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Heart failure with preserved left ventricular ejection fraction in non-obstructive coronary artery disease: clinical utility of heart rate variability

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ABSTRACT

Aim. To evaluate the role of heart rate variability in the pathogenesis of chronic heart failure with preserved ejection fraction (HFpEF) in patients with non-obstructive coronary artery disease (CAD).

Materials and methods. The cross-sectional study included 65 patients (55.4% were males) with non-obstructive CAD. Non-obstructive CAD (stenosis < 50%) was confirmed by coronary computed tomography angiography. Heart rate variability (HRV) was evaluated by 24-hour Holter monitoring; parameters of time series and spectral analysis were analyzed.

Results. Depending on the presence of HFpEF, the patients were divided into 2 groups: group 1 (n = 48) included patients with HFpEF, and group 2 (n = 17) encompassed patients without it. In patients with HFpEF, a statistically significant decrease in the total HRV and parasympathetic effects on the heart rate, mainly at night, as well as increased activity of cerebral ergotropic systems were revealed. In group 1, the values of the time series analysis of HRV and QT dispersion based on the study of RR interval duration (SDANN and SDNNidx) had a significant direct relationship with the level of myocardial stress in diastole, the value of vascular resistance, and the E / e' ratio. The cut-off values of SDNNidx and pNN50 were identified, that may be used as markers for early diagnosis of HFpEF.

Conclusion. In patients with non-obstructive CAD and HFpEF, it is advisable to perform 24-hour Holter monitoring and assess HRV parameters by the time series analysis, which, compared with the spectral analysis, has a closer relationship with the characteristics of left ventricular diastolic function and afterload.

Keywords: heart failure, preserved ejection fraction, non-obstructive coronary artery disease, heart rate variability, biomarkers

Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at Cardiology Research Institute of Tomsk NRMC (Protocol No. 177 of 30.10.2018).

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Сердечная недостаточность с сохраненной фракцией выброса левого желудочка при неокклюзирующем коронарном атеросклерозе: клиническая полезность оценки вариабельности сердечного ритма

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РЕЗЮМЕ

Цель – оценить роль вегетативной дисрегуляции ритма сердца в патогенезе хронической сердечной недостаточности (ХСН) с сохраненной фракцией выброса (СНсФВ) у больных с необструктивным поражением коронарных артерий (КА).

Материалы и методы. В одномоментное исследование включено 65 пациентов (55,4% мужского пола) с впервые диагностированным необструктивным поражением КА. Необструктивное поражение КА (стеноз менее 50%) подтверждено данными компьютерной коронарной ангиографии. Вариабельность сердечного ритма исследовали посредством суточного мониторирования электрокардиограммы (ЭКГ), рассматривая показатели временного и спектрального анализа.

Результаты. В зависимости от наличия СНсФВ пациенты были разделены на две группы: в первую ($n = 48$) вошли больные с СНсФВ, во вторую ($n = 17$) – пациенты без ХСН. У пациентов с СНсФВ на фоне неокклюзирующего атеросклероза коронарного русла обнаружено статистически значимое снижение общей вариабельности сердечного ритма и парасимпатических влияний на сердце преимущественно в ночное время, а также повышенная активность церебральных эрготропных систем. Установлено, что у пациентов первой группы значения показателей временного анализа дисперсии ритма сердца, основанных на исследовании продолжительности интервалов R-R ЭКГ (SDANN и SDNNidx), имели прямую статистически значимую связь с уровнем миокардиального стресса в диастолу, величиной сердечно-сосудистого сопротивления, а также соотношением скорости трансмитрального кровотока в раннюю фазу диастолы и скорости раннего диастолического смещения боковой части фиброзного кольца митрального клапана. Определены пороговые значения SDNNidx и pNN50, которые у таких пациентов могут использоваться в качестве маркера для ранней диагностики СНсФВ.

Заключение. У пациентов с необструктивным поражением КА и СНсФВ при выполнении суточного мониторирования ЭКГ целесообразна оценка параметров дисперсии ритма сердца, анализируемых временными методами, которые по сравнению с показателями спектрального анализа имеют более тесную связь с характеристиками диастолической функции и постнагрузки левого желудочка.

Ключевые слова: сердечная недостаточность, сохраненная фракция выброса, неокклюзирующий коронарный атеросклероз, вариабельность ритма сердца, биомаркеры

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

In the last decade, a lot of data have been obtained pointing to a wide variety of etiological factors and describing the features of their effect on the pathogenesis of heart failure with preserved ejection fraction (HFpEF). In the same patient, several mechanisms often coexist, initiating symptomatic chronic heart failure (CHF), but the degree of activation of each of them in patients with HFpEF can vary greatly [1, 2].

