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Prognostic value of myocardial flow reserve in patients with heart failure with preserved ejection fraction

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ABSTRACT

Aim. To study the prognostic value of myocardial blood flow (MBF) and myocardial flow reserve (MFR) parameters in patients with heart failure with preserved ejection fraction (HFpEF) and non-obstructive coronary artery disease (CAD) in risk stratification of HFpEF progression during a 12-month follow-up.

Materials and methods. The study included 58 patients with non-obstructive CAD and HFpEF (LVEF 62 [58; 66]%). Dynamic CZT-SRECT was used to evaluate MFR and MBF at rest (rest-MBF) and stress (stress-MBF). NT-proBNP levels were determined by the enzyme immunoassay. Diastolic dysfunction parameters were measured using 2D transthoracic echocardiography. Left ventricular systolic global longitudinal strain (GLS) was assessed using 2D speckle tracking.

Results. After a 12-month follow-up, the patients were retrospectively divided into 2 groups: group 1 ($n = 11$) included patients with an unfavorable course of HFpEF, group 2 ($n = 47$) encompassed patients with a favorable course of the disease. In group 1, the level of NT-proBNP was 3.8 times higher than in group 2 (284.5 [183.42; 716.73] and 1,071.4 [272.4; 2,168.1] pg / ml, respectively). MFR values in group 1 were lower by 45.4% ($p < 0.001$) than in group 2 (1.19 [0.86; 1.55] vs. 2.18 [1.7; 2.55], respectively). In group 1, rest-MBF levels were higher by 23.6% ($p = 0.046$) and stress-MBF was lower by 28.2% ($p = 0.046$) than in group 2. The multivariate regression analysis revealed that NT-proBNP levels (odds ratio (OR) 3.23; $p = 0.008$), GLS (OR 2.27; $p = 0.012$), and MFR (OR 8.09; $p < 0.001$) were independent predictors of adverse outcomes in HFpEF. Based on the ROC analysis, MFR levels ≤ 1.62 (AUC = 0.827; $p < 0.001$), GLS ≤ -18 (AUC = 0.756; $p = 0.002$), and NT-proBNP ≥ 760.5 pg / ml (AUC = 0.708; $p = 0.040$) may be considered as markers of adverse outcomes. However, the combined determination of NT-proBNP and MFR had a greater significance (AUC 0.935; $p < 0.001$) in risk stratification compared with the monomarker model, while the addition of GLS did not increase the significance of the analysis.

Conclusion. Levels of NT-proBNP, GLS, and MFR may be used as non-invasive markers of an adverse course of HFpEF in patients with non-obstructive CAD, while the combined determination of NT-proBNP and MBF increases the prognostic value of the analysis.

Keywords: heart failure, preserved ejection fraction, myocardial flow reserve, prognosis, natriuretic peptide

Conflict of interest. The authors declare the absence of obvious or 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, Tomsk NRMC (Protocol No. 177 of 30.10.2018).

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Прогностическая роль резерва миокардиального кровотока у больных с сердечной недостаточностью с сохраненной фракции выброса

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РЕЗЮМЕ

Цель. Изучение роли параметров миокардиального кровотока (MBF) и резерва миокардиального кровотока (MFR) у пациентов с сердечной недостаточностью с сохраненной фракцией выброса (СНсФВ) и необструктивным поражением коронарных артерий (КА) в стратификации риска прогрессирования СНсФВ в течение 12 мес наблюдения.

Материалы и методы. В исследование включено 58 пациентов с необструктивным поражением КА и СНсФВ (ФВЛЖ 62 [58; 66]%). С помощью динамической CZT-SRECT оценивали показатели MFR, MBF в покое (rest-MBF) и при нагрузке (на фоне введения стресс-агента аденозинтрифосфата, stress-MBF). Уровни NT-proBNP определяли с помощью иммуноферментного анализа. Параметры диастолической дисфункции измеряли с помощью двумерной трансторакальной эхокардиографии. Систолическая глобальная продольная деформация ЛЖ (GLS) оценивалась с помощью 2D-speckle tracking.

