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Predictors of an adverse course of heart failure with preserved left ventricular ejection fraction in patients with obstructive sleep apnea syndrome

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ABSTRACT

Aim. To study the relationship of obstructive respiratory disorders during sleep with subclinical development of right ventricular dysfunction and pulmonary hypertension, as well as with the risk of an adverse course of chronic heart failure (CHF) with preserved left ventricular ejection fraction (LVEF).

Materials and methods. The study included 86 men with moderate and severe forms of obstructive sleep apnea syndrome (OSAS) (with an apnea / hypopnea index (AHI) > 15 per hour). All patients had abdominal obesity and hypertension. Upon inclusion in the study, all patients underwent polysomnography and echocardiography according to the standard protocol with an additional assessment of the fractional area change in the right ventricular myocardium (ΔSRV) and the right ventricular stroke work index (RVSWI). Also, the content of the N-terminal brain natriuretic peptide precursor (NT-proBNP) in the blood serum was determined by enzyme immunoassay analysis. A six-minute walk test (6MWT) was performed after inclusion in the study and after 12 months of follow-up. Depending on the course of CHF during the follow-up, retrospectively, the patients were divided into 2 groups: with an unfavorable (n = 33) and favorable (n = 53) prognosis.

Results. A significant relationship between AHI and ΔSRV, RVSWI, NT-proBNP, and 6MWT was revealed. Based on the results of one-way correlation analysis, it was found that ΔSRV (odds ratio (OR) 2.51; 95% confidence interval (CI) 2.42–3.24; p = 0.0009), NT-proBNP (OR 1.92; 95% CI 1.32–2.78; p = 0.003), and AHI (OR 3.93; 95% CI 2.87–4.11; p = 0.018) were predictors of an adverse course of CHF. In a multivariate analysis, it was found that AHI was an independent predictor of an adverse course of CHF (OR 3.49; 95% CI 2.17–11.73; p = 0.0008), while the addition of NT-proBNP improved risk stratification of an adverse course of CHF (OR 4.66; 95% CI 3.87–13.11; $p < 0.0001$).

Conclusion. The fractional area change in the right ventricular myocardium (ΔSRV) can be considered as a non-invasive marker for determining the emerging right ventricular dysfunction and predicting adverse cardiovascular events in patients with preserved LVEF and OSAS. Moreover, the combined use of echocardiographic (ΔSRV) and laboratory (NT-proBNP) markers can improve risk stratification of CHF progression.

Key words: obstructive sleep apnea syndrome, chronic heart failure with preserved ejection fraction, right ventricular dysfunction, pulmonary hypertension.

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Предикторы неблагоприятного течения сердечной недостаточности с сохраненной фракцией выброса левого желудочка у больных с синдромом обструктивного апноэ во сне

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РЕЗЮМЕ

Цель. Изучить взаимосвязь обструктивных нарушений дыхания во сне с развитием дисфункции правого желудочка (ПЖ) и легочной гипертензии, а также с риском неблагоприятного течения хронической сердечной недостаточности (ХСН) с сохраненной фракцией выброса левого желудочка (ФВ ЛЖ).

Материалы и методы. В исследование включены 86 мужчин со среднетяжелой и тяжелой формами синдрома обструктивного апноэ во сне (СОАС) (с индексом апноэ/гипопноэ (ИАГ) более 15 в час). Все пациенты имели абдоминальное ожирение и артериальную гипертензию. При включении в исследование всем больным выполнено полисомнографическое исследование, а также эхокардиография по стандартному протоколу с дополнительной оценкой фракционного изменения площади и индекса работы миокарда правого желудочка (ΔSПЖ и ИРМПЖ), определено содержание предшественника мозгового натрийуретического пептида (NT-proBNP) в сыворотке крови методом иммуноферментного анализа. Тест 6-минутной ходьбы (ТШХ) выполняли после включения в исследование и через 12 мес наблюдения. В зависимости от характера течения ХСН за период наблюдения, ретроспективно, пациенты были разделены на две группы: с неблагоприятным (n = 33) и благоприятным (n = 53) прогнозом.

