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ЗНАЧЕНИЕ БИОМАРКЕРОВ В ДИАГНОСТИКЕ И ПРОГНОЗИРОВАНИИ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ В СТАРШЕМ ВОЗРАСТЕ

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The Value of Biomarkers in the Diagnosis and Prognosis of Heart Failure in Older Age

Резюме

Поиск надежных алгоритмов диагностики сердечной недостаточности с сохраненной фракцией выброса левого желудочка (ФВ ЛЖ) в старшем возрасте является актуальной проблемой, что обусловлено низкой специфичностью клинических проявлений и особенностями инволютивных процессов, происходящих в организме человека. В качестве альтернативного диагностического подхода возможно определение в крови лабораторных биохимических маркеров — перспективного метода диагностики, прогноза и контроля эффективности лечения. В статье рассматривается значение маркеров миокардиального стресса (мозговой натрийуретический пептид, N-терминальный мозговой натрийуретический пептид, срединный фрагмент предсердного натрийуретического пептида); «механического» миокардиального стресса (растворимый стимулирующий фактор роста, экспрессируемый геном 2 — sST2), копептина, галектина-3 у пациентов с сердечной недостаточностью и сохранённой ФВ ЛЖ, включая лиц старшего возраста, а также возможность их использования в амбулаторной практике для прогнозирования течения сердечной недостаточности. Обсуждается вклад мультимаркерной модели для комплексной оценки прогноза с учетом как «гемодинамической» стороны миокардиального стресса (перегрузка давлением или объемом, маркеры — натрийуретические пептиды), так и «механической» (фиброз / гипертрофия / ремоделирование сердца, маркер — sST2).

Ключевые слова: *хроническая сердечная недостаточность, сохранённая фракция выброса левого желудочка, амбулаторные пациенты, старший возраст*

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Abstract

The search for reliable algorithms for diagnosing heart failure with preserved left ventricular ejection fraction (LVEF) in elderly patients is an urgent problem due to the low specificity of clinical manifestations and the peculiarities of involutive processes occurring in the human body. As an alternative diagnostic approach, it is possible to determine in the blood laboratory biochemical markers — a promising method of diagnosis, prognosis and control of the effectiveness of treatment. The article examines the significance of myocardial stress markers (brain natriuretic peptide, N-terminal brain natriuretic peptide, median fragment of atrial natriuretic peptide); «mechanical» myocardial stress (soluble stimulating growth factor expressed by gene 2 — sST2), copeptin, galectin-3 in patients with heart failure and preserved LVEF, including older persons, as well as the possibility of their use in outpatient practice to predict the course of heart failure. The contribution of the multimarker model for a comprehensive assessment of prognosis is discussed, taking into account both the «hemodynamic» side of myocardial stress (pressure or volume overload, markers — natriuretic peptides), and «mechanical» (fibrosis / hypertrophy / heart remodeling, marker — sST2) myocardial changes.

Key words: *chronic heart failure, preserved left ventricular ejection fraction, outpatients, older age*

Conflict of interests

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BNP — brain natriuretic peptide, CHF — chronic heart failure, CI — confidence interval, EF — ejection fraction, FC — functional class, HF — heart failure, HFpEF — heart failure with preserved ejection fraction, LV — left ventricle, NPs — natriuretic peptides, NT-proBNP — N-terminal prohormone of brain natriuretic peptide, RR — risk ratio

Chronic heart failure (CHF) is a pressing problem facing medicine today. In the Russian Federation, annual mortality in patients with CHF reaches 6%, and 12% if the course is more severe [1]. Almost one in four patients with CHF dies within a year of being discharged from the hospital.

Early detection of adverse events, including decompensated CHF, is of utmost importance in primary health care where most patients with CHF are observed, especially elderly patients.

According to the EPOCH epidemiological study, the number of patients with preserved left ventricle (LV) ejection fraction (EF) in Russia from 2005 to 2017 increased by 21.5% and amounted to 53% of the population of patients with CHF [2]. According to the register of patients with CHF who visit outpatient clinics, preserved LVEF was detected in 78% of patients [3].

Similar data on the incidence of heart failure with preserved left ventricular ejection fraction (HFpEF) in Russia (84.1%) were obtained in the IMPROVEMENT HF population study (Russian part of the program) [4]. According to the Russian Register of patients with CHF, individuals with HFpEF prevailed (83%) among inpatient and outpatient patients with CHF FC I–IV; impaired LV systolic function was observed just in 17% of patients [4].

The studies conducted demonstrate a constantly increasing number of patients with preserved LVEF; therefore, HFpEF can be defined as one of the non-infectious epidemics of the 21st century [1].

Diagnosis of chronic heart failure with preserved left ventricular ejection fraction

The following are the main clinical signs of HFpEF: dyspnea during exercise, increased fatigue, decreased exercise tolerance [4].

To establish the diagnosis of HFpEF, the following conditions should be met:

1. Symptoms and clinical signs that are typical of HF.
2. Left ventricular ejection fraction ≥50%
3. Increased levels of natriuretic peptides (brain natriuretic peptide (BNP) > 35 pg/ml, or N-terminal prohormone of brain natriuretic peptide (NT-proBNP) > 125 pg/ml)
4. Corresponding structural changes of the heart (LV hypertrophy / left atrial (LA) dilation) and/or LV diastolic dysfunction [1, 5]

Challenges in the diagnosis of heart failure in elderly patients at the prehospital stage

Heart failure is hard to detect in elderly patients due to the low specificity of symptoms.