Результаты. Через 12 мес наблюдения больные ретроспективно были разделены на две группы: в группу 1 ($n = 11$) вошли больные с неблагоприятным течением СНсФВ, в группу 2 ($n = 47$) – с благоприятным. В группе 1 уровень NT-proBNP был выше в 3,8 раза, чем в группе 2 (284,5 [183,42; 716,73] и 1071,4 [272,4; 2168,1] пг/мл соответственно). Значения MFR были ниже в группе 1 на 45,4% ($p < 0,001$), чем в группе 2 (1,19 [0,86; 1,55] vs 2,18 [1,7; 2,55] соответственно). Уровни rest-MBF были выше на 23,6% ($p = 0,046$), а stress-MBF ниже на 28,2% ($p = 0,046$) в группе 1, чем в группе 2. При проведении многофакторного регрессионного анализа уровни NT-proBNP (отношение шансов (ОШ) 3,23; $p = 0,008$), GLS (ОШ 2,27; $p = 0,012$) и MFR (ОШ 8,09; $p < 0,001$) оказались независимыми предикторами неблагоприятного течения СНсФВ. По данным ROC-анализа, уровни MFR ≤1,62 (AUC = 0,827; $p < 0,001$), GLS ≤–18 (AUC = 0,756; $p = 0,002$) и NT-proBNP ≥760,5 пг/мл (AUC = 0,708; $p = 0,040$) можно рассматривать в качестве маркеров неблагоприятных исходов. Однако комбинированное определение NT-proBNP с MFR обладало большей значимостью (AUC 0,935; $p < 0,001$) в стратификации риска по сравнению с мономаркерной моделью, тогда как добавление GLS не увеличивало значимость анализа.

Заключение. Уровни NT-proBNP, GLS и MFR могут использоваться в качестве неинвазивных маркеров неблагоприятного течения СНсФВ у пациентов с необструктивным поражением КА, при этом комбинированное определение NT-proBNP и MBF увеличивает прогностическую значимость анализа.

Ключевые слова: сердечная недостаточность, сохраненная фракция выброса, резерв миокардиального кровотока, прогноз, натрийуретический пептид

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

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INTRODUCTION

Heart failure (HF), which was designated as a new epidemic in 1997, remains a serious and dire clinical and public health problem worldwide [1]. Approximately 50% of patients with HF are diagnosed with preserved left ventricular ejection fraction (LVEF) [2], and the prevalence of HF with preserved ejection fraction (HFpEF) increases by about 1% annually compared to HF with reduced LVEF [3]. At the same time, 5-year survival of patients with HFpEF is comparable to some types of non-hematological cancers [4], and the cost of treatment is associated with high economic costs, amounting to 1–2% of the total healthcare expenditures. According to forecasts, by 2030, the annual cost of treatment in this cohort of patients will reach 69.8 billion dollars [5].

Currently, the mechanisms of development and progression of HFpEF remain not fully understood [6]. At the same time, a lack of an accurate understanding of its pathophysiology determines a lack of adequate therapy according to current guidelines [7]. Recently, a new innovative theory of the development and progression of HFpEF has been proposed, which is based on coronary microvascular dysfunction (CMD) [8]. The results of a number of international studies using invasive or non-invasive diagnostic methods support the assumption that CMD occurs much more often than previously established, including patients with HFpEF [9]. V.L. Murthy et al. found that 53% of patients with non-obstructive coronary artery disease (CAD) and angina showed signs of mental stress-induced myocardial ischemia [10]. According to a meta-analysis of 56 studies involving 14,427 patients, the proportion of patients with CMD in the general population was 41% [9], while the prevalence of CMD in patients with HFpEF increased to 75–85% [11, 12].

Myocardial flow reserve (MFR), quantified as the ratio of hyperemic myocardial blood flow to resting blood flow, is used for a functional assessment of ischemia in large and small vessels. In the absence of subepicardial coronary artery occlusion, it is a marker of CMD [13]. Currently, magnetic resonance imaging (MRI) of the heart and positron emission tomography (PET) are among the main methods for diagnosing CMD, but their use for assessing myocardial perfusion parameters has not found wide application in clinical practice due to complexity and high cost of the methods [14, 15]. Another method for determining absolute perfusion parameters is dynamic myocardial perfusion single-photon emission computed tomography (SPECT) [16]. This technique has appeared relatively recently, with the advent of a new class of gamma cameras equipped with cadmium – zinc – telluride (CZT) detectors. The method, along with PET, has been sufficiently tested and validated, and is also more accessible for visualizing microcirculatory changes in the coronary bed [17]. However, the predictive value of MFR and MBF parameters, obtained using CZT detectors, in risk stratification of HFpEF progression has not yet been evaluated.

