NEURO-HUMORAL MEDIATORS IN PROGRESSION OF CORONARY ARTERY DISEASE WITH CONCOMITANT OBESITY (REVIEW)

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https://doi.org/10.35339/ic.6.4.200–209

Abstract

Cardiovascular diseases are the main cause of death worldwide. Priority in the structure of the cardiovascular diseases belongs to coronary artery disease (CAD) and especially to its acute form - acute myocardial infarction. AMI largely determines mortality, economic losses in most countries of the world. Modern epidemiological studies have shown the relationship between obesity and cardiovascular diseases, as well as between obesity and individual cardiovascular risk factors such as hypertension and hyperlipidemia. Cardiac troponin is a biomarker of choice for the diagnosis of acute myocardial infarction. However, after reperfusion therapy the actual level of Tn may be misleading due to the phenomenon of washout and the 12-hour expectation of peak levels remains the Achilles heel of this biomarker. Activation of neurohumoral systems in the acute period of the myocardial infarction promotes the expansion of the necrosis zone, the development of myocardial ischemia, bnormal heart rhythm and acute heart failure. Despite the large number of detected and studied neurohormones, our knowledge of the role of these peptides in the development of myocardial infarction and its complications is very limited. That is why studying of new biomarkers, such as copeptin and midregional proadrenomedullin, is perspective and interesting for scientist all over the world.

Keywords: *acute myocardial infarction, coronary artery disease, obesity, copeptin, MRproADM.*

Cardiovascular diseases are the main cause of death worldwide [1–6]. Priority in the structure of the cardiovascular disease belongs to coronary artery disease (CAD) and especially to its acute form - acute myocardial infarction (AMI), which is an urgent clinical condition, due to necrosis of the area of the heart muscle as a result of disturbance of its blood supply [6–7].

In most economically developed countries, cardiovascular diseases rank first among the causes of morbidity, disability and mortality, although their prevalence varies considerably in different regions [8–9]. This represents half of all deaths and 2.5 times more than all malignant neoplasms taken together. The annual economic losses due to death from the cardiovascular disease in the US amount to 56900 million dollars. In Ukraine, these diseases are the main cause of mortality and morbidity of the population. If in 1939 cardiovascular diseases accounted only for 11% in the general structure of the causes of mortality, in 1980 this number increased by more than 50%, and in 2010 – 76%.

Since 1995 in Ukraine a progressive increase in mortality due to cardiovascular diseases has been observed, reaching one of the highest levels in Europe – 63.6%. Coronary artery disease is ranked first (66.8%) in the structure of mortality from cardiovascular diseases. At the same time, in our country there are significantly lower rates of hospitalization of patients with AMI (109 per 100 thousand population, compared with 295 per 100 thousand population in the USA). In turn, the hospital mortality rate for AMI in Ukraine exceeds the European indicators (12.9% vs. 8–8.4%). In Ukraine the mortality rate is 10063 out of 594796 persons.

AMI largely determines mortality, economic losses in most countries of the world [10–11].

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The cause of each second mortality among adults is AMI and cerebral stroke. Implications of AMI are marked in months and years. Thus, according to the American Heart Association, 18% of men and 35% of women undergo recurrent MI during 6 years after acute coronary syndrome, moreover 22% of men and 46% of women become disabled due to development of severe heart failure (HF), and 30–40% of patients develop left ventricular (LV) dysfunction [12].

This problem affects the low and middle income countries [13–16]. More than 80% of deaths from cardiovascular diseases occur in these countries almost equally among men and women. By 2030, it is projected that about 23.6 million people will die due to heart attacks and mainly from heart disease and stroke. In the world 17.5 million people die due to cardiovascular diseases annually, and 1.2 million of them are our compatriots. The leading nosological form in the structure of the coronary artery disease is the AMI with elevation of ST segment (STEMI) for many years [17].

The present peculiarity is that 40% of deaths are attributed to people of working age, 25–64 years old, and Ukraine is no exception in this matter. The prevalence of heart and vascular diseases mainly depends on lifestyle and risk factors. Lifestyle changes and risk factors may slow down the development of the disease both before and after the onset of clinical symptoms [18–19].

