.05.005.

22. Manikkan AT. Elevated troponin i levels in diabetic ketoacidosis without obstructive coronary artery disease. *J Endocr Soc*. 2018;2(9):1020–1023. doi: 10.1210/js.2018-00152.

23. Stacy SR, Suarez-Cuervo C, Berger Z, et al. Role of troponin in patients with chronic kidney disease and suspected acute coronary syndrome: a systematic review. *Ann Intern Med*. 2014;161(7):502–512. doi: 10.7326/M14-0746.

24. Chaulin AM, Karslyan LS, Grigorieva EV, et al. Metabolism of cardiac troponins (literature review). *Complex Issues of Cardiovascular Diseases*. 2019;8(4):103–115. (In Russ). doi: 10.17802/2306-1278-2019-8-4-103-115.

25. Chaulin AM, Grigoryeva YuV, Duplyakov DV. Comboridity of chronic obstructive pulmonary disease and cardiovascular diseases: general factors, pathophysiological mechanisms and clinical significance. *Journal of Clinical Practice*. 2020;11(1):112–121. (In Russ). doi: 10.17816/clinpract21218.

26. Gupta S, Alagona P Jr. Troponins: not always a myocardial infarction. *Am J Med*. 2008;121(9):e25–e29. doi: 10.1016/j.amjmed.2008.03.026.

27. Klinkenberg LJ, van Dijk JW, Tan FE, et al. Circulating cardiac troponin T exhibits a diurnal rhythm. *J Am Coll Cardiol*. 2014;63(17):1788–1795. doi: 10.1016/j.jacc.2014.01.040.

28. Klinkenberg LJ, Wildi K, van der Linden N, et al. diurnal rhythm of cardiac troponin: consequences for the diagnosis of acute myocardial infarction. *Clin Chem*. 2016;62(12):1602–1611. doi: 10.1373/clinchem.2016.257485.

29. Mueller M, Vafaie M, Biener M, et al. Cardiac troponin T: from diagnosis of myocardial infarction to cardiovascular risk prediction. *Circ J*. 2013;77(7):1653–1661. doi: 10.1253/circj.CJ-13-0706.

30. Das B, Mishra TK, Trinath KM. Cardiac troponins: current status. *JICC*. 2017;7(1):1–5. doi: 10.1016/j.jicc.2016.12.006.

31. Tan NS, Goodman SG, Cantor WJ, et al. Efficacy of early invasive management after fibrinolysis for ST-segment elevation myocardial infarction in relation to initial troponin status. *Can J Cardiol*. 2016;32(10):1221.e11–1221.e18. doi: 10.1016/j.cjca.2016.01.010.

32. Pervan P, Svagusa T, Prkacin I, et al. Urine high-sensitive troponin I measuring in patients with hypertension. *Signa Vitae*. 2017;13(3):62–64. doi: 10.22514/SV133.062017.13.

33. 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. *Комплексные проблемы сердечно-сосудистых заболеваний*. 2017;6(S4):13–14. (In Russ).

34. Mirzaii-Dizgah I, Riahi E. Salivary troponin I as an indicator of myocardial infarction. *Indian J Med Res*. 2013;138(6):861–865.

35. Mair J, Artner-Dworzak E, Lechleitner P, et al. Early diagnosis of acute myocardial infarction by a newly developed rapid immunoturbidimetric assay for myoglobin. *Br Heart J*. 1992;68(5):462–468. doi: 10.1136/hrt.68.11.462

36. Rebalka IA, Hawke TJ. Potential biomarkers of skeletal muscle damage. *Biomark Med*. 2014;8(3):375–378. doi: 10.2217/bmm.13.163.

37. Zager RA. Marked protection against acute renal and hepatic injury after nitrited myoglobin + tin protoporphyrin administration. *Transl Res*. 2015;166(5):485–501. doi: 10.1016/j.trsl.2015.06.004.

38. Newby LK, Storrow AB, Gibler WB, et al. Bedside multimarker testing for risk stratification in chest pain units: The chest pain evaluation by creatine kinase-MB, myoglobin, and troponin I (CHECKMATE) study. *Circulation*. 2001;103(14):1832–1837. doi: 10.1161/01.cir.103.14.1832.