The aim of the study was to investigate the prognostic value of MBF and MFR parameters in patients with HFpEF and non-obstructive CAD in risk stratification of HFpEF progression during a 12-month follow-up.

MATERIALS AND METHODS

The study was performed in accordance with the Declaration of Helsinki and approved by the local Ethics Committee at the Cardiology Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences (Protocol No. 177 of 30.10.2018). An informed written consent was obtained from all patients prior to enrollment in the study.

Inclusion criteria: 1) non-obstructive (< 50%) CAD; 2) LVEF ≥ 50% measured by echocardiography; 3) left ventricular diastolic dysfunction (DD) /increased left ventricular filling pressure according to echocardiography; 4) sinus rhythm; 5) NT-proBNP ≥ 125 pg / ml; 6) a signed informed consent to participate in the study.

Exclusion criteria: 1) previous myocardial infarction; 2) elective coronary revascularization and / or previous coronary revascularization; 3) systolic blood pressure > 160 mm Hg; 4) symptomatic hypotension with the mean systolic blood pressure < 90 mm Hg; 5) second- or third-degree atrioventricular block, sick sinus syndrome; 6) persistent or chronic atrial fibrillation and / or atrial flutter; 7) valvular insufficiency or aortic stenosis ≥ grade 2; 8) hypertrophic and dilated cardiomyopathy; 9) previous pulmonary embolism with increased pulmonary hypertension ≥ 45 mm Hg; 10) severe form of bronchial asthma and / or chronic obstructive pulmonary disease; 11) pathology of the thyroid gland; 12) glomerular filtration rate (CKD-EPI) < 30 ml / min / m^2.; 13) Child-Pugh class C liver failure; 14) acute and chronic inflammatory diseases of the heart; 15) hemoglobin level < 100 g / dl; 16) stroke or transient ischemic attack within 90 days prior to inclusion in the study; 17) obesity (body mass index > 35 kg / m^2); 18) life-threatening uncontrolled arrhythmias.

Preparation for coronary computed tomography angiography (CCTA) was carried out according to a standard protocol. The preparation included taking beta blockers and prednisolone, avoiding caffeine-containing drinks and foods, excluding glucophage (metformin), viagra, etc., painkillers (advil or motrin). In addition, patients were instructed about the contraindications of the procedure associated with allergic reactions, pregnancy and kidney disease. Before each scan, heart rate and blood pressure were assessed. All patients received 0.5 mg nitroglycerin sublingual.

For contrast-enhanced scanning, 70–90 ml of a non-ionic contrast agent (iopamidol 370 mg, Bracco Diagnostics, Italy) was injected intravenously through an 18G catheter inserted through the cubital vein at the rate of 5–5.5 ml / s followed by 60 ml of 0.9% NaCl. Axial images, curvilinear multiplanar and transverse reformations, and thin-slab maximum intensity projections were used to analyze the data set. All studies were analyzed on the hybrid tomograph (Advantage Workstation 4.6, GE Healthcare). According to the modified classification proposed by the American Heart Association, coronary arteries were divided into 16 segments [18].

Preparation of patients for dynamic myocardial perfusion SPECT, study protocol, and recording and processing of static and dynamic scintigraphic data are described in previous works [16]. Twenty-four hours prior to the study, beta blockers, nitrates, calcium channel antagonists, caffeine, and methylxanthine derivatives were discontinued. Studies were performed in the morning, on an empty stomach, against the background of sinus rhythm, according to a two-day rest – stress protocol using the radiopharmaceutical 99mTc-methoxy-isobutyl-isonitrile (99mTc-MIBI), which was administered intravenously as a bolus at a dose of 260–444 MBq. To perform the study under stress, the stress agent adenosine triphosphate (ATP) was used, which was administered using an intravenous infusion pump at a dose of 160 µg / kg / min for 4 minutes.