One of the markers of severe clinical condition and congestion in patients with CHF is dyspnea when bending over (bendopnea: from English «to bend over» and Greek pneō — «to breathe») that appears in the first 30 seconds. Bending over leads to increased venous

return and filling pressure of the left heart, right atrium and pulmonary capillary wedge, which contributes to dyspnea, especially in cases of initially high filling pressure of heart chambers [6].

It has been established that bendopnea is the only type of dyspnea that is not associated with respiratory problems or coronary heart disease (CHD), which means that this symptom has potential in the differential diagnosis of CHF, especially in elderly patients [7, 8].

Weakness, fatigue and a longer recovery time after exercise in elderly patients without myocardial damage are due, among other things, to aging processes (senile asthenia, sarcopenia) and/or comorbidities.

Cognitive impairments and hearing problems make it difficult to take patient history and complaints in this group of patients, making it hard to assess symptoms and make the right diagnosis. In addition, such impairments lead to decreased adherence to therapy. For example, the estimated prevalence of bilateral hearing loss for sounds with a threshold of hearing more than 25 dB is 27% among patients aged 60 to 69; 55% among patients aged 70 to 79, and 79% among patients 80+ [9].

Searching reliable algorithms for the diagnosis of HFpEF in elderly patients is challenging due to the low specificity of clinical signs [5, 10, 11].

Biomarkers in the diagnosis of CHF

Due to the low specificity of HF symptoms and poor diagnosis at early stages, and the possible insufficient or incorrect interpretation of echocardiograms, biochemical markers in the blood can be considered a possible alternative diagnostic approach [1, 12].

Clinical guidelines developed by Heart Failure Society, Russian Society of Cardiology and Russian Scientific Medical Society of Internal Medicine describe a diagnostic algorithm with the examination of a patient with CHF, starting with ECG and determining the natriuretic peptides (NPs) level; based on the results, a decision is made on the need for echocardiography (Echo-CG) [1]. Chronic Heart Failure Clinical Guidelines published in 2020 recommend determining the levels of brain natriuretic peptide and N-terminal prohormone of brain natriuretic peptide in blood for all patients with a presumptive diagnosis of CHF [5].

The concept of molecular biomarkers became widespread during the last decade. In addition to their diagnostic value, biomarkers are considered a high-potential method for selecting therapeutic measures and monitoring the effectiveness of treatment [13].

Markers of myocardial stress (brain natriuretic peptide, N-terminal prohormone of brain natriuretic peptide, mid-regional pro-atrial natriuretic peptide) have the highest diagnostic value in cases of CHF [13].

Natriuretic peptides

Natriuretic peptides are a family of hormones secreted by the myocardium; they are the diagnostic gold standard for heart failure.

NPs have a similar biochemical structure with an amino-acid core ring and N-amine and C-carboxyl terminal fragments, which allows their combination into one group [12, 14] (Table 1).

A- and B-types of NPs are synthesized in the body as inactive prohormones. In the course of secretion, molecules of prohormones are cleaved by proteases into active C-terminal and inactive N-terminal fragments. N-terminal fragments — N-terminal pro-A-type natriuretic peptide, or NT-proANP, and N-terminal pro-B-type natriuretic peptide, or NT-proBNP — are biologically inert and have diagnostic value. C-terminal fragments are active and are hormones — ANP and BNP [12, 14].

Table 1. *Natriuretic peptide family [15-17]*

Peptide	Place of synthesis	Function
Atrial natriuretic peptide (А-тип НУП, ANP, ПНУП)	Cardiomyocytes of the atria and ventricles of the heart	Diuretic, natriuretic, antihypertensive effects
Brain natriuretic peptide (В-тип НУП, BNP, МНУП)	Cardiomyocytes of the atria and ventricles of the heart, brain	Diuretic, natriuretic, antihypertensive effects
C-type natriuretic peptide (С-тип НУП, CNP)	Brain, bone tissue, vascular endothelium	Factor of local regulation of blood vessels and bones
Dendroaspis natriuretic peptide (D-тип НУП, DNP)	First obtained from snake venom (green mamba). In the human body, DNP-like peptide is found in the blood plasma and atrial myocardium [18]	The C-terminal fragment of the D-type NP together with the C-type NP are used to create chimeric natriuretic peptides, in particular, cenderitide
Urodilatin (URO)	Distal renal tubule cells	It is formed from a precursor hormone (proANP) and is involved in the regulation of sodium reabsorption

Table 2. Causes of the increased content of natriuretic peptide [12, 21, 22]

Cardiac	Noncardiac
Heart failure	Older age
Acute coronary syndrome	Ischemic stroke
Pulmonary embolism	Subarachnoid hemorrhage
Myocarditis	Chronic kidney disease
Left ventricular hypertrophy	Paraneoplastic syndrome
Hypertrophic or restrictive cardiomyopathy	Liver dysfunction (mainly cirrhosis with ascites)
Heart valve pathology	Chronic obstructive pulmonary disease
Congenital heart defects	Severe infection, including pneumonia and sepsis
Atrial and ventricular tachyarrhythmias	Severe burns
Atrial fibrillation	Obesity
Surgical procedures involving the heart	Conditions accompanied by increased cardiac output (sepsis, hyperthyroidism)
Pulmonary hypertension	Anemia

Basic physiological effects of NPs are listed below [12, 14, 19–21]:

- Regulation of myocyte growth;
- Inhibition of fibroblast proliferation;
- Cytoprotective anti-ischemic effect;
- Effect on the endothelium of coronary vessels;
- Effect on the contractility of cardiomyocytes;
- Vasodilation;
- Increased glomerular filtration rate;
- Increased natriuresis and diuresis;
- Suppression of the activity of the sympathetic nervous system;
- Suppression of the activity of the renin-angiotensin-aldosterone system;
- Inhibition of endothelin-1;
- Regression of hypertrophy and fibrosis in target organs.