It is known that an imbalance of the autonomic nervous system is one of the possible mechanisms for the development of CHF and its decompensation [3–5]. In particular, the results of the Women's Health Initiative cohort study that included 28,603 postmenopausal women (mean age 62.6 years) without coronary artery disease (CAD) and CHF demonstrated that low total heart rate variability (HRV) was associated with an increased risk of hospitalization for HFpEF (odds ratio (OR) 1.22; 95% confidence interval (CI) 1.02–1.47) [5].

A number of researchers have found a relationship between HRV and expression of inflammation and coagulation markers in patients with a high risk of developing cardiovascular complications, including patients with CHF and acute coronary syndrome [6–9]. In particular, it was found that activation of the cholinergic anti-inflammatory pathway, in which efferent inhibition of proinflammatory cytokines by the vagus nerve occurs, leads to a decrease in the content of systemic inflammation-associated proteins [10], and non-invasive stimulation of the vagus nerve through activation of the α7 nicotinic acetylcholine receptor can provide anti-inflammatory, antioxidant, and anti-apoptotic effects [11].

There are a few studies that reveal the relationship between changes in HRV and the development of CAD and CHF, as well as an increase in all-cause mortality [3, 9, 12]. The analysis of HRV in patients with CAD has shown that autonomic dysregulation is associated with multivessel coronary artery disease and the presence of coronary artery occlusions and lesions of the left coronary artery and plays an important role as a screening tool for high-risk groups [13]. It has been established that reduced HRV in CAD patients is associated with age, late postinfarction heart remodeling, development of left ventricular systolic and diastolic dysfunction, and the clinical severity of heart failure [14] and is involved in the development of electrical instability of the heart [15]. At the same time, we have not been able to find works on the assessment of HRV in patients with HFpEF and non-obstructive CAD in the available scientific literature.

The aim of the study was to evaluate the role of HRV in the pathogenesis of HFpEF in patients with non-obstructive CAD.

MATERIALS AND METHODS

The study was conducted in accordance with the provisions of the Declaration of Helsinki and approved by the local Ethics Committee at Cardiology Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences (Protocol No. 177 of 30.10.2018). All patients signed an informed consent to participate in the study.

The study included 48 patients (60.4% were men) aged 61.5 (55; 60) years with new-onset HFpEF and non-obstructive CAD (group 1). The control group consisted of patients without symptoms and signs of CHF of comparable age (group 2). *Inclusion criteria:* non-obstructive (< 50%) CAD; left ventricular diastolic dysfunction / increased left ventricular (LV) filling pressure and preserved LV ejection fraction (EF); N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥ 125 pg / ml; a signed informed consent to participate in the study. *Exclusion criteria:* prior myocardial infarction; elective coronary revascularization or prior revascularization; elevated systolic or diastolic blood pressure (> 180 or > 110 mm Hg, respectively); systolic hypotension < 80 mm Hg; second / third-de-

gree atrioventricular block, sick sinus syndrome; high ectopic activity of the atria and / or ventricles (> 10 extrasystoles per hour); hypertrophic and dilated cardiomyopathy; valvular defect (mitral, tricuspid or aortic valve insufficiency or stenosis ≥ 2 degree); prior pulmonary embolism with pulmonary hypertension (systolic pressure in the pulmonary artery ≥ 45 mm Hg); chronic atrial fibrillation; severe course of bronchial asthma and chronic obstructive pulmonary disease; pathology of the thyroid gland, severe renal (glomerular filtration rate according to the CKD-EPI equation < 30 ml / min / m²) and liver failure; inflammatory diseases of the myocardium and pericardium; hemoglobin level < 100 g / l.

At the time of enrollment, the patients were not receiving optimal drug therapy, given the fact that CHF was newly diagnosed. The frequency of prescribing β-blockers ranged from 17.6 to 19.4%, angiotensin-converting enzyme (ACE) inhibitors – 11.8–19.4%, angiotensin II AT_1 receptor blockers – 17.6–29.4%, statins – 35.3–41.2%, and diuretics – 5.9–29.4%. The patients who received β-blockers discontinued to take them the day before 24-hour Holter monitoring.

The content of the soluble form of ST2 protein (sST2) and NT-proBNP in the blood serum *in vitro* was determined by enzyme-linked immunosorbent assay (ELISA). Photometric detection of immunochemical reaction passage was performed on the Infinite F50 microplate reader (Tecan, Australia). Fasting blood was sampled from the ulnar vein in the morning after 16-hour fasting into vacutainers. We used kits from Critical Diagnostics Presage® ST2 Assay (USA) and Biomedica (Canada).