To correct the attenuation, low-dose computed tomography of the chest was performed. All studies were performed on the Discovery NM/CT 570c hybrid tomograph (GE Healthcare, Milwaukee, WI, USA) equipped with a gamma camera with highly sensitive CZT detectors. The total effective radiation dose in the study (rest and pharmacological stress test) was ~6.25 mSv.

The resulting scintigraphic images were processed on the specialized Xeleris II workstation (GE Healthcare, Haifa, Israel). Myocardial perfusion, MBF, and MFR were assessed using specialized software Corridor 4DM SPECT and 4DM Reserve v.2015 (INVIA, Ann Arbor, MI, USA). For processing quantitative characteristics, the Net Retention model was used with attenuation correction.

According to myocardial perfusion SPECT data, standard semi-quantitative indices of myocardial perfusion impairment were determined: Summed Stress Score (SSS) – the sum of points during exercise, Summed Rest Score (SRS) – the sum of points at rest, Summed Difference Score (SDS) – the difference between exercise and rest, and also quantitative parameters: Stress Myocardial Blood Flow (stress-MBF) – myocardial blood flow during exercise, Rest Myocardial Blood Flow (rest-MBF) – myocardial blood flow at rest, and Myocardial Flow Reserve (MFR).

Philips Affiniti 70 ultrasound system was used to perform 2D transthoracic echocardiography.

All examinations were performed by one highly qualified specialist. The assessment of left ventricular diastolic dysfunction (LVDD) was based on 4 main parameters: early diastolic velocity of the lateral wall of the left ventricle (lateral e’), the average ratio of early diastolic mitral valve flow velocity to the average early diastolic mitral annular velocity (E/e’), left atrial volume index, and peak tricuspid regurgitation velocity [19]. LVDD was diagnosed in the presence of ≥ 3 abnormal values. LV systolic global longitudinal strain (GLS) was assessed using 2D speckle tracking.

Blood samples were obtained by venipuncture; adequate samples were centrifuged. Serum was separated and stored at –24 °C with one freeze – thaw cycle. The level of NT-proBNP was determined by the enzyme-linked immunosorbent assay (ELISA) using the Biomedica ELISA kit (Austria). Adverse outcomes were defined as the time to new symptoms / signs or aggravating symptoms/signs of HF, hospitalization for decompensated HFpEF, or death.

Statistical processing of the study results was performed using STATISTICA 10.0 and MedCalc 11.5.0.0 software. The data were presented as the median and the interquartile range Me (Q_{25}–Q_{75}). To test statistical hypotheses in the analysis of quantitative variables, the Mann – Whitney test was used to compare two independent samples. When analyzing qualitative variables, contingency tables were analyzed using the Pearson’s $\chi 2$ test. If there were cells with an expected frequency of less than 5, a two-tailed Fisher’s exact test or Yates’ correction (for 2x2 tables) was applied. To identify predictors of an unfavorable course of HFpEF, a ROC analysis was used with construction of characteristic curves and calculation of area under the curve (AUC). To identify factors that have a significant impact on the course and prognosis of the disease, a multivariate analysis was performed with calculation of an odds ratio (OR) with a 95% confidence interval (CI). The critical significance level p for all statistical procedures was taken equal to 0.05.

RESULTS

After 12 months of follow-up, the patients were retrospectively divided into 2 groups: group 1 ($n = 11$) included patients with an unfavorable course of HFpEF, group 2 ($n = 47$) encompassed patients with a favorable course of the disease (Table 1). Adverse cardiovascular events recorded during the follow-up period are shown in Fig. 1.