The low specificity of CHF symptoms, low availability and high probability of unreliable results of instrumental studies allow using biomarkers in the diagnosis of CHF.

NPs have both advantages (simple and affordable test, high prognostic value) and disadvantages (widely variable values due to gender, age and comorbidities) (Table 2). The increased level of biomarkers due to comorbidities and aging process is a problem due to the use of NPs in elderly patients with CHF.

Natriuretic peptides in outpatient practice

Natriuretic peptides for heart failure in outpatient practice were recommended in 2012 by the European Society of Cardiology experts and subsequently, in 2013, by the American College of Cardiology and the American Heart Association for Heart Failure. Main options for the outpatient use of natriuretic peptides:

- diagnosis of HF and its confirmation in cases of dyspnea, fatigue and edemas;
- exclusion of the alternative causes of dyspnea;
- assessment of the prognosis;
- achieving recommended drug treatment [12, 13, 23, 24].

Today, mid-regional pro-atrial natriuretic peptide (MR-proANP, A-type MR-NP), BNP and NT-proBNP are of the greatest diagnostic value; they have a number of advantages over other peptides:

- ANP and C-type NP have a short half-life of about 3–4 minutes.
- The half-life of BNP is about 20 minutes.
- High concentration and stability in blood due to a half-life of about two hours determine the greatest clinical and diagnostic value of NT-proBNP among other NPs [12, 14, 19]. The level of NT-proBNP in CHF correlates closely with the severity of disease, pulmonary artery wedge pressure, LVEF and LV end-diastolic pressure [21]. However, NT-proBNP is not a highly sensitive predictor of poor prognosis in the first 24 hours of decompensated HF.

According to Moertl et al. (2009), MR-proANP has high biological stability, is an independent predictor of death, and has comparable diagnostic value with BNP and NT-proBNP [25]. C-type NPs can be predominantly considered as markers of endothelial dysfunction [12].

In real practice, detecting NP levels is required not so much for confirmation as for the exclusion of heart failure. This is due to the same negative predictive value

in both gradual and acute development of heart failure (0.94–0.98) and a low positive predictive value in cases of gradually increasing CHF (0.44–0.57) and decompensation (0.66–0.67) [21]. Depending on the type of disease onset, different threshold values of NPs are used:

- For acute symptoms, the threshold value when the diagnosis of HF is unlikely is less than 100 pg/ml for BNP, less than 300 pg/ml for NT-proBNP, and less than 120 pg/ml for MR-ANP.
- For a gradual onset, BNP level to exclude HF should be less than 35 pg/ml, and NT-proBNP level should be less than 125 pg/ml [13, 21].

Diagnostically significant levels of BNP and NT-proBNP and specific features of their changes over time can vary significantly depending on the pathophysiological processes in various clinical situations [26].

According to a study of patients with abdominal sepsis, the threshold value for determining the risk of death on day 3–4 of stay in the intensive care unit is NT-proBNP level > 3,450 pg/ml with a sensitivity and specificity of 63.6% and 66.7%, respectively (area under ROC curve 0.708; p = 0.0041); on day 7–8 > 5,100 pg/ml (65.6% and 88.2%; area under ROC curve 0.806; p < 0.0001) [26].

A study of the early diagnosis of pulmonary hypertension by determining the concentration of plasma BNP in patients with chronic obstructive pulmonary disease without left ventricular HF yielded the following results: diagnostic sensitivity of the method — 90.9%, diagnostic specificity — 84.0%, predictive value of a positive result — 83.3%, predictive value of a negative result — 91.2%, threshold level — 269.5 pg/ml, area under curve — 0.924 [27].

A number of studies of BNP level in patients with acute asthma attack demonstrated that increased biomarker concentration with a high degree of probability indicates dyspnea of cardiac origin. BNP level of more than 300 pg/ml was used to verify cardiac dysfunction since a moderate increase in BNP (100–200 pg/ml) appears in cases of other pathological conditions accompanied by dyspnea. To exclude alternative causes of dyspnea in patients with CHF, BNP > 35 pg/ml and NT-proBNP > 125 pg/ml are diagnostically significant [12].

In the PRIDE multicenter study (the ProBNP Investigation of Dyspnea in the Emergency Department), mid-regional A-type natriuretic peptide (MR-ANP) in the model that included NT-proBNP proved to be an independent predictor of the diagnosis of HF and allowed to classify both false-negative and false-positive results of preliminary diagnosis correctly (odds ratio (OR) 4.34, 95% confidence interval (CI) 2.11–8.92, p < 0.001). Thus, mid-regional A-type NP fragment in combination with BNP or NT-proBNP has higher diagnostic accuracy than each of these biomarkers separately [13].