39. McCord J, Nowak RM, Hudson MP, et al. The prognostic significance of serial myoglobin, troponin I, and creatine kinase-MB measurements in patients evaluated in the emergency department for acute coronary syndrome. *Ann Emerg Med.* 2003;42(3):343–350. doi: 10.1016/s0196-0644(03)00411-6.

40. Kontos MC, Garg R, Anderson FP, et al. Ability of myoglobin to predict mortality in patients admitted for exclusion of myocardial infarction. *Am J Emerg Med*. 2007;25(8):873–879. doi: 10.1016/j.ajem.2007.01.002.

41. Lippi G, Mattiuzzi C, Comelli I, Cervellin G. Glycogen phosphorylase isoenzyme BB in the diagnosis of acute myocardial infarction: a meta-analysis. *Biochem Med (Zagreb)*. 2013;23(1):78–82. doi: 10.11613/bm.2013.010.

42. Rabitzsch G, Mair J, Lechleitner P, et al. Isoenzyme BB of glycogen phosphorylase b and myocardial infarction. *Lancet*. 1993;341(8851):1032–1033. doi: 10.1016/0140-6736(93)91129-a.

43. Rabitzsch G, Mair J, Lechleitner P, et al. Immunoenzymometric assay of human glycogen phosphorylase isoenzyme BB in diagnosis of ischemic myocardial injury. *Clin Chem*. 1995;41(7):966–978. doi: 10.1093/clinchem/41.7.966.

44. Singh N, Rathore V, Mahat RK, Rastogi P. Glycogen phosphorylase BB: a more sensitive and specific marker than other cardiac markers for early diagnosis of acute myocardial infarction. *Indian J Clin Biochem*. 2018;33(3):356–360. doi: 10.1007/s12291-017-0685-y.

45. Bar-Or D, Lau E, Winkler JV. A novel assay for cobalt-albumin binding and its potential as a marker for myocardial ischemia-a preliminary report. *J Emerg Med*. 2000;19(4):311–315. doi: 10.1016/s0736-4679(00)00255-9.

46. Wu AH. Cardiac markers. Pathology and laboratory medicine. 2nd ed. Totowa NJ: Humana; 2003. P. 259–277.

47. Bar-Or D, Curtis G, Rao N, et al. Characterization of the Co(2+) and Ni(2+) binding amino-acid residues of the N-terminus of human albumin. An insight into the mechanism of a new assay for myocardial ischemia. *Eur J Biochem*. 2001;268(1):42–47. doi: 10.1046/j.1432-1327.2001.01846.x.

48. Mehta MD, Marwah SA, Ghosh S, et al. A synergistic role of ischemia modified albumin and high-sensitivity troponin T in the early diagnosis of acute coronary syndrome. *J Family Med Prim Care*. 2015;4(4):570–575. doi: 10.4103/2249-4863.174295.

49. Manini AF, Ilgen J, Noble VE, et al. Derivation and validation of a sensitive IMA cutpoint to predict cardiac events in patients with chest pain. *Emerg Med J*. 2009;26(11):791–796. doi: 10.1136/emj.2008.068130.

50. Kim Y, Kim H, Kim SY, et al. Automated heart-type fatty acid-binding protein assay for the early diagnosis of acute

myocardial infarction. *Am J Clin Pathol*. 2010;134(1):157–162. doi: 10.1309/AJCP0F6AXRCJMQQG.

51. Agnello L, Bivona G, Novo G, et al. Heart-type fatty acid binding protein is a sensitive biomarker for early AMI detection in troponin negative patients: a pilot study. *Scand J Clin Lab Invest*. 2017;77(6):428–432. doi: 10.1080/00365513.2017.1335880.

52. Reiter M, Twerenbold R, Reichlin T, et al. Heart-type fatty acid-binding protein in the early diagnosis of acute myocardial infarction. *Heart*. 2013;99(10):708–714. doi: 10.1136/heartjnl-2012-303325.