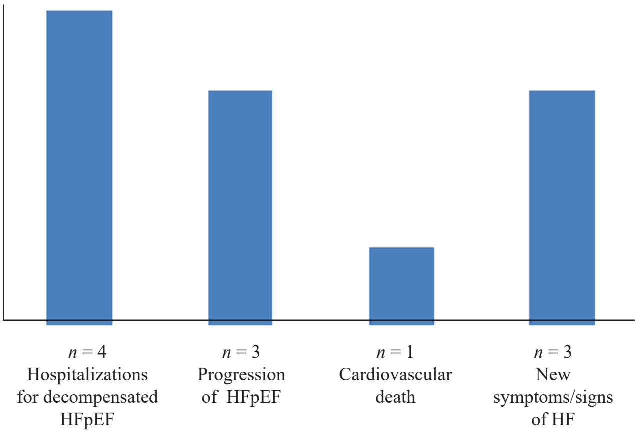

Fig. 1. Frequency of adverse cardiovascular events during 12-month follow-up

According to the main clinical and demographic characteristics, the groups were comparable, except for the NT-proBNP values ($p < 0.001$). In group 1, the level of NT-proBNP was 3.8 times higher than in group 2 (284.5 [183.42; 716.73] and 1,071.4 [272.4; 2,168.1] pg / ml, respectively).

In patients with an unfavorable course of HFpEF, the absolute value of GLS was lower by 27.1% ($p = 0.003$) than in individuals with a favorable course of the disease (–14.5 [12; 18.9]% and –19.9 [14; 21.4] %, respectively; $p = 0.003$). Septal e′ was lower by 23.6% ($p = 0.008$) in group 1 than in group 2 (5.5 [4.9; 6.7) versus 7.2 (6.9; 8.01) cm, respectively). E/e’ values were higher by 14.7% ($p = 0.041$) and LAVI was higher by 17.8 ($p = 0.021$) in patients with adverse outcomes of HFpEF compared to patients with a favorable course of the disease (Table 2).

Semi-quantitative parameters of LV myocardial perfusion did not differ significantly in the studied groups. MFR values were lower in group 1 by 45.4% ($p < 0.001$) than in group 2 (1.19 [0.86; 1.55] vs. 2.18 [1.7; 2.55], respectively). The value of rest-MBF in patients with an unfavorable course of HFpEF was higher by 30.1% than that in the group with a favorable course of the disease ($p = 0.046$), while stress-MBF in group 1 was lower by 28.2 % ($p = 0.014$) than in group 2 (Table 3).

MFR and rest-MBF levels were correlated with NT-proBNP levels ($r = –0.368$; $p = 0.007$ and $r = 0.354$; $p = 0.042$, respectively). MFR values were also correlated with LAVI ($r = –0.464$; $p = 0.001$), lateral e’ ($r = 0.314$, $p = 0.012$), and GLS ($r = 0.504$, $p = 0.009$), while rest-MBF was correlated with E/e’ ($r = 0.512$; $p = 0.002$).

Table 1

Clinical and demographic characteristics of patients depending on the course of HFpEF

Parameter	Group 1, *n* = 11	Group 2, *n* = 48	*p*
Age, years, *Me* (Q_{25}–Q_{75})	62 (54.0; 67.0)	60.0 (53.0; 68.0)	0.124
Men, *n* (%)	7 (63.6)	29 (60.4)	0.912
Body mass index, kg / m^2, *Me* (Q_{25}–Q_{75})	32.4 (29.9; 34.8)	30.19 (27.8; 33.3)	0.174
Hypertension, *n* (%)	8 (72.7)	32 (66.7)	0.257
Diabetes mellitus, *n* (%)	3 (27.3)	14 (29.2)	0.863
COPD, *n* (%)	2 (18.2)	11 (22.9)	0.315
Smoking, *n* (%)	3 (27.3)	10 (20.8)	0.311
GFR, ml / min / 1.73 m^2, *Me* (Q_{25}–Q_{75})	69.8 (57.0; 78.5)	71.0 (59.0; 81.0)	0.745
Total cholesterol, mmol / l, *Me* (Q_{25}–Q_{75})	4.34 (3.76; 5.23)	4.67 (3.98; 5.54)	0.976
HbA1c, %, *Me* (Q_{25}–Q_{75})	5.7 (5.2; 6.8)	5.4 (5.3; 6.9)	0.721
LDL-C, mmol / l, *Me* (Q_{25}–Q_{75})	3.19 (1.78; 3.65)	1.65 (1.99; 3.34)	0.457
HDL-C, mmol / l, *Me* (Q_{25}–Q_{75})	1.07 (0.85; 1.31)	1.06 (0.96; 1.26)	0.896
Triglycerides, mmol / l, *Me* (Q_{25}–Q_{75})	1.69 (1.23; 1.97)	1.67 (1.22; 1.92)	0.235
Hemoglobin, g / dl, *Me* (Q_{25}–Q_{75})	133 (127; 143)	135 (128; 142)	0.675
Potassium, mmol / l, *Me* (Q_{25}–Q_{75})	4.56 (4.01; 5.12)	4.87 (4.43; 5.21)	0.346
Fibrinogen, g / l, *Me* (Q_{25}–Q_{75})	3.27 (3.14; 3.14)	3.17 (2.86; 3.43)	0.844
NT-proBNP, pg / ml, *Me* (Q_{25}–Q_{75})	1,701.4 (272.4; 2,168.1)	284.5 (183.4; 716.7)	<0.001