Echocardiography (EchoCG) was performed for all patients according to a standard protocol using the EPIQ system (Philips Ultrasound Inc., USA). The structures of the heart were visualized using B- and M-scans according to the standard technique. An obligatory criterion for diagnosing HFpEF was the value of LVEF ≥ 50%. All studies were conducted by one highly qualified specialist. The assessment of LV diastolic function was based on four parameters: early diastolic velocity at the lateral mitral annulus (lateral e'), the ratio of peak early diastolic velocity of the transmitral flow to the mean early diastolic velocity at the mitral annulus (E/e'), left atrial volume index, and peak tricuspid regurgitation velocity. LV diastolic dysfunction was diagnosed if at least three of the four parameters discussed were outside the reference range. LV global longitudinal strain (GLS) was assessed using 2D speckle tracking. Some of the parameters were calculated using the formulas:

– left ventricular end-systolic elastance (Es) = ESP / ESV; where ESP is LV end-systolic pressure, ESV is LV end-systolic volume.

– arterial elastance (Ea) = ESP / SV; where SV is stroke volume.

– LV myocardial stress (MS) in systole = SBP × ESP / LV PWT in systole × (1 + (LV PWT / ESD)); where SBP is systolic blood pressure, ESD is LV end-systolic dimension, and PWT is posterior wall thickness.

– LV myocardial stress (MS) in diastole = DBP × EDP / LV PWT in diastole × (1 + (LV PWT / EDD)); where DBP is diastolic blood pressure, EDD is LV end-diastolic dimension, and PWT is posterior wall thickness.

LV MS is a parameter that characterizes the force of myocardial fibers per unit cross-section of the LV wall and quantitatively reflects the values of LV pre- and afterload. At the end of diastole, it expresses preload, and at the end of systole, it expresses afterload (dynes / cm²).

HRV was assessed by 24-hour Holter monitoring. At least 12 hours before and during 24-hour ECG monitoring, the patients were forbidden to drink coffee, tea, and cola and to smoke. During the ECG recording, routine daily activities were allowed. The parameters of HRV quantification were analyzed: SDNN – standard deviation of all normal RR (NN) intervals of the sinus rhythm; SDANN – standard deviation of the average NN-intervals for each of the 5-minute segments during a 24-hour recording; SDNNidx – mean of the standard deviations of NN intervals in all 5-minute segments of a 24-hour recording; RMSSD – square root of the mean of the squares of differences between adjacent NN intervals; NN50 (100, 200) is the number of pairs of adjacent NN intervals that differ by more than 50 (100, 200) ms; pNN50 (100, 200)% is the value of NN50 (100, 200) divided by the total number of NN intervals in the analyzed recording period.

At the same time, the parameters of the HRV time series analysis were interpreted as follows: the parameters obtained by processing direct measurements of RR intervals (in particular, SDNN, SDANN, SDNNidx) generally reflect the degree of efferent sympathetic influences on the heart (with an increase in sympathetic efferentation, the values of the parameters decrease), whereas the parameters calculated on the basis of the difference between the RR intervals (RMSSD, NN50, pNN50) reflect tension in the

parasympathetic nervous system (with an increase in the efferent activity of the vagus nerve, the values of the parameters rise). Using the spectral analysis, the power of the spectrum was estimated in the range of very low (< 0.04 Hz) frequencies (VLF is a parameter which is associated with the activity of cerebral ergotropic systems and the renin – angiotensin system), low (0.04–0.15 Hz) frequencies (LF is a marker of sympathetic modulation), and high (0.15–0.4 Hz) frequencies (HF is a marker of the parasympathetic nervous system activity), and the LF / HF ratio (the so-called sympatho-vagal balance) was determined.

All patients underwent coronary computed tomography angiography. For contrast-enhanced scanning, 70–90 ml of a nonionic contrast agent (370 mg Iopamidol, Bracco Diagnostics, Italy) was injected intravenously through an 18G catheter at a flow rate of 5–5.5 ml / s.

Statistical processing was performed using the STATISTICA 10.0 software (StatSoft Inc., USA). The normality of distribution of the variables was assessed using the Shapiro – Wilk test. The homogeneity of variance was assessed using the Levene's test. Quantitative data were presented as the median and the interquartile range *Me* (Q_{25} ; Q_{75}). The Mann – Whitney *U*-test was used to test statistical hypotheses when comparing two independent samples. To search for relationships between variables, a correlation analysis was used with the calculation of the Spearman's rank correlation coefficient. For qualitative features, contingency tables were analyzed using the Pearson's χ^2 test or Fisher's exact test, when the expected value in any of the cells in the table with given boundaries was below 10. To assess the sensitivity and specificity of the models and select the cut-off values, the ROC analysis was used with the construction of curves and the calculation of the area under the curve (AUC). AUC value > 0.70 was considered significant. The marginal significance level of *p* for all statistical analysis procedures used was 0.05.