53. Erlikh AD, Katrukha AG, Trifonov IR, et al. Acute coronary syndrome without ST-segment elevation on ECG. The prognostic value of determining the cardiac form of the protein, fatty acid binding. The results of the 12-month follow-up. *Kardiologiia*. 2005;45(5):13–21 (In Russ).

54. Jones JD, Chew PG, Dobson R, et al. The prognostic value of heart type fatty acid binding protein in patients with suspected acute Coronary Syndrome: a systematic review. *Curr Cardiol Rev*. 2017;13(3):189–198. doi: 10.2174/1573403X13666170116121451.

55. Ye XD, He Y, Wang S, et al. Heart-type fatty acid binding protein (H-FABP) as a biomarker for acute myocardial injury and long-term post-ischemic prognosis. *Acta Pharmacol Sin*. 2018;39(7):1155–1163. doi: 10.1038/aps.2018.37.

56. Richards AM, Nicholls MG, Espiner EA, et al. B-type natriuretic peptides and ejection fraction for prognosis after myocardial infarction. *Circulation*. 2003;107(22):2786–2792. doi: 10.1161/01.CIR.0000070953.76250.B9.

57. Staub D, Nusbaumer C, Zellweger MJ, et al. Use of B-type natriuretic peptide in the detection of myocardial ischemia. *Am Heart J*. 2006;151(6):1223–1230. doi: 10.1016/j.ahj.2005.06.045.

58. Niu JM, Ma ZL, Xie C, Zhang ZQ. Association of plasma B-type natriuretic peptide concentration with myocardial infarct size in patients with acute myocardial infarction. *Genet Mol Res*. 2014;13(3):6177–6183. doi: 10.4238/2014.February.21.6.

59. Park M, Vittinghoff E, Shlipak MG, et al. Associations of N-terminal pro-B-type natriuretic peptide with kidney function decline in persons without clinical heart failure in the Heart and Soul Study. *Am Heart J*. 2014;168(6):931–939.e2. doi: 10.1016/j.ahj.2014.09.008.

60. Drewniak W, Szybka W, Bielecki D, et al. Prognostic significance of NT-proBNP Levels in patients over 65 presenting acute myocardial infarction treated invasively or conservatively. *Biomed Res Int*. 2015;2015:782026. doi: 10.1155/2015/782026.

61. Islam MN, Alam MF, Debnath RC, et al. Correlation between Troponin-I and B-Type natriuretic peptide level in acute myocardial infarction patients with heart failure. *Mymensingh Med J*. 2016;25(2):226–231.

62. Reesukumal K, Pratumvinit B. B-type natriuretic peptide not TIMI risk score predicts death after acute coronary syndrome. *Clin Lab*. 2012;58(9-10):1017–1022. doi: 10.7754/clin.lab.2012.111201.

63. Khan SQ, Quinn P, Davies JE, Ng LL. N-terminal pro-B-type natriuretic peptide is better than TIMI risk score at predicting death after acute myocardial infarction. *Heart*. 2008;94(1):40–43. doi: 10.1136/hrt.2006.108985.

64. Hamid SA, Baxter GF. Adrenomedullin: regulator of systemic and cardiac homeostasis in acute myocardial infarction. *Pharmacol Ther*. 2005;105(2):95–112. doi: 10.1016/j.pharmthera.2004.08.012.

65. Ishimitsu T, Ono H, Minami J, Matsuoka H. Pathophysiologic and therapeutic implications of adrenomedullin in cardiovascular disorders. *Pharmacol Ther*. 2006;111(3):909–927. doi: 10.1016/j.pharmthera.2006.02.004.

66. Yuyun MF, Narayan HK, Ng LL. Prognostic significance of adrenomedullin in patients with heart failure and with myocardial infarction. *Am J Cardiol*. 2015;115(7):986–991. doi: 10.1016/j.amjcard.2015.01.027.

67. Chaulin AM, Aleksandrov AG, Karslyan LS, et al. Catestatin – a new cardiovascular system regulator (literature review). *Bulletin of Science and Practice*. 2019;5(6):129–136. (In Russ). doi: 10.33619/2414-2948/43/17.

