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CLINICAL VALUE OF BLOOD BIOMARKERS IN PATIENTS WITH CHRONIC HEART FAILURE

Abstract

Biomarkers (various laboratory biochemical markers), such as natriuretic peptides (NP), soluble ST2 receptor, copeptin, galectin-3, are widely studied in patients with chronic heart failure (CHF). The European Society of Cardiology recommends the blood NP assay in patients with suspected HF and to use its increase as one of the mandatory criteria for the diagnosis of CHF with preserved and mid-range ejection fraction. Dynamics of NP concentration may reflect the effectiveness of treatment and the necessity of drug titrations. Neprilyzin destroys NP, but does not destroy their precursors, including NT-proBNP. Therefore, it is reasonable to use NT-proBNP as a marker of treatment efficacy and prognosis when using neprilysine inhibitors (sacubitril), which combine the group of ARNI (sacubitril/valsartan). ST2 is a protein receptor for interleukin-33 (IL-33). The transmembrane ST2 (ST2L) binds to IL-33 and forms the IL-33/ST2L complex, which has a cardioprotective effect, prevents the development of myocardial hypertrophy, fibrosis and apoptosis. The soluble ST2 receptor (sST2) is a "trap" for IL-33 and neutralizes the protective effects of the IL-33/ST2L complex, which leads to hypertrophy and fibrosis of the myocardium, dilatation of the chambers and reduction of the myocardial contractility. It can be considered as a marker of unfavorable prognosis in heart failure, but it is not specific. Copeptin is a part of arginine-vasopressin, or antidiuretic hormone, precursor, which plays an important role in the pathogenesis of CHF. Since arginine-vasopressin has a short half-life and is unstable outside the body, copeptin is being actively studied. Its level increases during the CHF decompensation and relates with the functional class of CHF. A combined measurement of the concentration of copeptin and NP may improve the risk stratification in CHF patients. Galectin-3 is a peptide that stimulates the activation of fibroblasts and the development of fibrosis. It increases in CHF patients and is associated with the severity of the condition, systolic and diastolic LV dysfunction and prognosis. Currently, NPs are the best biomarkers that can and should be used in routine clinical practice. To prove the need for widespread use of other biomarkers, additional research is needed.

Key words: *chronic heart failure, biomarkers, biochemical analysis, myocardial infarction, natriuretic peptides, brain natriuretic peptide, NT-proBNP, soluble ST2 receptor, copeptin, galectin-3, prognosis, risk stratification, diagnosis, treatment, management*

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CNP — C-type of natriuretic peptide, DNP — D-type of natriuretic peptide, NT-proANP — N-terminal atrial natriuretic peptide, NT-proBNP — N-terminal brain natriuretic peptide, AVP — arginine vasopressin, ADH — antidiuretic hormone, ADH — antidiuretic hormone, ARB — angiotensin II receptor blocker, SCD — sudden cardiac death, ACEI — angiotensin-converting enzyme inhibitor, CAD — coronary artery disease, IL — interleukin, IL-33 — interleukin-33, BNP — brain Natriuretic Peptide, NP — natriuretic peptide, PC — postinfarction cardiosclerosis, ANP — atrial natriuretic peptide, SBD — systolic blood pressure, GFR — glomerular filtration rate, CVD — cardiovascular disease, CCE — cardiovascular events, LV EF — left ventricular ejection fraction, FC — functional class, CHF — chronic heart failure, ECHO-CG — echocardiographic examination.

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Chronic heart failure (CHF) is a consequence of many cardiovascular diseases (CVD), one of the final stages of the cardiovascular continuum [1,2]. CHF is a condition accompanied by a significant deterioration in the quality and reduction in the patient's life expectancy [1,2]. The prevalence of CHF in the population is quite high. According to epidemiological studies in the Russian Federation, it is 7–10%. In addition, the prevalence of CHF increases with age: from 1% of people in the age group of 50 to 59 years, up to 10% of those who are older than 80 years [3]. According to the Framingham study, five-year survival after the onset of clinical CHF symptoms is only 25% in men and only 38% in women [4].

Since the clinical signs of CHF are not specific enough, and during the echocardiographic study (ECHO-CG) it is not always possible to identify diagnostically significant changes, in the case of suspected CHF it is possible to determine the blood laboratory biochemical markers — biomarkers, among which are currently known natriuretic peptides, soluble ST2 receptor, copeptin, galectin-3 as an alternative diagnostic approach [5]. Said biomarkers are the subject of this review.