Today, determining of NPs levels is included in the diagnostic procedures described in Chronic Heart Failure Clinical Guidelines of the Russian Society of Cardiology (RSC) approved by the Ministry of Health of the Russian Federation in 2020, and is also a required component for the diagnosis of HFpEF according to the recommendations of the European Society of Cardiology [1, 5, 12, 20]. BNP and NT-proBNP, with their proven predictive value, indicate the body response to "hemodynamic" (overload by pressure or volume) myocardial stress, while other markers indicate the response to "mechanical" stress (fibrosis, hypertrophy, cardiac remodeling) However, the wide variability of NPs values, which depends on gender, age and comorbidity, is a disadvantage of this group of biomarkers. Currently, there is a strong interest in studying new markers of CHF, such as soluble ST2 receptor (soluble suppression of tumorigenesis-2, sST2), copeptin, galectin-3 [12, 22].

Soluble ST2 receptor

Soluble ST2 receptor is a biomarker of "mechanical" myocardial stress that belongs to the interleukin-1 receptor family and is expressed in cardiomyocytes, as well as in vascular endothelial cells and type II pneumocytes [12, 22, 28, 29].

Mean normal concentration of sST2 is 18 ng/ml; concentration above 35 ng/ml indicates increased risk of cardiovascular events [12]. The receptor has two isoforms: trans-membrane (membrane-bound) form (ST2L) and soluble circulating form (sST2). Interleukin-33 (IL-33) is the functional ligand for both isoforms; it is secreted by fibroblasts and, when bound to the trans-membrane receptor form (ST2L), forms the IL-33/ST2L complex that has a protective antihypertrophic and antifibrotic effect on cardiomyocytes and prevents cardiomyocyte apoptosis [28].

The soluble form (sST2) binds to IL-33 and removes it from the bloodstream, blocking the cardioprotective effects of IL-33/ST2L and contributing to cardiomyocyte hypertrophy, myocardial fibrosis, ventricular dysfunction, and adverse cardiac remodeling. It was found that sST2 has diagnostic and prognostic value in patients with decompensated HF, acute coronary syndrome and progressive HF. In 2013, sST2 was included in the recommendations for HF by the American College of Cardiology and American Heart Association as an additional biomarker for risk stratification in patients with acute and chronic heart failure [12, 28–30].

sST2 in outpatient practice

The role of sST2 in predicting the risk of negative outcomes in outpatients with CHF is best described in the results of two large meta-analyses.

In the meta-analysis by Aimo A. et al. (2017), the results of seven sST2 studies in patients with CHF were combined. The relationship between sST2 and all causes of mortality was investigated in 6,372 patients; the relationship between sST2 and death from cardiovascular diseases was analyzed based on the available data from five studies involving 5,051 patients. According to the results, sST2 is an independent predictor of all-cause mortality (hazard ratio (HR) 1.75; 95% CI: 1.37–2.22; $p < 0.001$) and death due to cardiovascular causes (HR 1.79; 95% CI: 1.22–2.63; $p < 0.001$) and can be used to stratify the risk of death in elderly outpatients with CHF. The predictive power of this marker increases when the patient receives optimal drug treatment [31].

In another meta-analysis, sST2, together with NT-proBNP and high-sensitive troponin T, was considered a predictor of negative outcomes in outpatients with CHF. According to the results of the analysis of 4,268 patients (median age 68 years, 75% men, 65% with ischemic etiology of HF, 87% have LVEF < 40%) with a median follow-up period of 2.4 years, the overall mortality rate was 31%; mortality due to cardiovascular causes was 22%; 24% of patients were hospitalized at least once for worsening heart failure. The optimal cut-off value for sST2 to predict all-cause mortality, cardiovascular death, and hospitalizations for heart failure was 28 ng/ml. In a model that includes age, gender, body mass index, ischemic etiology of HF, LVEF, HF FC (NYHA), glomerular filtration rate, drug treatment for HF, NT-proBNP, and high-sensitive troponin T, every doubling of sST2 increased the risk of death from all causes by 26%, increased cardiovascular death by 25%, and increased hospitalizations for heart failure by 30%. In this meta-analysis, sST2 showed predictive value for three clinically significant endpoints regardless of N-terminal-proBNP, high-sensitivity troponin T and established risk factors. This biomarker was additionally considered a component of a multimarker model of risk stratification in patients with CHF, which includes tests for sST2, N-terminal-proBNP and troponin T. Within this