Результаты. Выявлена значимая взаимосвязь между ИАГ и ΔSПЖ, ИРМПЖ, ТШХ, уровнем NT-proBNP. На основании результатов однофакторного корреляционного анализа установлено, что ΔSПЖ (отношение шансов (ОШ) 2,51; 95%-й доверительный интервал (ДИ) 2,42–3,24; p = 0,0009), NT-proBNP 1,92; 95%-й ДИ 1,32–2,78; p = 0,003), ИАГ (ОШ 3,93; 95%-й ДИ 2,87–4,11; p = 0,018) были предикторами неблагоприятного течения ХСН. При проведении многофакторного анализа установлено, что независимым предиктором неблагоприятного течения ХСН являлся ИАГ (ОШ 3,49; 95%-й ДИ 2,17–11,73; p = 0,0008), при этом добавление NT-proBNP улучшало стратификацию риска неблагоприятного течения ХСН (ОШ 4,66; 95%-й ДИ 3,87–13,11; p < 0,0001).

Заключение. Фракционное изменение площади ПЖ ΔSПЖ можно рассматривать в качестве неинвазивного маркера для определения формирующейся правожелудочковой дисфункции и прогнозирования неблагоприятных сердечно-сосудистых событий у больных с сохраненной ФВ ЛЖ и СОАС. При этом комбинированное использование эхокардиографического (ΔSПЖ) и лабораторного (NT-proBNP) маркеров позволяет улучшить стратификацию риска прогрессирования ХСН.

Ключевые слова: синдром обструктивного апноэ во сне, хроническая сердечная недостаточность с сохраненной фракцией выброса, правожелудочковая дисфункция, легочная гипертензия.

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

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено этическим комитетом ЧУЗ «Клиническая больница ‘‘РЖД-Медицина” г. Новосибирск» (протокол № 27 от 16.04.2018).

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INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is a metabolic disorder associated with abdominal obesity and an increased risk of cardiovascular complications. A number of large, clinically controlled, prospective studies have demonstrated the relationship between obstructive sleep apnea and arterial hypertension, heart rhythm and conduction disturbances, as well as an increased risk of sudden cardiac death at night [1–5].

The significance of OSAS is determined by its wide prevalence, high frequency of severe metabolic and cardiopulmonary complications, and mortality [6, 7]. Thus, in the United States, more than 40 million patients with sleep disorders are observed, of which about 10 million people suffer from OSAS [8]. In Russia, there are no accurate data on the epidemiology of OSAS, but given high prevalence of the main risk factors for this syndrome, such as obesity, smoking, and thyroid diseases, it can be assumed that this syndrome is characterized by quite high prevalence among the Russian population.

One of the important links in the pathogenesis of sleep apnea syndrome is overload of the right ventricle due to a periodic increase in intra-abdominal pressure during apnea. Another important pathogenetic mechanism is development of pulmonary hypertension against the background of nocturnal intermittent hypoxemia, that leads to hyperactivation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), development of the endothelial dysfunction with increased expression of endothelin-1, and activation of hypoxic pulmonary vasoconstriction [9, 10].

In addition, endothelial dysfunction caused by acidosis of the vascular wall is accompanied by overexpression of vasoconstrictors (thromboxane A2, endothelin-1) and inhibition of the production of vasodilators (nitric oxide and prostacyclin) [11]. It was shown that in OSAS, an episode of apnea is followed by a period of hyperventilation with a characteristic rise in the negative pressure in the chest and an increase in the right ventricular inflow, which subsequently leads to dilatation of the inferior vena cava and the right atrium, right ventricular hypertrophy, and activation of NT-proBNP [12, 13]. It is possible that these factors initiate the emergence and progression of global right ventricular dysfunction and pulmonary hypertension.

However, the complexity of interpreting right ventricular dysfunction and the mechanisms of pulmonary hypertension progression as prognostic factors of OSAS is determined by the fact that this syndrome is often accompanied by other risk factors for cardiovascular pathology, in particular, with obesity, insulin resistance, arterial hypertension, chronic obstructive pulmonary disease, and portal hypertension [14, 15]. Consequently, in cardiology practice, the use of modern approaches to multifactorial risk stratification of cardiovascular complications for selecting the optimal pathogen-specific therapy has significant advantages over assessing individual parameters, such as the functional class of pulmonary arterial hypertension (PAH) (according to the World Health Organization (WHO), or 6MWT). The effect of OSAS on the cardiovascular system is mediated by a number of factors. Therefore, well-designed clinical trials are necessary to assess this effect in detail and develop specific approaches to prevention and treatment of cardiovascular complications of OSAS.