Natriuretic peptides

Among the main biomarkers of CHF are natriuretic peptides (NPs) [6]. The value of NP in CHF has been studied in numerous studies, and therefore the European Society of Cardiology recommends to determine the blood NP level in patients with suspected CHF (Figure 1) and to use the increase in its concentration as a diagnostic test for CHF with mid-range and preserved left ventricular ejection fraction (LV EF), Table 1.

NP is a family of related peptides comprising atrial natriuretic peptide (atrial natriuretic peptide, A-type, ANP), brain natriuretic peptide (brain natriuretic peptide, B-type NP, BNP), and later identified C-type NP (CNP) and D-type NP (DNP). The main reason for the increase in NP production is the volume overload of the heart cavities [8, 9].

A similar molecular structure allows combining NPs into one group. They are characterized by the presence of a ring-shaped amino acid nucleus, N-amine and C-carboxyl fragments. The difference between all NP is provided by different amounts of amino acids included in their composition. A- and B-types of NP are synthesized in the body as inactive prohormones [10, 11]. Proteases provide their cleavage into two fragments: active C-terminal and inactive N-terminal. Active C-terminal fragments are actually hormones — ANP and BNP. N-terminal fragments are N-terminal atrial (N-terminal pro-A-type natriuretic peptide, or NT-proANP) and T-terminal brain natriuretic peptides (N-terminal pro-B-type natriuretic peptide, or NT-proBNP), inactive, and they have diagnostic value [10, 11, 12].

Although modern laboratory technologies make it possible to identify all three NPs, the definition of BNP and its precursor NT-proBNP has a number

Table 1. *CHF diagnosis criteria [1, 2, 7]*

Criteria	HFrEF	HFmrEF	HFpEF
1 Clinical pattern	Symptoms and/or signs of heart failure*	Symptoms and/or signs of heart failure*	Symptoms and/or signs of heart failure*
2 LV EF	<40%	40-49%	≥50%
3 NP		↑ NP**	↑ NP**
4 ECHO data		a. Structural cardiac changes (LVH, dilation of LA) and / or b. DD	a. Structural changes in the heart (LVH, dilation of LA) and / or b. DD
Required number of criteria	2	4	4

* — Symptoms and / or signs may not be observed in the early stages of HF and in patients treated with diuretics; ** — BNP> 35 pg / ml and / or NT-proBNP> 125 pg / ml;
LV EF — left ventricular ejection fraction, HFrEF — heart failure (HF) with low (decreased) LV EF, HFmrEF — HF with middle range (intermediate) LV EF, HFpEF — HF with preserved LV EF; NP-natriuretic peptide, BNP-brain NUP, NT-proBNP — N-terminal fragment of BNP, LVH — left ventricular hypertrophy, LA — left atrium, DD — diastolic dysfunction

of advantages. The disadvantage of ANP is that it is more susceptible to factors such as exercise, changes in body position, and has a shorter half-life, which in active ANP is only 3-4 minutes. CNP can be considered as a marker of mainly endothelial dysfunction.

NP receptors are present in the brain, vascular bed, kidneys, adrenal glands and lungs [10, 11, 12]. Under the influence of NP there is dilation of afferent arterioles and constriction of efferent arterioles, an increase in renal blood flow and glomerular filtration rate (GFR). Also, NPs inhibit sodium and