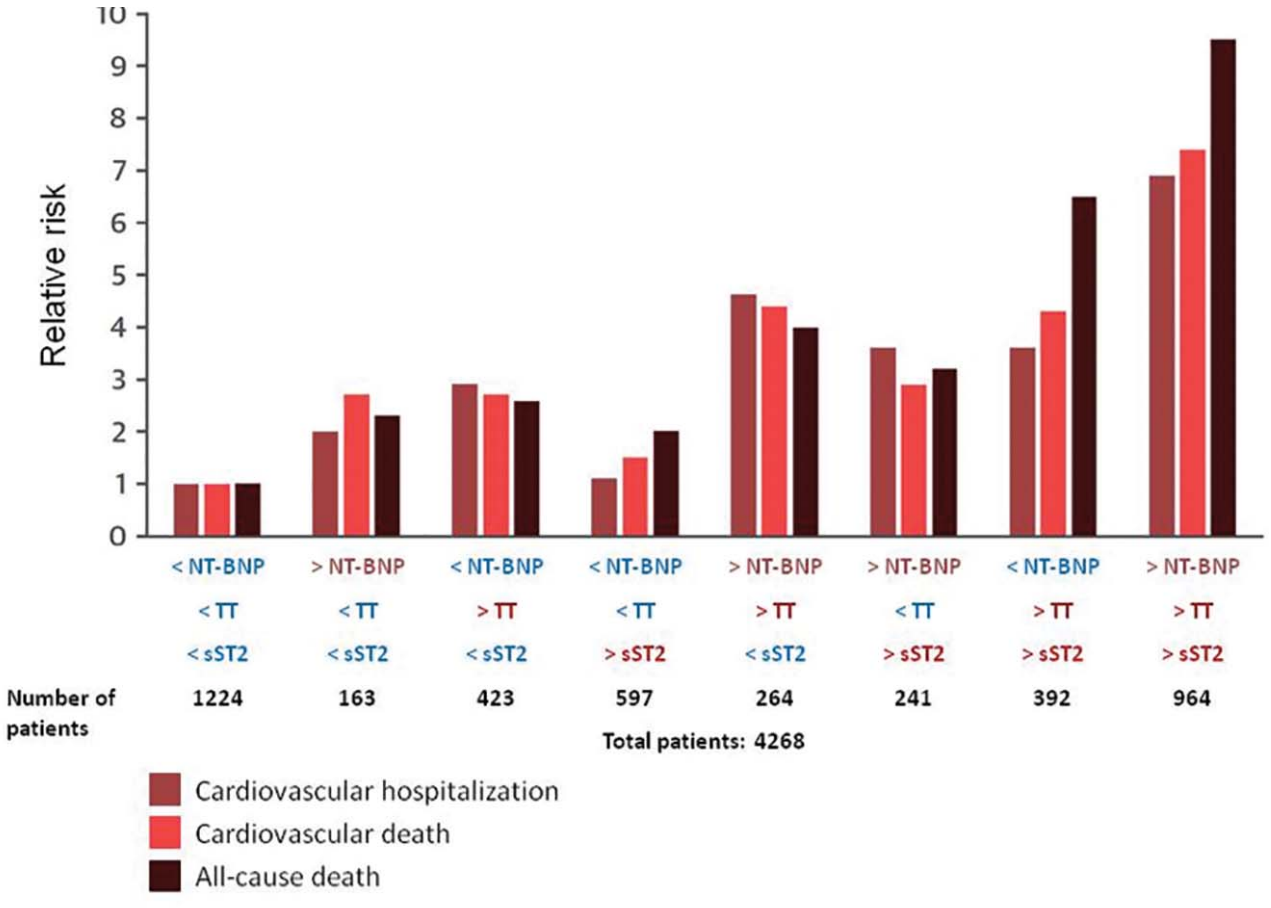

Figure 1. *Multimarker model of risk of adverse outcome in patients with different levels of biomarkers*

NT-BNP *— N-terminal pro-B-type natriuretic peptide,* ***TT*** *— high-sensitivity troponin T,* ***sST2*** *— soluble suppression of tumorigenesis-2. The following biomarker levels are used as cut-off values in this model: high-sensitivity troponin T — 18 ng / l, N-terminal natriuretic peptide pro-B-type — 1360 ng / l; sST2 — 27 ng / ml*

model, patients were divided according to the median concentration of biomarkers (troponin T — 18 ng/l; N-terminal-proBNP — 1,360 ng/l; sST2 — 27 ng/ml). In patients with sST2 levels ≥ 27 ng/ml, the risk of death from all causes, cardiovascular death and hospitalization for decompensated HF was higher by 100%, 50%, and 10%, respectively, compared with patients with sST2 levels < 27 ng/ml. In patients with the level of each marker (troponin T, N-terminal-proBNP, sST2) above the median level, the risk of death from all causes, cardiovascular death and hospitalization for decompensated HF was higher by 850%, 640% and 590%, respectively. (Fig. 1) [32].

sST2 in patients with heart failure with preserved left ventricular ejection fraction

Despite the large amount of research data, the diagnostic value of sST2 in patients with HFpEF remains poorly studied.

The number of patients with preserved LVEF in the study above was only 5% (n = 201) of 4,268. The following sST2 levels were determined as cut-off values to predict endpoints in this group of patients:

- for the risk of all-cause mortality — 30 ng/ml,
- for the risk of death from cardiovascular causes — 30 ng/ml,
- for the risk of hospitalizations for decompensated CHF — 29 ng/ml.

The risk of death from all causes in the cases of these cut-off values in the subgroup of patients with preserved LVEF and sST2 level > 30.0 ng/ml was almost double that in patients with preserved LVEF and sST2 level ≤ 30.0 ng/ml (HR 1.97, 95% CI: 1.21–3.21; p = 0.007). The probability of hospitalization for decompensated HF in the subgroup of patients with preserved LVEF and sST2 level > 29.0 ng/ml is almost one and a half times higher than in patients with preserved LVEF and sST2 level ≤ 29.0 ng/ml (HR 1.47, 95% CI: 1.02–2.14, p = 0.040) [32].

Due to the small number of patients with preserved LVEF, the predictive value of sST2 in relation to death and hospitalization is less reliable than for the group of patients with low LVEF [32]. Results of other studies evaluating the significance of sST2 concentration in CHF patients with preserved LVEF are also not convincing enough.