RESULTS

At the time of inclusion in the study, the groups were comparable in most clinical and demographic characteristics (Table 1). Patients of group 1 smoked more often and had impaired carbohydrate metabolism, while there were no statistically significant differences in the level of glycated hemoglobin.

Table 1

Baseline clinical and demographic characteristics

Parameter	Group 1, *n* = 48, (+) HFpEF	Group 2, *n* = 17, (–) HFpEF	*p*
Age, years, *Me* (Q_{25} ; Q_{75})	61.5 (55; 66)	62 (58; 63)	0.124
Men, *n* (%)	29 (60.4)	7 (41.2)	0.059
BMI, kg / m^2, *Me* (Q_{25} ; Q_{75})	29.7 (27.6; 32.0)	30.8 (28.35; 33.95)	0.254
Hypertension, *n* (%)	39 (81.2)	13 (76.5)	0.161
Type 2 DM, *n* (%)	11 (22.9)	2 (11.8)	0.013
HbA1c, %, *Me* (Q_{25} ; Q_{75})	6.3 (5.8; 7.5)	6.1 (6.0; 7.6)	0.068
COPD, *n* (%)	5 (10.4)	1 (5.9)	0.718
Smoking, *n* (%)	15 (31.25)	3 (17.6)	0.011
GFR, ml / min / 1.73 m^2	82.8 (67.3; 82.7)	85 (71; 89)	0.476
Total cholesterol, mmol / l, *Me* (Q_{25} ; Q_{75})	4.98 (3.67; 5.25)	5.09 (3.76; 6.5)	0.532
LDL-C, mmol / l, *Me* (Q_{25} ; Q_{75})	3.13 (2.15; 3.51)	2.33 (1.24; 3.37)	0.856
HDL-C, mmol / l, *Me* (Q_{25} ; Q_{75})	1.07 (0.85; 1.31)	1.52 (1.25; 1.79)	0.889
Triacylglycerols, mmol / l, *Me* (Q_{25} ; Q_{75})	1.78 (1.23; 1.97)	1.26 (1.17; 1.36)	0.870
Hemoglobin, g / l, *Me* (Q_{25} ; Q_{75})	134 (121; 143)	145 (140; 157)	0.464
Potassium, mmol / l, *Me* (Q_{25} ; Q_{75})	4.67 (4.12; 5.01)	4.47 (4.43; 5.01)	0.517
Fibrinogen, g / l, *Me* (Q_{25} ; Q_{75})	3.27 (3.14; 3.14)	3.16 (2.86; 3.36)	0.767
NT-proBNP, pg / ml, *Me* (Q_{25} ; Q_{75})	404.2 (249.5; 1,533.4)	58 (43.65; 74.35)	0.004
sST2, ng / ml, *Me* (Q_{25} ; Q_{75})	29.18 (23.17; 31.09)	19.42 (18.24; 22.29)	0.012

Note: BMI – body mass index; DM – diabetes mellitus; GFR – glomerular filtration rate; COPD – chronic obstructive pulmonary disease; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; HbA1c – glycated hemoglobin; NT-proBNP – N-terminal pro-brain natriuretic peptide; sST2 – soluble form of the ST2 protein.

In patients with non-obstructive CAD and HFpEF, compared to patients of the control group, we noted early signs of depressed LV contractility associated with changes in the characteristics of pre- and afterload (Table 2), in particular, impaired mechanics of the LV (decrease in LV global longitudinal strain: –14.4% [–13.1; –17.6] vs –18.9% [–14.4; –21.4], $p = 0.003$), increased myocardial stress in diastole, reflecting true hemodynamic load on the heart muscle (157.48 [142.06; 164.70] dynes / cm^2 vs 142.15 [133.31; 149.97] dynes / cm^2, $p = 0.028$) and arterial elastance (0.60 [0.55; 0.92] mm Hg / ml vs 0.56 [0.53; 0.61] mm Hg / ml, $p = 0.021$) against the background of a decrease in end-systolic elastance (2.30 [1.64; 3.0] mm Hg / ml vs 0.56 [2.75; 3.16] mm Hg / ml, $p = 0.018$).