In European countries there is a trend towards reduction in mortality from myocardial infarction (MI). In Ukraine, on the contrary, an intensive index is 6–8 times higher than that in countries of Europe, Japan, and the USA [20–21].

Modern studies show that the main causes of the high prevalence of coronary artery disease are risk factors such as hypertension, smoking, diabetes mellitus, dyslipidemia, age, family history, alcohol consumption, and obesity, whose pace of growth has become threatening scales [22, 23].

According to the World Health Organization (WHO), obesity is recognized as a non-infectious "epidemic of the 21st century" and is one of the five major risk factors for death. Epidemiological studies indicate a rapid increase in the number of obese patients in all countries of the world. Obesity (body mass index (BMI) more than 30 kg/m^2) affects from 9 to 30% of the population in the developed countries of the world [24–25]. Annually, about 2.8 million people die because of overweight or obesity [26]. Obesity is a heterogeneous disease. There are various factors contributing to obesity: features of the genotype, dysregulation of lipolysis and lithogenesis, disorders of the hypothalamic-pituitary adrenal system, dysfunction of various peptides and neurotransmitters, impaired functions of appetite centers [26–28].

Modern epidemiological studies have shown the relationship between obesity and cardiovascular diseases, as well as between obesity and individual cardiovascular risk factors such as hypertension and hyperlipidemia. In obesity, a number of hemodynamic changes occur, in particular, an increase in the volume of circulating blood and cardiac output with relatively normal vascular resistance [29]. It is believed that high blood pressure in obese patients is mainly due to increased cardiac output with "inadequately normal" peripheral resistance [29, 30].

As a result of the INTERHEART study, it has been shown that obesity is an independent risk factor for coronary artery disease [31]. The incidence of coronary artery disease in both sexes and at any age is directly proportional to BMI. Some authors have shown that the ratio of the waist circumference to the hips circumference (WC/HC) is a better dependence of obesity and development of cardiovascular complications than BMI [32–35]. With excessive body weight, the relative risk of coronary artery disease is statistically insignificant, but with the progression of obesity, the risk increases by 1.5–2 times. For example, in women with MI, patients with excess body weight and obesity are seen in 74.6%, and with normal body weight – only in 25.4%.

Despite the existence of a close relationship between obesity and cardiovascular disorders, the molecular genetic bases remain not fully defined. It is known that adipose tissue secretes a large number of biologically active substances – adipocytokines, which can provide either local auto- and paracrine effects or systemic endocrine effects, as well as to promote and counteract the development of cardiovascular disease. Obesity is not only an independent factor in the risk of cardiovascular complications, but also a trigger mechanism for the development of cardiovascular disease.

Presence of obesity is accompanied by the changes of the structure and functions of the heart. The effect of obesity on cardiovascular mortality can be explained by its effect on the compensatory change in the structure and function of the myocardium, aimed at satisfying higher metabolic needs. In obese people, adaptation of cardiac activity leads to eccentric left ventricular hypertrophy, which is an important

prognostic factor for AMI development, sudden death and congestive heart failure, regardless on the presence of hypertension. Left ventricle hypertrophy is also an important risk factor for sudden cardiac death.

In foreign sources, the concept of "adipose pathology" has appeared, which implies anatomical and functional deviations in adipocytes and adipose tissue, which can directly contribute to the development of cardiovascular disease through pericardial and perivascular effects on myocardium and blood vessels [36].

The rapid growth of the prevalence of obesity among persons of working age, the relationship of excess body weight with cardiovascular disease, and the effect of obesity on an increase in the percentage of patients with cardiac event, such as acute coronary syndrome are forced to more deeply study the problems of comorbidity in this cohort of patients and determined the relevance of the chosen problem.

The assessment of the patient's health is carried out using standard biological parameters that act as indexes, the main criteria of which are visibility, ease of implementation and early appearance. The latter position is especially important in the diagnosis of urgent conditions, such as AMI. That is why in 2000, cardiac troponin (Tn) replaced creatinine kinase MB-fraction (CK-MB) as a biomarker of choice for the diagnosis of AMI. Strengthening the position of cardiac troponins as the desired biomarkers for the diagnosis of AMI today is evident for both researchers and practitioners. The current international document containing the criteria for diagnosis of AMI, calls cardiac troponins "predominant biomarkers for the diagnosis of AMI" [37, 38]. Creation of new generations of highly sensitive tests for measurement of serum cardiac Tn can reveal the majority of cases of AMI already at the arrival of patients into the hospital [39, 40].