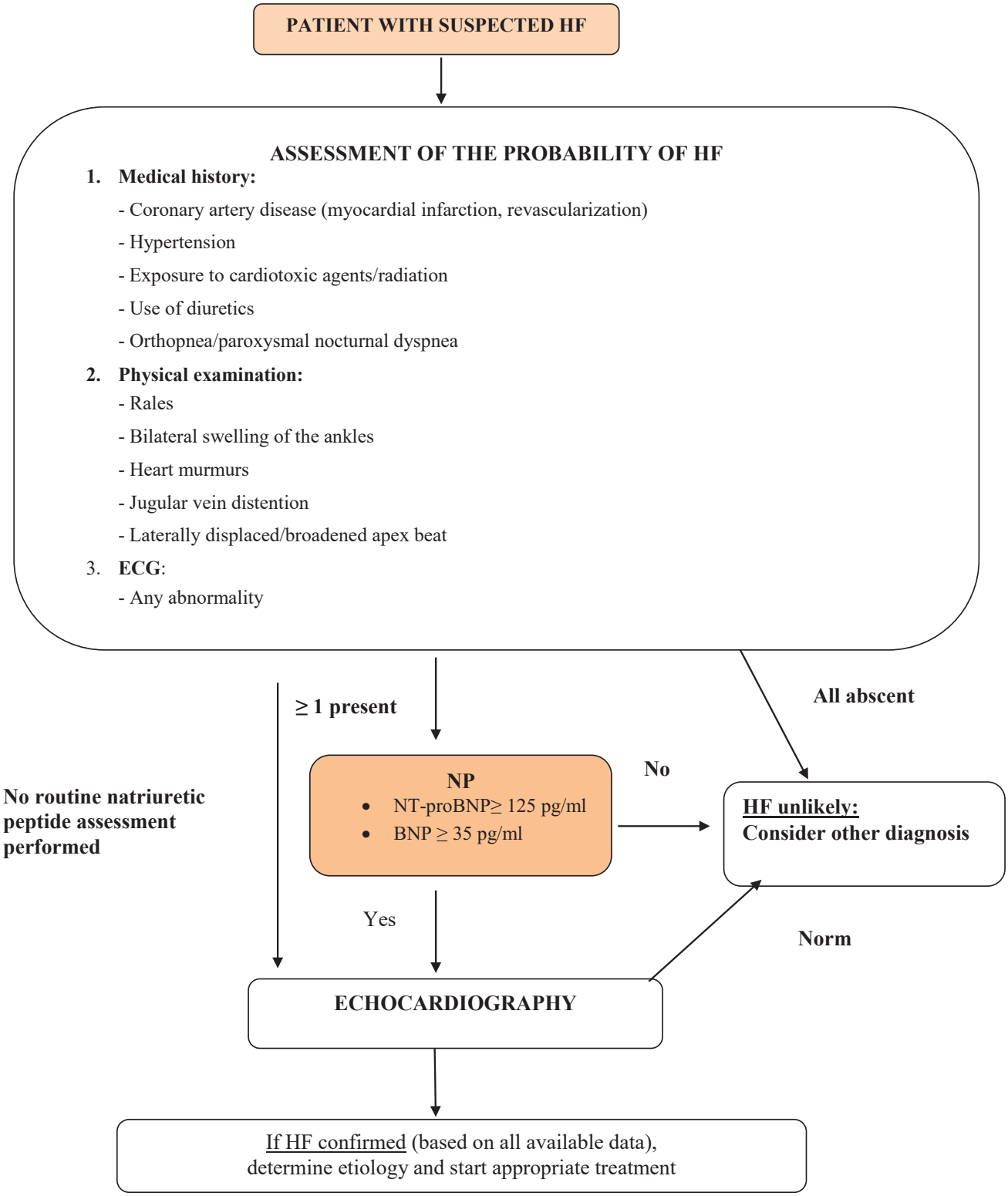

Figure 1. *CHF diagnosis algorithm [2]*

water reabsorption caused by the action of angiotensin II on the proximal tubules, prevent the action of antidiuretic hormone (ADH) on the cortical parts of the collecting tubes and inhibit sodium reabsorption in the medullary parts of the collecting tubes, thereby increasing natriuresis and diuresis, reduce preload. In addition, they inhibit the secretion of renin, aldosterone, inhibit the activity of the sympathetic nervous system, reduce the activity of proliferation and hypertrophy [10, 11, 12].

Normal serum values of NPs have certain variability due to age and gender specificity: their concentration increases with age and is higher in women [13]. In 90% of young healthy subjects BNP level is <25 pg/ml; and NT-proBNP is ≤70 pg/ml. For patients with compensated CHF the upper limit of normal values for BNP is 35 PG/ml and for NT-proBNP it corresponds to 125 PG/ml; for acute decompensation of HF, the maximum acceptable values are 100 pg/ml and 300 pg/ml respectively, and for ANP the optimal value is <120 pmol / l [14, 15]. These diagnostic values are used both in HF with reduced LV EF (CHFrEF) and HF with preserved (CHFpEF) and mid-range (CHFmrEF) LV EF [14, 15].

In 1986, Burnett J. for the first time demonstrated an increase in the blood concentration of ANP with advanced CHF [16]. A little later, Mukoyama M. et al. showed a direct relationship between the level of BNP and the functional class (FC) of CHF [17] during examination of patients with HF of different genesis. At present, the use of BNP and NT-proBNP definitions for diagnosis and assessment of HF severity is widely recommended [18]. Both biomarkers have approximately equal sensitivity and specificity [19, 20].

Determination of NP level in patients with suspected HF in both acute and non-acute onset of the disease is an exclusion test. The normal NP level in an untreated patient practically excludes significant HF, making further research methods unnecessary (Figure 1) [21].