The results of the HRV assessment revealed that patients with HFpEF, compared to persons without CHF, had chronotropic incompetence throughout the entire monitoring period, manifested by a decrease ($p < 0.01$) in the values of time series parameters: SDNNidx (night) by 29.9% (47 [44; 65] ms and 67 [52; 208] ms, respectively) and SDNNidx (day) by 14.3% (56 [52; 71] ms and 64 [55; 183] ms, respectively), as well as a decrease in the values of most parameters characterizing the parasympathetic nervous system activity ($p < 0.01$) mainly at night – RMSSD by 73.9% (23 [12; 31] ms and 40 [32; 328] ms, respectively), NN50, NN100, NN200 – by 5–8 times, pNN50(100, 200)% – by 2.5–6 times.

In patients with HFpEF, compared to patients without CHF, a significant change in the HRV frequency characteristics was revealed, indicating an increase in the influence of cerebral ergotropic structures with simultaneous inhibition of the parasympathetic nervous system activity: an increase in VLF ($p = 0.004$) and a decrease in CHF ($p = 0.016$). Table 3 shows the parameters of HRV, for which statistically significant differences were found. Other parameters did not differ between the groups.

Table 2

Echocardiography findings in patients of groups 1 and 2, *Me* (Q_{25}; Q_{75})

Parameter	Group 1, $n = 48$, (+) HFpEF	Group 2, $n = 17$, (–) HFpEF	p
LVEF, %	62 (58.5; 65)	65 (64; 66)	0.392
LA, mm	42 (39; 46)	40 (38; 43)	0.734
LV EDV, ml	111 (100; 125)	108 (97.5; 116)	0.306
LV ESV, ml	37.5 (32; 43)	34.5 (33.5; 39.5)	0.205
IVS, mm	10.5 (10.5; 11.1)	9.75 (9.0; 10)	0.065
LVPW, mm	10 (9; 10)	9.5 (9.0; 10.0)	0.329
Peak E, cm / sec	77 (69; 94)	63 (56; 72)	0.032
Peak A, cm / sec	65 (63; 88)	69 (66; 76.5)	0.053
E/A	1.29 (1; 1.36)	0.9 (0.74; 1.0)	0.024
E/e’	13.5 (13; 13.6)	12 (11; 13)	0.019
LAVI, ml / m^2	2.8 (2.78; 2.87)	2.6 (2.3; 2.76)	0.021
LV MMind, g / m^2	87 (80; 97)	82 (75.5; 86.5)	0.283
MS in diastole, dyne / cm^2	157.48 (142.06; 164.70)	142.15 (133.31; 149.97)	0.028
Ea, mm Hg / ml	0.60 (0.55; 0.92)	0.56 (0.53; 0.61)	0.021
Es, mm Hg / ml	2.30 (1.64; 3.0)	2.75 (2.55; 3.16)	0.018

Note: LAVI – left atrial volume index; LV – left ventricle; PW – posterior wall, MMind – myocardial mass index; EDV – end-diastolic volume; ESV – end-systolic volume; LA – left atrium; IVS – interventricular septum; Peak E – the peak velocity of early diastolic flow; Peak A – the peak flow velocity due to atrial systole; E/A - ratio of the peak early diastolic flow velocity (E) to the flow at atrial systole (A); E/e’ - the ratio of peak early diastolic velocity of the transmitral flow to the mean early diastolic velocity at the mitral annulus; Ea – atrial elastance; Es – end-systolic elastance of the left ventricle.

Table 3

HRV parameters in patients of groups 1 and 2, *Me* (Q_{25}; Q_{75})

Parameter	Group 1, $n = 48$, (+) HFpEF	Group 2, $n = 17$, (–) HFpEF	p
Mean NN during the day, ms	978 (897; 993)	835 (732; 959)	0.003
SDNNidx at night, ms	47 (44; 65)	67 (52; 208)	0.003
SDNNidx all day, ms	56 (52; 71)	64 (55; 183)	0.039
RMSSD at night, ms	23 (12; 31)	40 (32; 328)	0.001

Table 3 (continued)

Parameter	Group 1, *n* = 48, (+) HFpEF	Group 2, *n* = 17, (–) HFpEF	*p*
NN50 at night, *n* (%)	494 (352; 1,671)	2,681 (627; 18,518)	0.002
pNN50 at night, %	2.8 (1.2; 9.50)	13.9 (5.1; 61.5)	0.002
NN100 at night, *n* (%)	47 (24; 164)	368 (135; 8,485)	0.001
pNN100 at night, %	0.2 (0; 0.9)	1.4 (0.5; 33.5)	0.001
NN200 at night, *n* (%)	28 (9; 34)	191 (31; 2,037)	0.003
NN200 all day, *n* (%)	289 (43; 534)	400 (141; 12,571)	0.029
pNN200 during the day , %	0.4 (0; 0.9)	1 (0.2; 16.1)	0.010
pNN200 at night, %	0.1 (0; 0.1)	0,6 (0.2; 31.4)	0.001
pNN200 all day, %	0.3 (0.1; 0.9)	0.9 (0.2;21.3)	0.016
VLF, ms^2	2,570 (1,992; 3,016)	2,341 (1,634; 2,731)	0.004
HF, ms^2	347 (214; 509)	514 (371; 627)	0.016