Tn is a protein that is released from myocytes when irreversible damage to the myocardium occurs. The main structural contractile unit of the myocyte is the sarcomer who forms ordered thick and thin fibers. Thin fibers contain actin fiber and troponin-tropomyosin complex. Troponins (I, T and C) in the 1:1:1 ratio are part of the troponin complex, which is associated with tropomyosin. Tn together with actin forms the thin filaments of myocytes - a very important component of contractile apparatus of striated muscle cells. All three troponins are involved in calcium-dependent regulation of the reduction-relaxation act [41]. Tn I is an inhibitory subunit of this complex that binds actin during the relaxation and inhibitory ATPase activity of an actomyosin, thus preventing muscle contraction in the absence of calcium ions. Tn T is a regulatory subunit that attaches the troponin complex to the thin filaments, and thus participates in a calcium-regulated act of contraction.

Tn I and T are found in three isoforms unique in structure for each type of transverse striped muscle (fast, slow and cardiac), since they are encoded by different genes. Cardiac isoform Tn I is significantly different from isoform Tn I, which is localized in skeletal muscle. About 44% of the amino acid sequence of the cardiac isoform Tn I is specific for this protein. In addition, Tn I contains an additional N-terminal polypeptide consisting of 31 amino acid residues. Thus, Tn I is a completely specific myocardial protein. The molecular weight of Tn I is about 24,000 daltons. The cardiac form of Tn T also significantly differs according to its molecular structure from the two types of Tn T that are localized in the skeletal muscle (fast and slow muscle): there are 43% differences in the amino acid sequence of heart muscle Tn T and the slow skeletal muscle and 56% of the difference from fast skeletal muscle. Thus, Tn T is a completely specific protein for the heart. The molecular weight of Tn T is 34500 daltons. cTn I and Tn T can be differentiated from similar skeletal muscle proteins immunochemically with monoclonal antibodies, which is used in their immunoassay methods [41].

Cardiac Tn C in contrast to Tn I and Tn T is absolutely identical to the structure of muscle Tn C and, consequently, is not a cardiospecific protein.

In case of damage of the myocardium, after 4–6 hours due to the development of irreversible necrotic changes, Tn enters the peripheral blood flow, peak concentration is reached in the first 12–24 hours from the onset of AMI. Cardiac isoforms of Tn for a long time retain their presence in peripheral blood: Tn I is determined for 5–7 days (0–0.5 ng/ml), Tn T is determined up to 14 days (0–0.1 ng/ml). It is advisable to study Tn I when examining patients both in the early and late terms, after the manifestation of clinical symptoms. Even a slight increase in Tn levels suggests an additional risk for the patient, since there is a clear correlation between the level of growth of Tn in blood and the size of the damage zone of the myocardium [41]. Positive troponin is associated with an increased risk of an adverse outcome for 30 days (HR 1.96, P = 0.003). This

test is useful in addressing the issues of choosing tactics for the management of patients with acute coronary syndrome, including patients with unstable angina pectoris. Tn has never detected in the peripheral blood flow of healthy individuals. His appearance is an alarm signal about necrotic damage of the myocardium. In acute coronary syndrome, elevated levels of Tn I are considered as a sign of myocardial ischemia caused by platelet activation and aggregation and leading to necrosis. Increasing the concentration of Tn I in patients with unstable angina suggests an unfavorable prognosis and the risk of developing an MI within the next 4–8 weeks. The specificity of the determination of cardiac Tn I in the blood is 95% and exceeds the specificity for CK-MB and myoglobin. The development of AMI is accompanied by a large destruction of cardiomyocytes and a significant release of cardiac Tn T in blood, which can increase by 20–400 times [42]. The amount of cardiac Tn T in blood increases in proportion to the volume and depth of MI. The absolute diagnostic sensitivity range of AMI for cardiac Tn T is 125–129 hours, for CK-MB and lactate dehydrogenase – 22 and 70 hours, respectively. The level of heavy chains of myosin begins to increase only from the middle of second day, exceeding the initial values in 5–6 times, and decreases in one week after the occurrence of AMI.