Morwani J. et al. were the first to prove that BNP levels were significantly different in the groups of patients with postinfarction cardiosclerosis (PC) with reduced LV EF and subjects with relatively reduced and normal LV EF in comparison with people without cardiac disease [22]. Similar data were obtained in the study by Davidson N. et al. [23]. Further studies also confirmed the inverse correlation between the level of NT-proBNP and LV EF [18, 21].

Fattah E. et al. found statistically significant positive correlation of the BNP level and severity of mitral insufficiency according to echocardiography (ECHO-CG) [24].

According to McDonagh T. A. et al., it was shown that the prevalence of LV systolic dysfunction according to transthoracic ECHO-CG in the examined group was more than 3% in the study which included 1,252 patients of different age groups by random sampling. The sensitivity and specificity of elevated BNP level of more than 17.9 pg/ml for the detection of systolic LV dysfunction were 77% and 87% respectively, among the examined patients, and the negative predictive value was 97.5%. In the subgroup of patients in the age cohort older than 55 years with coronary artery disease (CAD), in which the rate of LV diastolic dysfunction was 12.1%, test sensitivity was 92%, specificity was 72%, and the negative predictive value was 98.5% [25].

The study conducted by E. V. Alexandrov revealed a strong direct correlation between the deceleration time of early diastolic blood flow at ECHO-CG and blood BNP level, and it was shown that the probability of accurate prognosis is higher than 98% [26].

The data of the diagnostic examination in 1,586 patients with suspected HF (the Breathing Not Properly Multinational Study) provide the following results: for BNP level of 100 pg/ml sensitivity was 90%, specificity was 76%, positive and negative prognostic value was 79 and 89% respectively, and diagnostic accuracy was 83% [27].

According to the results of the British study titled Natriuretic Peptide Study, for NT-proBNP 125 ng/ml the positive and negative prognostic value is 0.44 and 0.97 respectively, and for BNP 100 PG/ml — 0.59 and 0.87 respectively [28].

The study conducted by Aspromonte N. et al. included 357 individuals with and without HF. In the group of patients with CHF, BNP concentration was 469 pg/ml on average, and in the group without signs of LV dysfunction — 43 pg/ml. During the statistical analysis, patients with diagnosed HF were divided into 3 subgroups: with the presence of diastolic dysfunction, systolic dysfunction, as well as combined LV dysfunction. In these three subgroups BNP concentrations were on average 373, 550 and 919 pg/ml respectively. For the

BNP level of 80 pg/ml sensitivity was 84% and specificity — 91% [29].

In the English and American study to determine BNP level in patients with an acute cardiac asthma attack, it was shown that an increase in its concentration with a high degree of probability indicates in favor of dyspnea of cardiac genesis. The researchers noted that for the verification of cardiac dysfunction in such conditions, a sufficiently high rate of BNP is significant (more than 300 pg/ml), while its moderate rise (100-200 pg/ml) occurs in other pathological conditions accompanied by dyspnea [30, 31].

It was also found that the monitoring of the level variation of the peptide and its precursor has a higher informative value for the verification of pressure in the heart cavities than the insertion of the Swan-Ganz catheter [32, 33].

In addition to the primary diagnosis, the use of BNP and NT-proBNP level determination to assess the prognosis and efficacy of therapy is also discussed. Thus, the high concentration of BNP is associated with a poor prognosis, and the decrease in its level correlates with the best prognosis [33]. At the same time, a number of major studies evaluating the efficacy of enhanced therapy aimed at reducing BNP level gave contradictory results, which does not currently allow widely recommending an adjustment of the treatment on the basis of the change in BNP level [32].

SAVE and CONSENSUS II studies have demonstrated that BNP level is a significant prognostic factor indicating the risk of recurrent acute MI, development of HF and death not only in patients with MI, but also in patients with unstable angina [35].

Gong H. et al. revealed in patients with different cardiac pathology that BNP not only significantly correlated with clinical data and transthoracic ECHO-CG parameters, but was also the strongest independent predictor of sudden cardiac death (SCD) [36].

According to Daniels L. et al., it was shown that an increase in NT-proBNP level by more than 300 pg/ml in combination with moderate or severe LV diastolic dysfunction, or an isolated increase in NT-proBNP by more than 600 pg/ml, or an increase in BNP by more than 100 pg/ml significantly worsened the prognosis [37].

The influence of NT-proBNP level on the probability of development of SCD was demonstrated in a large-scale population-based study titled Cardiovascular Health Study. It included 5,447 patients of the older age group with 289 cases of SCD for mean follow-up period of more than 12 years. Elevated levels of NT-proBNP significantly correlated with mortality independently of other risk factors [38].