In the study by Santhanakrishnan R. et al. (2012), sST2 level was higher in patients with CHF and preserved LVEF (n = 50) compared with healthy subjects (n = 50). However, after correcting for age, gender and clinical parameters, the difference was not statistically significant. In this study, sST2 demonstrated no ability to distinguish between groups depending on the presence of CHF and LVEF value [33].

Wang Y. C. et al. (2013), examined 107 patients with hypertensive disease and LVEF > 50% (65 ± 12 years, 57 males); among them 68 (64%) with HFpEF. Results of this study included data demonstrating that sST2 is more preferable for making the right diagnosis of HFpEF (area under ROC curve 0.80, 95% CI 0.70–0.89, p < 0.001) than N-terminal proBNP (area under ROC curve 0.70, 95% CI 0.58–0.79, p = 0.003). Multivariate analysis confirmed that the sST2 level > 13.5 ng/ml was independently associated with the presence of HFpEF in patients with hypertensive disease (HR 11.7, 95% CI 2.9–47.4, p = 0.001) [34].

Jhund P. S. et al. (2014) studied sST2 significance in 296 patients from the PARAMOUNT study. According to the data obtained, a higher level of sST2 is associated with elderly age, male gender, atrial fibrillation (AF), a higher class of HF (NYHA), N-terminal-proBNP level and a lower glomerular filtration rate. Increased sST2 levels were associated with higher [E/e' (severity of LV diastolic dysfunction)] and enlarged LA. This association remained unchanged after excluding patients with atrial fibrillation. In a multivariate model, male gender (p = 0.04) and left atrial volume (p < 0.001) were independently associated with higher sST2 levels [35].

In most studies, AF was an exclusion criterion. In their paper, E. A. Polyanskaya et al. (2020) assessed sST2 as an early marker of HFpEF in 60 patients with persistent AF aged 67.0 [58.0; 78.5] years. In patients with HFpEF and persistent AF, correlation analysis demonstrated a direct and strong correlation between N-terminal-proBNP and sST2 (r=0.726; p < 0.05). This study revealed that in patients with persistent AF, sST2 level in blood higher than 16 ng/ml can be used as an alternative to N-terminal-proBNP for the early diagnosis of CHF with preserved LVEF (area under curve = 0.89), with a sensitivity of 80% and specificity of 83% [36].

In a study by Parikh R. H. et al. (2016), which included 3,915 elderly patients without HF, sST2 > 35 ng/ml was associated with HF (HR 1.20; 95% CI: 1.02–1.43) over a median follow-up of 11.7 years and with death from cardiovascular diseases (HR 1.21; 95% CI: 1.02–1.44) during the median follow-up of 13.7 years.

SST2 levels >35 ng/ml were significantly associated with HF: HFpEF developed in 354 patients (HR 1.52; 95% CI: 1.12–2.07), HF with low LVEF — in 298 patients (HR 1.93; 95% CI: –1.432.61). However, after correction for clinical risk factors, this relationship lost its significance both for HFpEF (HR 1.27; 95% CI: 0.92–1.75) and HF with low LVEF (HR 1.38; 95% CI 0.98–1.93). The authors

of the study consequently concluded that sST2 has a limited role as an independent predictor of HF in the elderly population [37].

The sST2 biomarker has a high diagnostic value, but its increase is found in a number of diseases with a predominant Th2 immune response, such as bronchial asthma, pulmonary fibrosis, rheumatoid arthritis, collagen vascular diseases, sepsis, trauma, malignant neoplasms, fibroproliferative disorders, helminth infections, and ulcerative colitis [12, 13, 29].

Studies on sST2 receptor concentration in HFpEF have shown mixed results. This is due to the retrospective nature of studies and non-uniform inclusion criteria that lead to meta-analysis problems. Nevertheless, the sST2 biomarker can be used to predict HFpEF, also at the outpatient stage [28].

Galectin-3

Galectin-3 is secreted by macrophages and is a β-galactoside-binding protein involved in fibrosis and myocardial remodeling processes [13, 28]. Galectin-3 is associated with HF and is involved in many processes that play a role in the pathophysiology of LVEF. These processes include the following:

- proliferation of myofibroblasts,
- fibrogenesis,
- tissue regeneration,
- inflammation,
- ventricular remodeling [28].

Myocardial fibrosis leads to increased stiffness of heart muscle and is the main component of HFpEF. Fibrosis develops due to collagen synthesis (or reduced collagen degradation), inflammation and oxidative stress [28]. Collagen deposition, decreased extensibility of titin and elasticity of cardiomyocytes increase diastolic stiffness of the left ventricle. Schiattarella G. G. et al. (2019) described a new mechanism of the development of LV diastolic stiffness based on the decrease in unfolded protein response, leading to the accumulation of destabilized myofilament proteins in the myocardium (Fig. 2) [38, 39].