However, after reperfusion therapy the actual level of Tn may be misleading due to the phenomenon of washout. Peak level of Tn occurs after 12 hours and remains elevated for 10 days or more. Despite the fact that the use of Tn for the diagnosis of AMI and risk stratification should be helpful for management of patients with chest pain, the 12-hour expectation of peak levels remains the Achilles' heel of this biomarker. More sensitive forms of Tn [43] and new biomarkers were introduced to correct this disadvantage. The activation of circulating (plasma) and local (myocardial) neurohormonal systems plays an important role in the pathogenesis of the MI and its complications. This is initially compensatory in nature to maintain an adequate pumping function of the heart in response to hemodynamic overload and decrease the mass of the functioning myocardium, but may subsequently become maladaptive. Most neurohumoral shifts are mediated by vasoconstrictor and vasodilator responses. The first ones are implemented through the sympathetic adrenal system (SAS), renin-angiotensin-aldosterone system (RAAS), vasopressin, antidiuretic hormone, serotonin, endothelin, thromboxane A2; the other - through the calicrein-kinin system, the system of brain natriuretic peptide (BNP), prostaglandins I2 E2, endothelium-dependent relaxing factor, and others.

Activation of neurohumoral systems in the acute period of the MI promotes expansion of the necrosis zone, development of myocardial ischemia, heart rhythm and acute heart failure (AHF) [44]. The increase in the activity of neurohormonal systems, which is stored at a later date after a myocardial infarction, leads to the development of pathological cardiac remodeling, manifested by the syndrome of chronic heart failure, left ventricle myocardial dysfunction and heart rhythm disorders [44]. Despite the large number of detected and studied neurohormones, our knowledge of the role of these peptides in the development of MI and its complications is very limited. Mechanisms of the effect of neurohormones on the forecast are also not fully understood. In most studies, end points are used for lethality or major cardiovascular complications, as they are easy to determine, but they can all be the result of various pathophysiological processes [44].

The current recommendations of the European Society of Cardiology for the treatment of acute coronary syndrome without ST elevation in 2015 say that there is possibility to use novel biomarkers such as midregional pro-adrenomedullin (ADM) and copeptin for diagnostic and prognostic purposes [38].

Copetin was first described by Holwerda in 1972 [45]. The detection of the glycopeptide was amazing. The glycoprotein of such a relatively low molecular weight (extract from the posterior lobe of the pituitary gland containing a glycopeptide with a molecular weight of about 3200) has never been isolated before [90]. The precursor for vasopressin and copetin is pre-provasopressin, which consists of 164 amino acids, including the signal peptide, vasopressin, copetin and neurophysin II.

The process of synthesis is primarily carried out due to the endocrine mechanism in the nucleus of the hypothalamus (paraventricular and supraoptic in the cerebellar neurons). Pro-vasopressin enters the posterior part of the gland through the pituitary funnel. Mature vasopressin excretes in the next stage with the enzymatic transformation with the help of copeptin and neurophysin II. The secretion of neurohypophysis occurs in response to osmotic and hemodynamic changes [46]. Another way of synthesis passes

through hormone-producing neurons in the hypothalamus, where it is synthesized in the corticotrophin-releasing hormone. In this case, vasopressin directly affects the endocrine cells of the pituitary gland through portal circulation. The elimination of adrenocorticotropin and cortisol in response to stress stimulation reveals significant synergism between corticotrophin-releasing hormone and vasopressin, which confirms the importance of stress as an important factor in the startup of vasopressin production, which then stimulates the release of adrenocorticotropin [47].

Copeptin is a more stable vasopressin surrogate with known effects of osmoregulation and cardiovascular homeostasis. Vasopressin is believed to contribute to [46] increased peripheral vasoconstrictive resistance, thus increasing the load and tension of the ventricle; an increase in protein synthesis in myocytes, which leads to hypertrophy and [47] vasoconstriction of the coronary arteries. These effects are mediated by the receptor V1, while the effect on V2 receptors causes water retention in the renal tubules. Vasopressin acts on three types of receptors: V1, which is responsible for vasoconstriction; V2, which has antidiuretic effect; and V3 which is involved in the release of adrenocorticotropin [46]. V1 receptors are most often located within smooth muscle of the arterial wall and cause vasoconstriction due to intracellular influx of calcium ions via G-protein [46]. V1 receptors are also located in the cells of the heart muscle, but their effectiveness has not been clarified. V2 receptors are in the renal tubules and, by increasing intracellular cyclic adenosine monophosphate (cAMP), have a double action on water: they contribute to the synthesis of matrix ribonucleic acid encoding aquaporin 2 – a protein that forms membrane channels; and they are also involved in the transport of this protein in the renal collecting canal that allows water to be absorbed from the urine [48]. These receptors are currently targets for pharmacological therapy [49, 50].