Data from the Russian clinical study conducted at the Cardiology Research Institute, Tomsk, which convincingly shows a significant association between elevated NT–proBNP levels and post-infarction myocardial remodeling with reduced contractile ability of the left ventricle, and with high myocardial-arterial stiffness, calculated according to the criterion of ventricular-vascular coupling EA/Es, are of some interest. The study included 140 patients at the median age of 60 years with coronary artery disease associated with CHF NYHA II-IV developed secondary to post-infarction and (or) ischemic LV myocardial dysfunction. Increase of EA/Es ratio>1.29 in patients with CHF of III-IV FC along with increase in blood NT-proBNP level by more than 303.4 PG/ml was characterized by prognostically unfavorable course of the disease [39].

Richards M. was the first to suggest that in patients with CHF of II-III FC therapy selection under BNP control is more accurate than based on clinical parameters [40].

The IMPRESS (Inhibition of Metalloproteinase in a Randomized Exercise and Symptoms Study in Heart Failure) study demonstrated a statistically significant decrease in NP with clinically effective doses of angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARB) in one and two years from the beginning of drug therapy [41].

Similar data were obtained in the course of experimental work conducted by Tang S., Peng D. during the study of pharmacological properties of valsartan and benazepril in patients with HF [42].

If the research data on the study of ACEI and ARB are identical, the results of the effect of beta-blockers on NP level are very contradictory. A number of works indicate its reduction with administration of beta-blockers. In particular, Andreev D. A. et al. concluded that the switching of patients with moderate HF from therapy with so-called "non-recommended" beta-blockers to bisoprolol

was accompanied by an improvement in clinical status, quality of life, inotropic heart function and a decrease in NT-proBNP level in patients with initially higher values, regardless of the decrease in heart rate [43].

However, there is evidence of an increase in NP level under the influence of drugs of this pharmacological group. For example, the results of a New Zealand study showed that 6 weeks after the start of treatment with metoprolol in 60 patients with HF, high FC and EF <40% there was a statistically significant increase in BNP, NT-proBNP, ANP and NT-proANP levels [44].

Very similar data are presented in the recently published work by Broch K. dedicated to the study of the metoprolol effect on NT-proBNP level in patients with CHF of I-II FC [45].

The TIME-CHF study is by far one of the largest multi-center (n=499) studies [46]. It included elderly patients with diagnosed CHF of II-IV FC and LV EF ≤45%. Patients had a history of hospitalization for decompensated HF in the last 10-12 months and baseline NT-proBNP of more than 400 pg/ml for patients younger than 75 years or more than 800 pg/ml for patients older than 75 years. The protocol included patients with both reduced and preserved LV EF. The target levels of NT-proBNP are below 400 pg/ml or 800 pg/ml (according to the age). After 1.5 years of standard complex therapy, there were no significant differences in the effect on survival of the groups (HR 0.91, 95% CI 0.72–1.14, p=0.39). Despite significantly more frequent changes of therapy in the group of BNP there were no detected inter-group differences in the change of FC of CHF and the marker level. Further statistical analysis depending on the age of the patients showed that in individuals in the age group younger than 75 years, treatment under NP control leads to a reduction in mortality (HR 0.42, 95% CI 0.24-0.75, p=0.002) and hospitalization due to decompensated HF. At the same time, in patients older than 75 years the efficacy of this therapy approach was not revealed, and in this group there was more common excessive decrease in BP and the phenomenon of renal failure in 10.5% of patients versus 5.5% in patients who were on standard treatment [46].

According to the results of the Russian study conducted by A.A. Skvortsov, the long-term treatment of patients with the use of monitoring of NP level reduces the rate of decompensated CHF and mortality from CVD compared to standard therapy,

Table 2. *High NP level causes [1, 2, 18]*

Cardiac	Non-cardiac
Heart failure	Elderly age
Acute coronary syndrome	Ischemic stroke
Pulmonary embolism	Subarachnoid haemorrhage
Myocarditis	Impaired renal function
Left ventricular hypertrophy	Dysfunction of the liver (mainly cirrhosis with ascites)
Hypertrophic or restrictive cardiomyopathy	Severe infections (including severe pneumonia and sepsis)
Congenital and acquired heart defects	Paraneoplastic syndrome
Atrial and ventricular tachyarrhythmias, including atrial fibrillation	Chronic obstructive pulmonary disease
Cardioversion, discharges of an implantable cardioverter-defibrillator	Obstructive sleep apnea
Heart contusion	Pulmonary hypertension
Cardiac surgery	Anemia
Pericarditis	Severe metabolic and endocrine disorders (e.g., thyrotoxicosis, diabetic ketoacidosis)
Cardiotoxic effect of chemotherapy	Severe burns

and significantly affects the change in quality of life, clinical, functional state and ECHO-CG parameters [47].