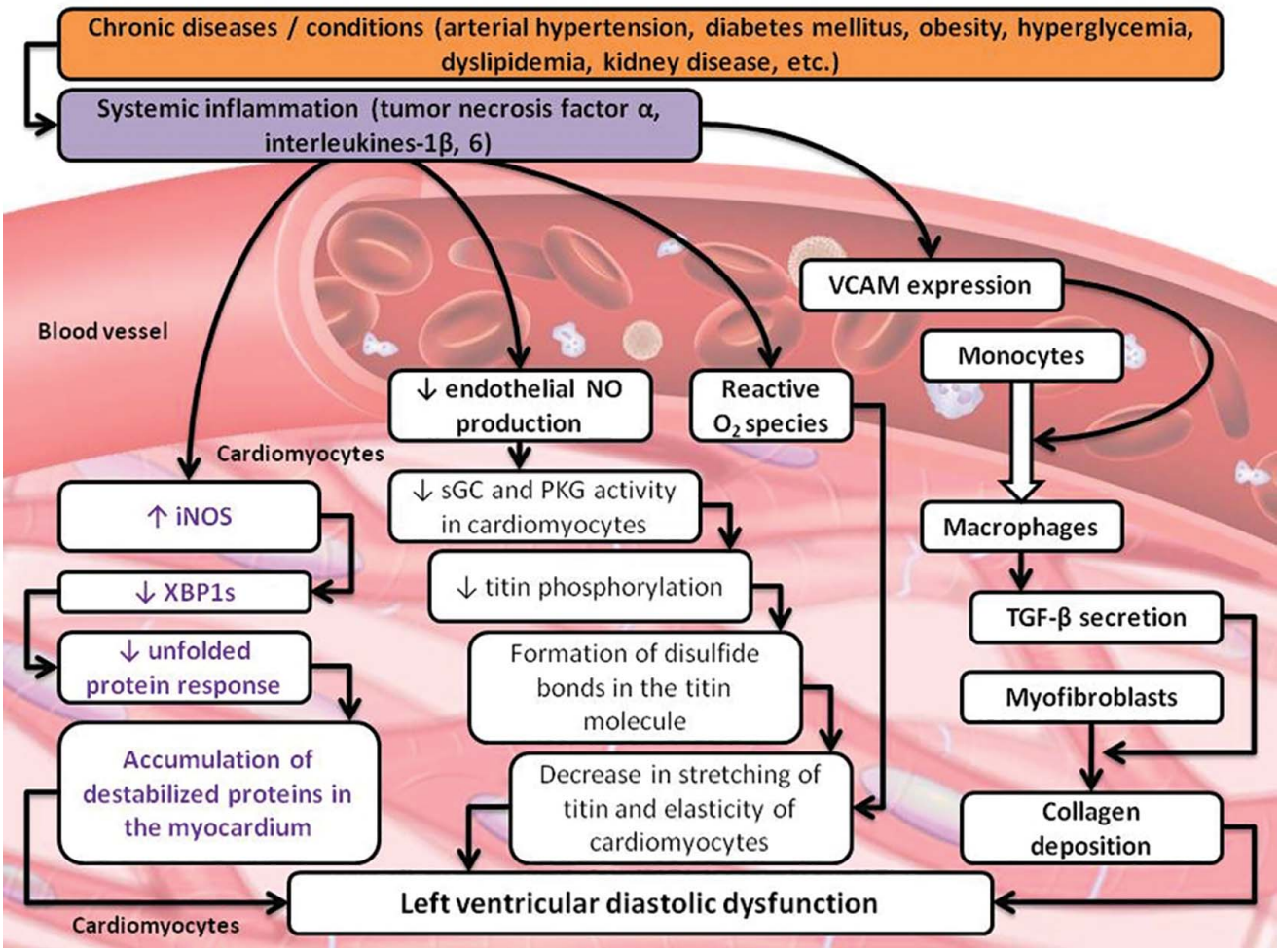

Figure 2. *Pathogenetic mechanisms of development of left ventricular diastolic stiffness*

VCAM *— vascular-cell adhesion molecules;* ***TGF-β*** *— transforming growth factor β;* ***NO*** *— nitric oxide;* ***sGC*** *— soluble guanylate cyclase;* ***PKG*** *— protein kinase G;* ***iNOS*** *— inducible NO synthase;* ***XBP1s*** *— spliced X-box binding protein 1*

Galectin-3 in patients with heart failure with preserved left ventricular ejection fraction

The clinical and diagnostic value of galectin-3 in patients with HFpEF is described in a number of studies [28]. Galectin-3 was, for the first time, identified as a predictive marker of HF in the PRIDE study [40]. In several subsequent studies, this marker proved to be an independent predictor of mortality [13, 41–45] and hospitalizations [13, 44, 45]. The COACH study (Coordinating study evaluating Outcomes of Advising and Counselling in Heart failure), after 18 months of follow-up of 592 patients with NYHA grade II–IV HF, with correction for age, gender, BNP, glomerular filtration rate (GFR), and diabetes, showed that galectin-3 was an independent predictor of overall mortality and repeated hospitalizations for HF (HR 1.38, 95% CI: 1.07–1.78; p= 0.015). A higher prognostic value was observed in patients with preserved LVEF [46].