Note: Mean NN – the average value of the duration of all RR (NN) intervals of sinus rhythm; SDNNidx – mean of the standard deviations of NN intervals in all 5-minute segments of a 24-hour recording; RMSSD – square root of the mean of the squares of differences between adjacent NN intervals; NN50(100, 200) – the number of pairs of adjacent NN intervals that differ by more than 50 (100, 200) ms; pNN50(100, 200)% – the value of NN50 (100, 200) divided by the total number of NN intervals in the analyzed recording period; VLF – spectrum power in the range of very low (< 0.04 Hz) frequencies; HF – spectrum power in the range of high (0.15–0.4 Hz) frequencies.

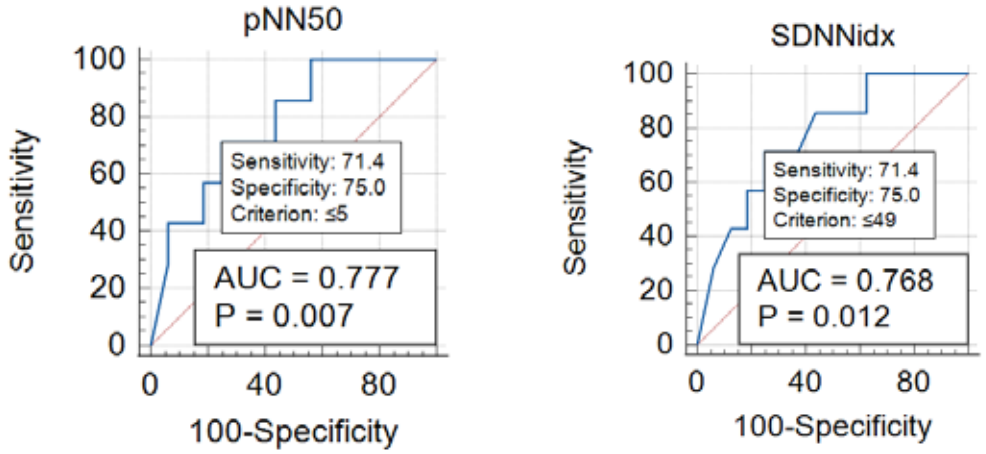

Figure. Cut-off values for SDNNidx (day) and pNN50 (night) for the optimal binary classification of patients with non-obstructive CAD depending on the presence or absence of HFpEF (ROC analysis): y-axis – sensitivity (%), x-axis – 100 minus specificity (%). The boxes represent the sensitivity and specificity scores for the respective decision rule threshold (criterion), as well as the AUC values and the significance level *p*.

Based on the ROC analysis, the values of SDNNidx ≤ 49 ms (AUC = 0.768; $p = 0.012$) and pNN50 ≤ 5 ms (AUC = 0.777; $p = 0.007$) were determined as cut-off values, which are associated with the presence of HFpEF in patients with non-obstructive CAD (Figure).

The results of the correlation analysis demonstrated the relationship between HRV studied by the time series parameters (in particular, SDANN) and the level of sST2 in the blood serum ($r = 0.354$; $p = 0.018$), but not the "classical" CHF biomarker – NT-proBNP. It was also established for the first time that the SDANN value was correlated with MS in diastole ($r = 0.35$; $p = 0.006$), and SDNNidx was correlated with arterial elastance ($r = 0.301$; $r = 0.045$).

DISCUSSION

It is known that autonomic dysregulation is one of the mechanisms for the development of CHF with reduced LVEF and is characterized by a steady increase in sympathetic excitation and a decrease in parasympathetic activity [4, 16]. The results of the analysis of turbulence and QT dispersion (in particular, SDNN) of the heart rate make it possible to identify individuals at the highest risk of adverse outcomes among patients with HFpEF [17]. HRV is also impaired in

symptomatic CAD, especially after myocardial infarction, and is inversely associated with the progression of CAD [12, 18, 19]. In particular, in patients with cardiovascular diseases without signs of myocardial ischemia, an inverse correlation ($p < 0.05$) was established between the presence of non-obstructive (< 50%) stenosis of one or more coronary arteries, on the one hand, and the value of pNN50 (for the anterior interventricular branch and right coronary artery – $r = –0.387$ and $r = –0.365$, respectively, and for the anterior interventricular branch with RMSSD – $r = –0.404$), as well as the power of the spectrum in the HF range ($r = –0.393$, $p < 0.05$), on the other.