68. Meng L, Wang J, Ding WH, et al. Plasma catestatin level in patients with acute myocardial infarction and its correlation with ventricular remodelling. *Postgrad Med J*. 2013;89(1050):193–196. doi: 10.1136/postgradmedj-2012-131060.

69. Liu L, Ding W, Zhao F, et al. Plasma levels and potential roles of catestatin in patients with coronary heart disease. *Scand Cardiovasc J*. 2013;47(4):217–224. doi: 10.3109/14017431.2013.794951.

70. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. *Clin Chem*. 2006;52(1):112–119. doi: 10.1373/clinchem.2005.060038.

71. Kelly D, Squire IB, Khan SQ, et al. C-terminal provasopressin (copeptin) is associated with left ventricular dysfunction, remodeling, and clinical heart failure in survivors of myocardial infarction. *J Card Fail*. 2008;14(9):739–745. doi: 10.1016/j.cardfail.2008.07.231.

72. Reinstadler SJ, Klug G, Feistritzer HJ, et al. Copeptin testing in acute myocardial infarction: ready for routine use? *Dis Markers*. 2015;2015:614145. doi: 10.1155/2015/614145.

73. Nobian A, Mohamed A, Spyridopoulos I. The role of arginine vasopressin in myocardial infarction and reperfusion. *Kardiol Pol*. 2019;77(10):908–917. doi: 10.33963/KP.14986.

74. Kim KS, Suh GJ, Song SH, et al. Copeptin with high-sensitivity troponin at presentation is not inferior to serial troponin measurements for ruling out acute myocardial infarction. *Clin Exp Emerg Med*. 2020;7(1):35–42. doi: 10.15441/ceem.19.013.

75. Jeong JH, Seo YH, Ahn JY, et al. Performance of copeptin for early diagnosis of acute myocardial infarction in an emergency department setting. *Ann Lab Med*. 2020;40(1):7–14. doi: 10.3343/alm.2020.40.1.7.

76. Budnik M, Białek S, Peller M, et al. Serum copeptin and copeptin/NT-proBNP ratio — new tools to differentiate takotsubo syndrome from acute myocardial infarction. *Folia Med Cracov*. 2020;60(1):5–14. doi: 10.24425/fmc.2020.133481.

77. Bogdanov AR, Zaletova TS, Sentsova TB, et al. Biomarkers of the renin-angiotensin-aldosterone system as predictors of heart failure in obese patients. *Serdechnaia nedostatochnost'*. 2014;84(3):160–166. (In Russ).

78. McAlpine HM, Morton JJ, Leckie B, et al. Neuroendocrine activation after acute myocardial infarction. *Br Heart J*. 1988;60(2):117–124. doi: 10.1136/hrt.60.2.117.

79. Liu J, Masoudi FA, Spertus JA, et al. Patterns of use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers among patients with acute myocardial infarction in China from 2001 to 2011: China PEACE-Retrospective AMI Study. *J Am Heart Assoc*. 2015;4(2):e001343. doi: 10.1161/JAHA.114.001343.

80. Pitt B, Bakris G, Ruilope LM, et al.; EPHESUS Investigators. Serum potassium and clinical outcomes in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS). *Circulation*. 2008;118(16):1643–1650. doi: 10.1161/CIRCULATIONAHA.108.778811.

AUTHORS INFO

The author responsible for the correspondence:

Aleksey M. Chaulin, postgraduate/assistant of the department, MD; **address:** 171, Artsibyeshevskaya street, 443001 Samara, Russia; **e-mail:** alekseymichailovich22976@gmail.com, **SPIN-код:** 1107-0875, **ORCID:** https://orcid.org/0000-0002-2712-0227

Dmitry V. Duplyakov, MD, PhD, Professor; **phone:** +7 (846) 373-70-64, **e-mail:** duplyakov@yahoo.com, **SPIN-код:** 5665-9578, **ORCID:** https://orcid.org/0000-0002-6453-2976

https://doi.org/10.17816/clinpract34284