It should be noted that neprilysin destroys ANP, BNP and CNP, but does not destroy NT-proBNP. Therefore, with neprilysin inhibitors, which are part of a new group of medicines ARNI (sacubitril/valsartan) levels and effects of ANP, BNP and CNP increase whereas NT-proBNP level does not increase due to neprilysin inhibition and retains its value as a marker of therapeutic efficacy and prognosis [50].

Thus, NP today are generally recognized markers of HF, their high value in determining the prognosis and risk stratification of patients with HF has been repeatedly proven in numerous clinical studies. Their determination should be an integral part of CHF diagnosis, especially with preserved and mid-range LV EF [1,2]. The change of their concentration, mainly NT-proBNP, makes it possible to judge the efficacy of the therapy and the need for dose titration. However, due to the wide variability of NP values, depending on age and gender and concomitant pathology (may increase in acute coronary syndrome, pulmonary embolism, heart contusions, after cardioversion, stroke, renal dysfunction, liver cirrhosis, paraneoplastic syndrome, COPD, anemia, severe infections, burns, thyrotoxicosis, diabetic ketoacidosis, etc., Table 2), they are not ideal markers of HF. In this regard, there is a high interest in the study on new markers of CHF, which are able to reflect the various links in the pathogenesis of the disease, which include the soluble ST2 receptor, copeptin, galectin-3.

Soluble ST2 receptor

ST2 is a receptor of protein nature belonging to the family of interleukins (IL). It is identified in two main forms: transmembrane (ST2L) and soluble (sST2) [49]. The transmembrane form (ST2L) binds to its natural ligand, interleukin — 33 (IL-33), and forms the IL-33/ST2L complex [49]. It is known that this complex has a protective effect on cardiomyocytes experiencing mechanical stress due to hemodynamic load, prevents the development of myocardial hypertrophy and has an antifibrotic effect, and also prevents apoptosis, thereby protecting the cell from death [49, 50].

The soluble form has the opposite effect: sST2 circulating in the blood are a "trap" for IL-33, thereby neutralizing the protective effects of the IL-33/ST2L signaling system, which leads to hypertrophy and fibrosis of the myocardium, dilation of the heart chambers and a decrease in the contractile ability of the LV myocardium [49, 50].

The growing interest in studying the activity of sST2 and ST2L in the pathogenesis of cardiovascular disease (CVD) increasingly pushes the practitioner to evaluate the sST2 receptor as a new marker of cardiovascular events (CVD) and adverse clinical outcomes primarily associated with HF and CAD [51].

The mean normal concentration of sST2 is 18 ng/ml, concentration above 35 ng/ml indicates an elevated risk of CVD [51].

Transient increase in the levels of sST2 was identified for the first time in the development of MI in mice after ligation of the coronary artery [52]. A sufficient number of studies investigating sST2 as a biomarker of CHF was subsequently conducted. In the PRIDE study, which included 600 patients with dyspnea, the concentration of sST2 was correlated with the degree of severity of HF symptoms, FC of CHF, LV EF and creatinine clearance. Patients with preserved LV systolic function had lower sST2 levels compared to patients with systolic dysfunction. In addition, the researchers concluded that the concentration of sST2 is a strict predictor of mortality in HF: in the group of patients with a marker level above the median, the risk of death increased by more than 11 times [53, 54].

According to Shah R., it was shown that high sST2 concentrations are associated with an increase in the size of the myocardium and a decrease in the contractility of the LV [55]. In addition, the association of the sST2 level increase with FC of HF was demonstrated. Mean level of sST2 in patients with I FC was 43.8 (18.4-200.0) ng/ml, II FC — 36.5 (18.4-127.2) ng/ml, III FC — 54.3 (21.5-200.0) ng/ml and IV FC — 72.2 (25.4-200.0) ng/ml, $p<0.05$ [55].

Mueller T. et al., in the study of sST2 levels in 137 patients with decompensation of CHF, showed a significant increase in the median marker concentration in patients who died. The authors concluded that sST2 is a strict predictor of annual mortality independent of other factors [56].

In the Ludwigshafen Risk and Cardiovascular Health Study, the role of ST2 in HF prognosis was examined in 1,345 patients with CAD. During the follow-up period, which lasted 9.8 years, 477 patients died. In the group of patients with the highest content of sST2, the risk of death was 2 times higher than in other groups [57].

The CLARITY-TIMI 28 study proved that regardless of the NT-proBNP precursor level the increase in sST2 concentration is a predictor of mortality from HF [58].