There are several hypotheses that explain the rapid release of vasopressin/copeptin after destabilization of CAD. Vasopressin reacts quickly as part of the endocrine stress axis, which results in the release of adrenocorticotropin and cortisol. Copeptin is considered a quick and immediate biomarker of an individual stress response [50]. An alternative to the secretion of the vasopressin/ copeptin trigger from the posterior lobe of pituitary gland may be stimulation of the baroreceptors by the threat of hypotension as a result of MI or direct damage of the cardiac baroreceptors. The above-mentioned possibility is confirmed by the fact that the highest increase in the level of copeptin after AMI is observed in patients with acute coronary syndrome (ACS) with elevation of ST segment [51].

Copeptin is a glycosylated, 39-amino acid-length C-terminal portion of the hormones of vasopressin and is produced together with vasopressin in the process of treating the precursor after hemodynamic or osmotic stimulus (hypovolemia, hyponatremia, osmotic pressure, pain, stress, hypoxia and acidosis). Copeptin is also known as a hormone of endocrine stress. Unlike vasopressin, copeptin is very stable in plasma at room temperature, which makes it possible to reliably measure. An increase in the concentration of copeptin after AMI was first reported by Kahn et al. [52] with the highest values registered at first day and further decrease within the next 2–5 days. Copeptin concentrations were higher in patients who died or had a heart failure compared with the rest. Copeptin is stable and easily studied. Taking into account that several studies focused on the participation of copeptin in various pathologies (AMI, cardiomyopathy, stroke, sepsis), the use of that parameter was well-known as an appropriate marker [52, 53]. Previously published data showed the diagnostic and prognostic value of copeptin in combination with cardiac Tn in patients with AMI [54–56]. Copetin, in addition to negative Tn T, may exclude MI [108]. In the case of copeptin levels <14 pg/ml and Tn T level less than 0.01, it is possible to exclude AMI with an area under the ROC curve of 0.97 (negative predictive value of 99.7%), eliminating the need for monitoring and serial blood tests in most patients. There is also evidence that measurment of copeptin allows rapid elimination of AMI in patients with suspected acute coronary syndrome [55, 56]. In the study of 487 patients in the intensive care unit [56], the level of copeptin increased (more than 14 μmol/L) within 4 hours after the onset of symptoms, despite the fact that the levels of cardiac Tn T did not increase (less than 99th percentile of the upper range of the task) These studies indicate that adding copeptin can be helpful in excluding AMI in patients with suspected ACS.

Interestingly, there is a question about the participation of copeptin in the pathogenesis of obesity and the metabolism of adipose tissue. According to Enhörning, increased levels of copeptin associated with an increase in BMI [56, 57].

Copeptin was found to be a prognostic marker of mortality or HF within 60 days of AMI. In

addition, the effect of copeptin on LV dysfunction persists for a long period after an acute event [56].

ADM, a 52-amino acid peptide, was first isolated from human pheochromocytoma cells by a group of Japanese scientists who have screened these cells for peptides that increase cAMP levels in platelets [58]. Physiologically, this hormone has natriuretic, vasodilating and hypotensive effects. ADM can be found in many tissues and organs, including cardiovascular, renal, pulmonary, brain vessels, gastrointestinal tract and endocrine tissue, where it functions as a circulating hormone, as well as a local autocrine and paracrine effector. ADM is a hemodynamically active vasodilator peptide with a potent hypotensive effect [59]. It also exhibits an acute inotropic, vasodilating, diuretic, and natriuretic effect, and it inhibits the production of aldosterone. There is evidence that ADM is one of the most important agents in the development and regulation of fatty metabolism [59].