Note: HbA1c – glycated hemoglobin; GFR – glomerular filtration rate according to the CKD-EPI equation; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol; COPD – chronic obstructive pulmonary disease

Table 2

Echocardiography parameters depending on the course of HFpEF, *Me* (Q_{25}–Q_{75})

Parameter	Group 1, *n* = 11	Group 2, *n* = 48	*p*
Left ventricular ejection fraction, %	59.5 (56; 62.5)	61 (59; 64)	0.456
End-systolic dimension, mm	43 (38; 47)	41.5 (36.5; 45.5)	0.544
End-diastolic dimension, mm	56.0 (49.5; 59.0)	54.5 (47.5; 57.5)	0.398
LVMMI, g / m^2	99.0 (88.5; 112.5)	97 (85.5; 109.5)	0.276
E/A ratio	1.04 (0.79; 1.34)	0.99 (0.74; 1.2)	0.516
Lateral e′, cm / m	5.5 (4.9; 6.7)	7.2 (6.9; 8.01)	0.008
Peak TRV, m / s	2.99 (2.95; 3.21)	2.92 (2.8; 3.11)	0.056
E/e’	14.5 (13.5; 15.0)	13 (12; 14)	0.041
LAVI, ml / m^2	38.3 (35.7; 51.1)	31.48 (29.5; 47.9)	0.021
LV global longitudinal strain, %	–14.5 (–12; –18.9)	–19.9 (14; 21.4)	0.003

Note: E/A – the ratio of the maximum blood flow velocity in the rapid ventricular filling phase to the maximum flow velocity in atrial systole; E/e’ – the ratio of the early mitral inflow velocity to tissue Doppler e´; LVMMI – left ventricular myocardial mass index; LAVI – left atrial volume index; TRV – tricuspid regurgitation velocity; lateral e’ – early diastolic velocity of the lateral wall of the left ventricle.

Table 3

Coronary flow reserve and myocardial blood flow parameters depending on the course of HFpEF, *Me* (Q_{25}–Q_{75})

Parameter	Group 1, *n* = 11	Group 2, *n* = 48	*p*
Stress-MBF, ml / min / g	1.07 (0.57; 1.22)	1.49 (1.09; 1.71)	0.014
Rest-MBF, ml / min / g	0.72 (0.52; 1.22)	0.55 (0.47; 0.77)	0.046
MFR	1.19 (0.86; 1.55)	2.18 (1.7; 2.55)	<0.001
SSS	3 (0; 4)	2 (0; 4)	0.563
SRS	0 (0; 1)	0 (0; 2)	0.423
SDS	2 (2; 3)	1 (0; 3)	0.221

Note: MFR – myocardial flow reserve; standard semi-quantitative indices of impaired myocardial perfusion: SSS – summed stress score; SRS – summed rest score; SDS – summed difference score.

In the multivariate regression analysis, NT-proBNP levels (OR 3.23; 95% CI 1.76–6.78; p = 0.008), GLS (OR 2.27; 95% CI 1.15–4.65; p = 0.012, and MFR (OR 8.09; 95% CI 5.12–19.98; p < 0.001) were independent predictors of an unfavorable course of HFpEF. According to the ROC analysis, MFR levels ≤ 1.62 (AUC = 0.827; p < 0.001), GLS ≤ –18 (AUC = 0.756; p = 0.002), and NT-proBNP ≥ 760.5 pg / ml (AUC = 0.708; p = 0.040) may be considered as markers of poor outcomes (Fig. 2, *a*). Comparison of the ROC curves showed no difference in the predictive value of the markers (p = 0.953) (Fig. 2, *b*). However, the combined determination of NT-proBNP with MFR was more significant (AUC = 0.935; p < 0.001) in risk stratification compared to the monomarker model (Fig. 3), whereas the addition of GLS (AUC = 0.885; p = 0.570) did not significantly increase the predictive value of the analysis.