Taking into consideration the limited use of NT-proBNP in the diagnosis of HFpEF, Kanukurti J. et al. (2020) evaluated the diagnostic capabilities of serum galectin-3 in comparison with NT-proBNP. The study included 63 patients with HFpEF and 20 patients in the control group, with comparable basic clinical parameters (p = 0.133). Median age in the control group was 57 years, in the trial group — 57.33 years. Mean levels of serum galectin-3 and NT-proBNP were significantly higher in the trial group than in the control group (26.59 ng/ml vs 5.27 ng/ml and 927 pg/ml vs 49.3 pg/ml, p < 0.0001). There was a weak positive correlation between serum levels of galectin-3 and NT-proBNP (r = 0.21, p = 0.048). At the threshold value of 10.1 ng/ml, galectin-3 sensitivity was 77.78%, specificity was 95% in the diagnosis of HFpEF cases, with a positive predictive value of 98% and a negative predictive value of 58.8% (area under ROC curve = 0.927). At the same time, NT-proBNP sensitivity at the threshold value of 160 pg/ml was 71.43%, and its specificity was 100% in the diagnosis of HFpEF cases with a positive predictive value of 100% and a negative predictive value of 52.6% (area under ROC curve = 0.871). There was a positive correlation of galectin-3 level with both NT-proBNP and the levels of lipid fractions. Due to the higher sensitivity and area under the ROC curve of galectin-3, its diagnostic value is higher than that of NT-proBNP, which suggests that galectin-3 is the best marker for the diagnosis of HFpEF. Simultaneous use of galectin-3 and NT-proBNP can significantly improve the detection of patients with HFpEF and provide higher accuracy of clinical diagnosis [47].

The study conducted by Cui Y. et al. (2018), which included 217 patients with HF (mean age of patients with HFpEF was 73 ± 9.19 years, n = 172; patients with HF with low LVEF — 71.14 ± 8.59 years, n = 45), analyzed the diagnostic and predictive value of galectin-3 and sST2. A lower LVEF corresponded to high concentrations of galectin-3 and NT-proBNP (p < 0.0001 for each marker), except for sST2 (p = 0.068 compared to control). According to ROC analysis results, galectin-3 and NT-proBNP allowed distinguishing patients with HFpEF from the control group with high accuracy (galectin-3: area under curve 0.819, 95% CI 0.75–0.89, p < 0,0001; NT-proBNP: area under curve 0.806, 95% CI 0.66–0.82, p < 0.0001). sST2 did not demonstrate the expected results (area under curve 0.584, 95% CI: 0.49–0.68; p = 0.17). After correction for clinical factors and NT-proBNP, a strong correlation was found between galectin-3 level and high risk of endpoints in patients with HFpEF, and the hazard ratio with increased galectin-3 level by one standard deviation was 2.33 (95% CI: 1.72–2.94; p = 0.009). In this study, galectin-3 demonstrated a superior ability compared to sST2 to differentiate patients with HFpEF from patients in the control group and individuals with HF with low LVEF [48].

Like sST2, Galectin-3 is a biomarker of interest, which is involved in pathophysiological processes relating to HFpEF. However, due to the lack of clinical algorithms that establish specific threshold values, the clinical significance of both galectin-3 and sST2 remains uncertain and requires further study.

Copeptin

Copeptin, a marker of cardiovascular diseases, is a C-terminal fragment of pro-vasopressin (CT-proAVP), resulting from the cleavage of the antidiuretic hormone (ADH) precursor. Copeptin is secreted in equimolar amounts to ADH and is more stable: concentrations of this biomarker in blood last for several days after blood sampling [12, 49]. Copeptin level in the blood of healthy individuals ranges from 1 to 12 pmol/l, with an average value of < 5 pmol/l [12].

Copeptin in patients with heart failure with preserved left ventricular ejection fraction

Hage C. et al. (2015) investigated the prognostic value of copeptin in patients with HFpEF in relation to a combined endpoint (all-cause mortality and hospitalization for HF). The sub-study included 86 patients with symptoms of acute HF and LVEF ≥ 45%. The follow-up period averaged 579 days. Patients with HFpEF demonstrated copeptin level higher than in the control group (13.56 (8.56; 20.55) and 5.98 (4.15; 9.42) pmol/l, respectively,

p < 0.001). A correlation was established between copeptin and NT-proBNP (r = 0.223; p = 0.040). Univariate Cox regression analysis revealed the predictive value of copeptin in relation to the combined endpoint (HR 1.56, 95% CI: 1.03–2.38; p = 0.037). However, after correction for NT-proBNP, this correlation was not significant (HR 1.39, 95% CI 0.91–2.12; p = 0.125).

Therefore, patients with HFpEF showed an increased copeptin level, which correlated with NT-proBNP level and has a prognostic value. Due to the paucity of data, further study of this biomarker in patients with HFpEF is required [50].

Conclusion

Heart failure with preserved left ventricular ejection fraction is now considered a comprehensive issue — a combination of many diseases with typical clinical manifestation and unfavorable prognosis. The vast majority of data available today were obtained from biomarker studies in patients with HF and low LVEF. There is a dearth of studies analyzing biomarkers in patients with HFpEF.

Biomarkers such as NPs, sST2, copeptin and galectin-3 can be considered instruments for risk stratification and assessment of prognosis in patients with CHF. The combination of biomarker data in a multimarker model can increase the predictive value. The multimarker approach in the diagnosis of HFpEF will allow a comprehensive assessment of prognosis, taking into account both the «hemodynamic» (pressure or volume overload, NPs as markers) and «mechanical» parts of myocardial stress (fibrosis / hypertrophy / heart remodeling, sST2 as a marker). Successful integration of the multimarker model into algorithms for the diagnosis of CHF with preserved LVEF requires clinical studies to establish the specific threshold value for each marker.

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All the authors contributed significantly to the study and the article, read and approved the final version of the article before publication

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