It is assumed that an increase in the activity of the RAAS is associated with an increased risk of adverse cardiovascular events, as well as with a decrease in renal sensitivity to atrial and cerebral natriuretic peptides [3]. All these neurohumoral disorders lead to pathological remodeling of the pulmonary microvasculature, contributing to the progression of right ven-

tricular dysfunction and pulmonary hypertension. The presence of the listed pathogenetic factors contributes to the formation of chronic cor pulmonale.

Until now, it is not completely clear what the main reason for the initiation and progression of pulmonary hypertension in OSAS is: the actual periodic episodes of respiratory arrest during sleep or the severity of chronic arterial hypoxemia associated with them. At the same time, the assessment of subclinical right ventricular dysfunction and pulmonary hypertension seems to be an important innovative strategy for early personalized diagnosis, prevention, and treatment of various cardiovascular pathologies, as well as a useful tool for assessing the effectiveness of the pathogen-specific therapy used [16].

The aim of the study was to assess the relationship of obstructive sleep breathing disorders with subclinical development of right ventricular dysfunction and pulmonary hypertension, as well as with the risk of an adverse course of CHF with preserved LVEF.

MATERIALS AND METHODS

The study protocol was approved by the local Ethics Committee at the Clinical Hospital "Russian Railways – Medicine" of Novosibirsk (Protocol No. 27 of 16.04.2018). All patients signed an informed consent to participate in the study. The study included males who met the inclusion / exclusion criteria below.

Inclusion criteria: 1) moderate and severe OSAS (with AHI > 15 per hour); 2) arterial hypertension (including patients with stabilization of blood pressure (BP) against the background of antihypertensive therapy) 3) abdominal obesity, waist circumference (WC) ≥ 92 cm, body mass index (BMI) ≥ 30 kg / m^2.

Exclusion criteria: 1) primary pulmonary hypertension; 2) history of pulmonary embolism with pulmonary hypertension (systolic pressure in the right ventricle ≥ 45 mm Hg); 3) severe bronchial asthma, chronic obstructive pulmonary disease (COPD); 4) lesions of the cardiac valvular apparatus (insufficiency of the mitral, tricuspid or aortic valves ≥ II degree); 5) hypertrophic and dilated cardiomyopathy; 6) coronary artery disease (CAD); 7) chronic atrial fibrillation; 8) decompensated CHF with reduced LVEF; 9) pathology of the thyroid gland, severe renal (Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation < 30 ml / min / m^2) and liver failure; 8) refusal to participate in the research.

In order to diagnose OSAS, polysomnography of nocturnal sleep was performed in all patients using the Somnolab2PSG diagnostic system (Weinemann, Germany). The severity of OSAS was assessed by AHI; the study included patients with moderate (14 < AHI < 30 per hour) and severe (AHI ≥ 30 per hour) OSAS. Also, according to the sleep study results, the level of average night saturation (SPO_2av.), desaturation index, and the presence of cardiac arrhythmias at night were assessed. All patients included in the study underwent 6MWT. Determination of the NT-proBNP content in the serum *in vitro* was performed by enzyme-linked immunosorbent assay (ELISA) using NTproBNP-ELISA-BEST reagents (VEKTOR-BEST, Russia) on the Multiskan FC microplate photometer (China).

The study included 86 males with moderate and severe OSAS (with AHI > 15 per hour) with the average age of 52 [31.0; 78.0] years. All patients included in the study were diagnosed with abdominal obesity (WC > 92 cm), BMI exceeded 30 kg / m^2. In all cases, arterial hypertension was identified, but against the background of optimally selected antihypertensive therapy at the time of inclusion in the study, the patients achieved target BP levels. In 33.7% of the patients (n = 29), functional class (FC) I CHF (according to New York Heart Association (NYHA)) was diagnosed, in 39.5% (n = 34) – FC II CHF (according to NYHA), in the rest of the cases (n = 23), the 6MWT distance was more than 550 meters. At the same time, the NT-proBNP levels in all cases exceeded the reference values > 125 pg / ml.

After 12 months of prospective follow-up, retrospectively, depending on the course of CHF, the patients were divided into 2 groups. Group 1 (n = 33) included patients with an unfavorable course of CHF, group 2 (n = 53) – patients with a favorable course of the disease. The criteria for an unfavorable course of CHF were hospitalization for decompensated CHF or progression of the pathology according to the 6MWT data (deterioration of the NYHA functional class).