Alan H.B. et al. found that sST2 variability in healthy individuals is lower compared with NP. The authors demonstrated that analytical variability of sST2 within 2 months was 4.2%, and biological individual variability — 11% [59]. The researchers proved that the measurement of this marker can be used for long-term monitoring of the course of CHF. Dieplinger et al. measured biological variability of sST2 for 6 weeks. It was 10.5%, which is consistent with the study of Alan H.B. et al. [60].

Nevertheless, despite the high diagnostic value of sST2, it should be remembered that its increase is also found in a number of other diseases, such as acute and chronic inflammatory, autoimmune diseases and asthma.

Copeptin: Derivative Form of Arginine Vasopressin

Arginine vasopressin (AVP), better known as antidiuretic hormone (ADH), is one of the key hormones involved in many physiological and pathophysiological processes, especially in the maintenance of cardiovascular homeostasis [61]. ProAVP, which is a precursor of AVP, is formed and subsequently released by 2 endocrine mechanisms interacting at the level of neurons [61].

In the first mechanism, proAVP is produced in large-cell neurons of the supraoptic and paraventricular nuclei of the hypothalamus. During axon transport to the posterior lobe of the pituitary gland proAVP is converted into AVP, neurophysin II and copeptin through a cascade of enzymatic reactions [61, 62]. The process is completed at the level of neurohypophysis. These three proteins are subsequently secreted from the neurohypophysis by hemodynamic or osmotic stimulation [62, 63].

In the second mechanism, the AVP precursor is synthesized in the parvocellular neurons of the hypothalamus, and then it enters the pituitary portal system and acts on the cells of the adenohypophysis [64].

In the bloodstream, AVP binds to three receptors: vascular receptor AV1R, renal AV2R and neuroendocrine AV3R. For AVP, AV1R receptors are the most common and predominant. Through the AV1R receptors, AVP induces a vasoconstrictive effect by increasing the level of intracellular calcium. Binding of AVP to the receptor AV2R has an antidiuretic effect. It is associated with an increase in the synthesis of aquaporin-2 in the kidneys, which stimulates an increase in the permeability of collecting tubes for water and strengthening its reverse absorption. In addition, endothelial cells of blood vessels also contain AV2R receptors that play an important role in the mechanisms of blood coagulation. Their activation increases the level of von Willebrand factor, factor VIII, and plasminogen activator in plasma [64]. The third type of AVP receptor — AV3R — is located in the anterior pituitary gland and is involved in the secretion of adrenocorticotropic hormone. In addition to binding to specific receptors, AVP is able to interact with oxytocin and certain purinergic receptors. Oxytocin receptors are localized in the endothelium of the vascular wall, and interaction with them leads to vasodilating action [64].

There are a number of challenges when determining AVP in the blood: short half-life, rapid elimination from the body and instability outside the body. In regard to these aspects, lately there has been active study of the protein copeptin which is related to arginine-vasopressin, synthesized in equimolar quantities of vasopressin and reflecting its nature and activity in the body. It should be noted that copeptin is a fairly stable peptide; its concentrations remain in the blood for several days after blood sampling [64].

Copeptin was first isolated by D. Holwerda in 1972 from the posterior pituitary gland of a pig [64]. Copeptin is a glycosylated protein with a molecular weight of 5000 Da from 39 amino acids with a leucine-enriched segment. This peptide is the C-terminal part of provasopressin (P-proAVP) and is released together with the AVP during the decomposition of the precursor [65]. The blood

copeptin level in healthy people ranges from 1 to 12 pmol/l with a mean value of <5 pmol/l, while males have higher peptide values in comparison with women; the difference in mean hormone value is around 1 pmol/l; there was no significant diagnostic difference between the concentrations in different age groups [64, 65]. Like AVP, copeptin level in blood plasma varies depending on changes in its osmotic pressure. The normal range of copeptin reflects the physiological secretion of AVP essential for maintaining the plasma osmotic pressure. However, in severe conditions, such as shock, sepsis, CVD, the release of AVP is reflected by sharp increase in plasma copeptin level, which has a high diagnostic and prognostic value [66].

In recent years, a number of researchers have demonstrated the clinical significance of this hormone as a biomarker of CHF. Vetrone F. and Santarelli S. found a significant increase in copeptin in patients with decompensated CHF — 42 (0-905) mmol/l, and with compensated CHF, the median biomarker concentration was 20 (0-887) pmol/l [67]. Silva Marques et al., Stephanie Neuhold noted the relationship between copeptin and FC of HF [68.69]. A fairly extensive study which included 577 patients with acute HF proved that patients with hormone levels of more than 57 pmol/l had an unfavorable prognosis for mortality within 3 months [70]. It is very important to note that the combined measurement of copeptin and NP concentration allows improving risk stratification in patients with CHF [71].