This allowed the authors to conclude that the severity and degree of CAD are associated with a shift in the autonomic regulation of the heart toward sympathetic predominance [18]. Other data have been published showing that HRV parameters are associated with the severity of occlusion, multivessel CAD, and lesions of the left coronary artery [19]. At the same time, according to other authors [20], after adjusting for age, sex, body mass index, and heart rate, statistically significant differences between patients with CAD and those with unchanged coronary arteries in a number of logarithmic HRV parameters (pNN10%, pNN20%, LF, and HF) disappeared.

In our study, it was found that in patients with HFpEF and non-obstructive CAD, the activity of most parasympathetic nervous system parameters was suppressed ($p < 0.01$) mainly at night. We also noted a significant change in the frequency characteristics of HRV during 24-hour Holter monitoring, indicating the primacy of sympathetic influences on the heart over parasympathetic ones, which is confirmed by the data of other researchers [12, 16, 17]. Primary suppression of parasympathetic activity in the mechanism of HRV reduction in cardiovascular diseases and the subsequent predominance of the sympathetic nervous system are confirmed by the results of a meta-analysis by S.C. Fang et al. [12].

The pathophysiology of the sympatho-vagal imbalance in cardiovascular diseases may be associated with the influence of risk factors, including obesity, diabetes mellitus and CAD [4, 12, 21, 22]. In our study, patients in group 1 were more often diagnosed with diabetes mellitus, which, according to a number of researchers [4, 12, 22], could also make a certain contribution to the development and progression of autonomic dysfunction. However, given a short duration of the disease, the absence of significant differences in the level of glycemic control according to the HbA1c assessment, and a small sample size, the contribution of this risk factor to the development mechanism and prognosis of HFpEF will be the subject of further research.

The principal mechanism of CAD leading to autonomic dysregulation is still unknown. Most researchers tend to believe that the balance between short-term and long-term HRV components, even in asymptomatic individuals without signs of myocardial ischemia with progression of CAD shifts toward parasympathetic withdrawal with the primacy of sympathetic regulation [4, 9, 12, 17, 18, 23]. This confirms the hypothesis that CAD is one of the determinants of HRV [20]. It is hypothesized that the cause of these changes in patients with typical cardialgia and the absence of atherosclerotic lesions in the coronary bed may also be coronary microvascular dysfunction [20, 22], which, in turn, has a trigger potential for changes in myocardial metabolism, activation of the neurohumoral system, and development of HFpEF [24]. At the same time, regulation of the microvasculature function varies significantly in different tissues depending on their function and nutritional needs. In particular, it has been proven that, for example, retinal microvessels do not have sympathetic innervation, and variability in the filling of the myocardial microvasculature is functionally directly related to HRV [25].

In non-obstructive CAD, HFpEF is triggered actually due to progressive impairment of the endothelial function, which affects a decrease in coronary and myocardial reserves, initiation of diastolic dysfunction, and overproduction of humoral factors leading to perivascular fibrosis and apoptosis of cardiomyocytes [26]. On the other hand, according to D. Aronson et al. [6], neurohormonal activation, manifested by overexpression of proinflammatory cytokines (interleukin (IL)-6, tumor necrosis factor (TNF)-α, and C-reactive protein (CRP)) [1, 8, 27], dysregulation of vascular tone in the context of a decrease in nitric oxide production, and excessive activity of biomarkers (renin, aldosterone, norepinephrine) leads to HRV depression. The authors showed that some HRV parameters in the time domain were inversely correlated with the level of endothelin 1 (SDNN, $r = –0.38$, $p = 0.002$; SDANN5, $r = –0.48$, $p < 0.0001$), while overexpression of endothelin 1 was also associated with some frequency parameters of HRV – with full power ($r = –0.32$, $p = 0.01$) and ultra-low frequency power ($r = –0.43$, $p = 0.0004$), but not with indices of parasympathetic (HF) or sympatho-vagal (LF) modulation. According to the correlation analysis of the data

obtained in our study, associations were found not only between the parameters of total HRV and the level of sST2 (r = 0.354; p = 0.018), but also with the traditional CHF biomarker NT-proBNP. In the CATSTAT-HF study, regardless of the NT-proBNP level, sST2 was an accurate predictor of in-hospital death and heart failure decompensation in 90 patients with ischemic and non-ischemic CHF (LVEF 43.4 ± 16.4%) [9].