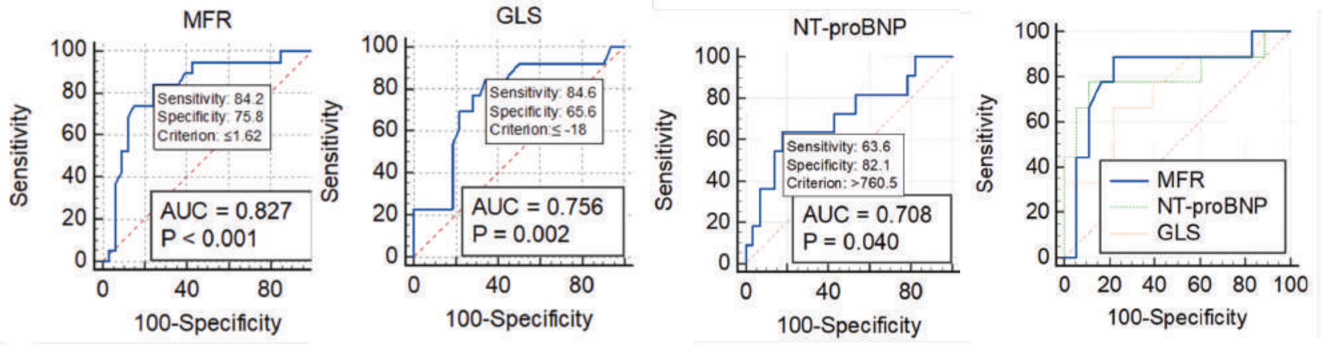

Fig. 2. Sensitivity and specificity of MFR, NT-proBNP, and GLS values in risk stratification of the unfavorable course of HFpEF in patients with non-obstructive coronary artery disease (ROC analysis)

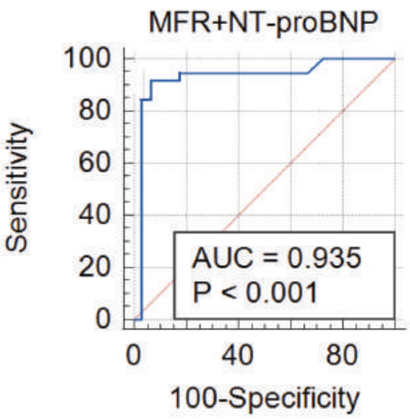

Fig. 3. Combined determination of MFR and NT-proBNP in the risk stratification of the unfavorable course of HFpEF in patients with non-obstructive coronary artery disease (ROC analysis)

DISCUSSION

The results of recent studies have shown that CMD may play an important role in the pathogenesis of HFpEF [12, 20], possibly because impaired perfusion causes damage to cardiomyocytes, which leads to a decrease in the functional reserve of the heart [21–24] and development of myocardial fibrosis [16]. Despite strong evidence in support of CMD, only a few studies have evaluated its role as a predictor of adverse HFpEF outcomes [15–19, 25, 26], and only one study found that a decrease in MFR on dynamic SPECT was an independent predictor of a high risk of major adverse cardiac events (MACE) [27].

The results of the COURAGE and ISCHEMIA studies showed that coronary artery revascularization was not associated with significant reduction of the incidence of MACE [28, 29]. The first international COVADIS study provided new evidence that the presence of CMD is an important problem and portends a high risk of MACE [30]. It was later found that impaired MFR is associated with an increased risk of all-cause mortality and the development of MACE [31]. J. Schroder et al. showed that CMD, assessed by Doppler echocardiography as coronary blood flow velocity in the anterior descending coronary artery, was also associated with an increased risk of rehospitalization for angina and all-cause mortality [32]. S. Kato et al. obtained and analyzed MRI-assessed MFR data in 163 patients with HFpEF (73 ± 9 years; 86 [53%] women). MFR values were significantly lower in patients with HFpEF and adverse cardiovascular events than in patients without them (1.93 ± 0.38 vs. 2.67 ± 0.52, p < 0.001) and were a predictor of cardiovascular death and hospitalizations for HF [33]. At the same time, significant negative correlations were found between MFR and global circumferential strain (r = –0.29, p< 0.001), GLS

($r = –0.33$, $p < 0.001$), right ventricular longitudinal strain ($r = –0.26$, $p < 0.001$), and serum BNP levels ($r = -0.32$, $p < 0.001$) [34].