Galectin-3

Currently, galectin-3 is considered as a promising biomarker for diagnosis and prognosis of CHF. The American Heart Association has included galectin-3 in the clinical protocol for the prevention and treatment of HF as a marker of stratification for patients at high risk of adverse clinical events [72].

Galectin-3 is a protein with a molecular weight of 26 kDa, belonging to the family of B-galactoside binding proteins [73]. Galectin-3 is widely distributed in the body; the peptide binds to a wide range of extracellular matrix proteins due to the presence in its structure of the collagen-like domain. Galectin-3 is expressed by macrophages, osteoblasts, fibroblasts and neutrophils. Especially important is that this peptide stimulates the activation of fibroblasts and the development of fibrosis in the future by increasing the activity of collagen and the activation of growth factor b. These processes play an important role in HF pathogenesis, as they lead to the development of cardiac remodeling and progression of LV dysfunction [74].

Currently, there is sufficient information on the role of galectin-3 in the development of CHF, progression of atrial fibrosis, and remodeling of heart cavities. Galectin-3 expression was found to be minimal or practically absent in healthy individuals and patients with compensated HF, while it was maximal at the peak of fibrosis and inflammation [73, 74]. Clinical studies have shown that the expression of galectin-3 increases in patients with reduced LV EF regardless of HF etiology, which allowed positioning galectin-3 as a marker of HF [73, 75, 76].

The first report on the role of galectin in the human body was presented by Sharma et al. [73.76]. The study of LV myocardial biopsy material in patients with aortic stenosis and with preserved or reduced LV EF demonstrated increased activity of the peptide in the myocardium in patients with reduced LV inotropic function [73, 76]. A subsequent PRIDE study showed a significant increase in galectin-3 in patients with acute HF compared with the control group (9.2 versus 6.9 ng/ml, p <0.001). The optimal threshold value of galectin-3 for the diagnosis of HF was 6.88 ng/ml, which had a sufficiently high sensitivity — 80%, but lower specificity — 52%. Further multiple factor analysis showed that the precursor of BNP has a more significant diagnostic ability compared to galectin-3. No correlation was found between galectin-3 and FC of CHF [77].

According to the HF-ACTION (Heart Failure: A Controlled Trial Investigating Outcomes of exercise training) study, galectin-3 levels were associated with higher FC, elevated serum creatinine levels, low maximum oxygen consumption, and lower systolic blood pressure (SBP) [78, 79].

In the study conducted by Yu.V. Dubolazova, which included patients with HF and preserved and reduced EF, it was shown that serum galectin-3 levels had a statistically significant correlation with LV EF ($p < 0.05$) [80].

The relationship of galectin-3 levels with ECHO-CG parameters was shown by a group of scientists led by Ravi V. Shah: elevated values of the biomarker

were associated with high LV filling pressure (E/E') (r=0.345, p=0.01) and disturbance of its relaxation in diastole — decrease in the peak velocity E' (r=-0.246, p=0.03); a relationship was found between the increase in galectin-3 concentration and the degree of regurgitation on the mitral and/or tricuspid valves (r=0.297 and r=0.258 respectively, p<0.005) [81].

According to the CARE-HF study to assess the effect of galectin-3 on the prognosis of patients with CHF of III-IV FC, the initial level of the marker was directly related to mortality and hospitalization due to HF. The level of plasma galectin-3 >30 ng/ml increased the risk of the end point (death and hospitalization due to CHF) by more than 2 times [82].

In a large cohort of the PREVEND study (Prevention of Real and Vascular END stage) baseline galectin-3 level was an independent predictor of total (but not cancer or cardiovascular) mortality [83].

A number of significant studies have shown the possibility of using galectin-3 as a biomarker of HF. Additional clinical studies are necessary to determine the possibility of its application in everyday clinical practice [84-86].

Conclusion

Thus, today NPs are recognized biomarkers that are included in the guidelines for the management of patients with heart failure. They can and should be used by therapists and cardiologists in real clinical practice. Their determination should be an integral part of the diagnosis of CHF, especially with preserved and mid-range LV EF. The variation of their levels, mainly NT-proBNP, can help in assessing the efficacy of treatment and the need for the drug dose titration. Additional studies are needed to confirm the diagnostic and prognostic value and to identify new highly specific and sensitive biochemical markers in patients with CHF.

Conflict of Interests

The authors declare no conflict of interests.

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