Previously, we showed that in patients with HFpEF corresponding to NYHA functional classes I–II and III, the level of sST2 was 28.8 and 46.3%, respectively, which was higher than in the control group [26]. Given the fact that no clear differences in the angiography characteristics were obtained, it is logical to assume that expression of one of the biomarkers studied at this stage, approaching the upper limit of the normal range, is pathogenetically associated with initiation of endothelial dysfunction and, possibly, development of perivascular fibrosis, which was confirmed in single studies of other scientists.

According to B. Arshi et al. [4], the role of the sympathetic nervous system in the development or progression of LV diastolic dysfunction and new-onset heart failure has not been widely studied, which emphasizes the need for new knowledge about the pathophysiology of autonomic regulation in patients with cardiovascular diseases leading to the development of HFpEF. In patients with HFpEF against the background of non-obstructive CAD, we found an increase in the early transmitral flow velocity (E) and a significant increase in the E/e' ratio, which was related to an increase in the activity of the sympathetic nervous system. At the same time, in patients of group 1, the values of the time series parameters of QT dispersion based on the study of the duration of RR intervals (SDANN and SDNNidx) had a direct significant relationship with MS in diastole, the value of arterial elastance, and the E/e' ratio.

Comparison of these results with the data of other authors turned out to be difficult, since they are presented in the scientific literature in single studies. In particular, A.-M. Vintilaˇ et al. [28] refer to the results of a retrospective study by A. Jian et al. (2019), who found that of all the analyzed HRV parameters, only SDANNidx was associated with left atrial dilatation. A. Tanindi et al. (2012) showed that in patients with HFpEF, compared to healthy volunteers, lower HRV values were detected, and HRV depression was directly associated with the progression of LV diastolic dysfunction. Finally, the results of the examination of patients retrospectively included in the population-based Rotterdam study revealed significant associations of HRV parameters (RMSSD and SDNN adjusted for heart rate) with parameters of transmitral flow and tissue Doppler in diastole, as well as the left atrial size [4].

The presence of such associations between parameters of autonomic regulation of the heart rate, diastolic dysfunction, and the level of the humoral biomarker that is not directly related to hemodynamic overload but affects the development and progression of cardiac hypertrophy, myocardial fibrosis, and myocardial dysfunction, in our opinion, reflects the compensatory negative activation of neurohormonal pathways that trigger the development and progression of HFpEF. These data suggest that a comprehensive assessment of HRV parameters, sST2 level, diastolic myocardial stress, and arterial elastance may be useful for early diagnosis of HFpEF.

There is no doubt that interpretation and correct comparison of the results of the HRV study in certain groups of patients can be difficult due to the often different duration of ECG recording, gender, and phenotypic (LVEF value) differences, which makes it necessary to continue research in this area.

CONCLUSION

When performing 24-hour Holter monitoring in patients with non-obstructive CAD and HFpEF, it is advisable to assess the parameters of QT dispersion using the time series analysis, which, compared to spectral analysis parameters, has a closer relationship with the characteristics of diastolic function and LV afterload. The cut-off values of SDNNidx (≤ 49 ms; AUC = 0.768; p = 0.012) and pNN50 (≤ 5 ms; AUC = 0.777; p = 0.007) were determined as a marker for early diagnosis of HFpEF.

Limitations of the study included**:** 1) a small sample size of patients; in this regard, at this stage of the study, we did not analyze HRV in subgroups of patients formed depending on the severity of HFpEF and the presence / absence of diabetes mellitus; 2) in this study, we did not evaluate the prognostic value of HRV depression (clinical outcomes and the prognostic value of QT dispersion parameters will be assessed in the currently ongoing 12-month cohort study).

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Grakova E.V. – conception and design of the study, coordination of the study, drafting of the article, final approval of the manuscript for publication. Kopeva K.V. – acquisition and interpretation of clinical data and HRV parameters, compilation of a database, statistical processing of the data, critical revision of the manuscript for important intellectual content, final approval of the manuscript for publication. Gusakova A.M. – determination of the levels of biomarkers in the blood serum, acquisition and interpretation of the data, compilation of a database, final approval of the manuscript for publication. Smorgon A.V. – carrying out of the echocardiography study, acquisition and interpretation of the data, compilation of a database, final approval of the manuscript for publication. Akhmedov Sh.D., Kalyuzhin V.V. – review of the literature, interpretation of the data, drafting of the article, final approval of the manuscript for publication. Teplyakov A.T. – coordination of the study, drafting of the article, final approval of the manuscript for publication.

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