A. Ahmed et al. showed that the severity of microcirculatory disorders is inversely proportional to the LV filling pressure, especially during exercise [22]. In another study including patients with suspected CAD with preserved LVEF who underwent PET, a decrease in MFR was associated with the presence of DD (OR 2.58; 95% CI 1.22–5.48) and a high risk of hospitalization due to decompensated HFpEF (OR 2.47; 95% CI 1.09–5.48) [17]. Patients with reduced MFR levels on PET and DD demonstrated a more than five-fold increased risk of hospitalization due to decompensated HFpEF ($p < 0.001$). However, J.H. Lam et al. found no relationship between echocardiography parameters of LVDD and CMD, assessed using myocardial contrast echocardiography at rest [33]. In another study that included patients with systolic dysfunction (LVEF < 35%) and non-obstructive CAD, MFR parameters were associated with E/e' values [34].

We have demonstrated for the first time that patients with an unfavorable course of HFpEF had lower MFR values according to dynamic SPECT, probably due to more pronounced changes in the microvascular bed. MFR and rest-MBF levels were correlated with NT-proBNP levels ($r = –0.368$; $p = 0.007$ and $r = 0.354$; $p = 0.042$, respectively). MFR values were also correlated with LAVI ($r = –0.464$; $p = 0.001$), lateral e' ($r = 0.314$, $p = 0.012$), and GLS ($r = 0.504$, $p = 0.009$), and rest-MBF was correlated with E/e' ($r = 0.512$; $p = 0.002$).

This suggests that factors that tip the balance towards cardiomyocyte damage in patients with existing CMD may worsen myocardial mechanics and increase the risk of HFpEF progression even in non-obstructive CAD. In particular, CMD leads to a decrease in the bioavailability of nitric oxide, and an increase in profibrotic cytokine signaling may contribute to a decrease in coronary microvascular rarefaction and an increase in myocardial fibrosis observed in HFpEF [17]. This interaction of disorders can synergize vascular and ventricular rigidity in CMD [35].

On the one hand, in patients with CMD, diffuse myocardial fibrosis leads to an endothelium-dependent increase in peripheral vascular resistance and an increase in resting blood flow. On the other hand, CMD associated with chronic systemic inflammation may contribute to periarteriolar fibrosis and microvascular rarefaction, leading to a decrease in stress-MBF [36]. The correlation of dynamic SPECT parameters with the biomarker of volume overload (NT-proBNP) and diastolic function parameters indicates a closer relationship between these processes, which, in particular, indicates the pathogenesis of HFpEF [8]. In addition, we found that the levels of NT-proBNP (OR 3.23; $p = 0.008$), GLS (OR 2.27; $p = 0.012$), and MFR (OR 8.09; $p < 0.001$) were independent predictors of an unfavorable course of HFpEF. According to the ROC analysis, MFR levels ≤ 1.62 (AUC = 0.827; $p < 0.001$), GLS $\leq –18$ (AUC = 0.756; $p = 0.002$). and NT-proBNP ≥ 760.5 pg / ml (AUC = 0.708; $p = 0.040$) can be considered as markers of adverse outcomes. However, the combined determination of NT-proBNP with MFR was more significant (AUC = 0.935; $p < 0.001$) in risk stratification compared to the monomarker model, while the addition of GLS (AUC = 0.885; p = 0.570) did not significantly increase the predictive value of the analysis.

CONCLUSION

The levels of NT-proBNP, GLS, and MFR can be used as non-invasive markers of an unfavorable course of HFpEF in patients with non-obstructive CAD, while the combined determination of NT-proBNP and MBF has a greater prognostic value in risk stratification of an unfavorable course of this pathology during 12-month follow-up.

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