Also, ADM has antihypertrophic, antiapoptotic, antifibrotic, antioxidant effects and angiogenesis effects. Biological activity of ADM in cardiovascular system consists in expansion of vessels [60] through production of nitric oxide, increase of cardiac output and induction of diuresis [61].

ADM, which is synthesized as part of a larger molecule of the precursor, is called preproadrenomedulin. In humans, this precursor consists of 185 amino acids [61]. However, the exact measurement of ADM until recently was hampered by its very limited stability in the test-tube. Thus, there was no a complete understanding of its diagnostic and therapeutic potential. However, a new method of immunoassay was developed. It measures the concentration of an inactive stable protein fragment that is released into the systemic bloodstream during the synthesis of ADM. Being called mid-regional proADM (MRproADM), it is a stable fragment of pro-ADM, which is produced in a ratio of 1:1 with active ADM. ADM is difficult to measure in plasma because it partially forms a complex with the factor of complement H and is rapidly removed from the bloodstream [62]. Thus, measurement of serum levels of MRproADM accurately reflects the level of ADM [62], and allows conducting functional clinical samples to determine the concentration of ADM [61–64]. According to this strategy, promising studies have evaluated the importance of ADM determining in emergency department patients. In the recently published study BACH (biomarkers in AHF), the main prognostic endpoint was the use of MRproADM compared with the B-type BNP to predict 90-day mortality in patients with a diagnosis of AHF [65]. The prediction of survival for 90 days for MR-proADM was 73% (95% confidence interval [CI]: 70% to 77%), while for BNP – 62% (95% CI: 58% to 66%) ($p<0.001$). In addition to Tn [66], copepin and ADM have not yet spread as prognostic markers that accurately predict short-term mortality. Finally, while an elevated ADM level is associated with an increased risk of short-term mortality, the low level allows it to be equated with a low mortality risk. In addition, it should be noted that MRproADM is a non-specific hemodynamic marker. Regardless of the presence of AHF, its high level indicates the severity of the underlying disease and the need for appropriate intervention. Ultimately, ADM may be similar to Tn in a marker that predicts short-term mortality. Nevertheless, a recent study using MRproADM showed that after AMI, an increase in MRproADM was associated with death and HF [66].

It has been shown that the level of ADM in plasma is significantly increased in patients with acute forms of CAD. Thus, it was noted that in patients with AMI, the concentration of ADM in blood plasma on the 2nd day after the onset of the disease significantly increased (12.3±8.8 versus 4.9±1.0 mmol/l, $p<0.001$) compared with healthy people [67]. Increased ADM level in blood of patients with LV dysfunction was noted. It has been experimentally established that cytokines, in particular, interleukin-1β and tumor necrosis factor (TNF)-α, whose content in AMI increases in parallel with myocardial damage, is stimulated by the in vitro ADM synthesis [68]. These results suggest that both LV dysfunction and peripheral vascular resistance changes are involved in ADM concentration increasing in patients with AMI. High values of the ADM are due to severe LV dysfunction. A connection between increased ADM level in blood and the presence of HF, which complicates the AMI [69], has been established. In addition, a negative correlation between the plasma content of ADM and LV ejection fraction [168] was demonstrated. This data became the reason for estimating the predictive value of ADM in patients with AMI. A correlation was found between plasma concentration of ADM for 2–4 days of AMI and mortality. However, since plasma ADM concentration in patients with AMI is noted in the earlier period (1st–2nd day from the onset of the disease), the predictive value of the concentration of ADM in blood for second day

of AMI is shown [69]. In an additional analysis in patients with severe LV dysfunction, it was noted that the ADM content in blood on the 2nd day was significantly higher in patients who died later than those who survived. At the same time, LV ejection fraction did not significantly differ between the two groups. The authors concluded that the concentration of ADM in blood on the 2nd day of AMI may complement ejection fraction as a prognostic marker, especially in patients with systolic dysfunction.

Thus, copeptin and MRproADM together with cardiac Tn occupy an important and promising place in the diagnosis of CAD, especially its acute forms, but the role of these factors in the course of CAD in the presence of metabolic disorders remains unexplored, as well as their possible influence on dynamics of these indicators, which requires further research.

Conflict of interests

The authors declare that they have no competing interests.

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Received: 22-May-2019
Accepted: 21-Oct-2019