The clinical and demographic characteristics of the examined patients with OSAS at the time of inclusion in the study are presented in Table 1. The groups were comparable in terms of the main characteristics, however, higher AHI (p = 0.0001) and NT-proBNP (p = 0.024) levels were associated with an unfavorable course of CHF.

Echocardiography (EchoCG) was performed in all patients according to the standard protocol on the EPIQ device (Philips Ultrasound, Inc., USA). The following parameters were assessed: the sizes of the left and right heart chambers, LVEF (according to Simpson method), left ventricular myocardial mass index,

interventricular septal thickness, wall thickness of the left and right ventricles, and systolic pressure in the pulmonary artery (determined according to the degree of tricuspid regurgitation using the continuous wave method). Evaluation of global systolic dysfunction of the right ventricle (RV) was also carried out by analyzing fractional changes in the RV area and the right ventricular myocardial work index. The fractional change in the RV area was calculated using the formula ΔSRV = 100 × (EDA – ESA / EDA), where EDA is the end-diastolic area of the RV and ESA is the end-systolic area of the RV. The right ventricular stroke work index (RVSWI) (right ventricular myocardial performance index) was calculated as the ratio of the sum of isovolumic relaxation (IVR) time and isovolumic contraction time (IVCT) to the ejection time (ET): RVSWI = (IVR + IVCT) \ ET (normal 0.28 ± 0.04).

Statistical processing of the study results was carried out using the STATISTICA 10.0 and Medcale 11.5.0.0 software. To check the statistical hypotheses when comparing 2 independent quantitative variables, the Mann – Whitney test was used, to compare 2 dependent variables, the Wilcoxon test was applied. Quantitative data were presented as the median and the interquartile range *Me* [Q_{25}; Q_{75}]. Qualitative data were presented as percentages and absolute values. For analysis of qualitative features, contingency tables were used with calculation of Pearson's χ^2 criterion. If there were cells with an expected frequency of less than 5, the two-sided Fisher's exact test was applied.

Table 1

Clinical and demographic characteristics of the examined patients

Parameter	Group 1, *n* = 33	Group 2, *n* = 53	*p*
Age, years, *Me* [Q_{25}; Q_{75}]	52 [33; 71]	50 [31; 78]	0.717
Body mass index, kg / m^2, *Me* [Q_{25}; Q_{75}]	36.1 [30.1; 74.8]	36.8 [30.06; 77.2]	0.268
AHI, per hour, *Me* [Q_{25}; Q_{75}]	46.0 [20.6; 85]	27.0 [14.0; 98.0]	**0.0001**
SPO_2av., %, *Me* [Q_{25}; Q_{75}]	92 [83; 95.5]	93 [76; 96]	0.148
Desaturation index, *Me* [Q_{25}; Q_{75}]	44.8 [13.0; 85]	27.5 [4; 78]	0.0005
FC I CHF (NYHA), *n* (%) FC II CHF (NYHA), *n* (%)	8 (24.2) 15 (45.5)	21 (39.6) 19 (35.8)	0.142 0.069
NT-proBNP, pg/ml	338 [168; 678]	278 [177; 815]	**0.024**
According to WHO: FC PAH of the 1st degree, *n* (%) FC PAH of the 2nd degree, *n* (%) FC PAH of the 3rd degree, *n* (%)	 12 (36.4) 11 (33.3) 1 (3.0)	 29 (54.7) 18 (33.9) 4 (7.5)	 0.097 0.058 0.105
6-minute walk test, m, *Me* [Q_{25}; Q_{75}]	416 [318; 634]	527 [318; 640]	0.014
SBPav., mm Hg, *Me* [Q_{25}; Q_{75}] DBPav., mm Hg, *Me* [Q_{25}; Q_{75}]	132 [128; 138] 88 [75; 94]	134 [128; 136] 88 [78; 95]	0.376 0.431
COPD, *n* (%)	9 (27.3)	13 (24.5)	0.345
Smoking, *n* (%)	12 (36.4)	15 (28.3)	0.877
Dyslipidemia, *n* (%)	17 (51.5)	23 (43.4)	0.453
Diabetes mellitus, *n* (%)	6 (18.2)	9 (17.0)	0.120
VPB (Lown's grade II–III), *n* (%)	8 (24.2)	13 (24.5)	0.245
Atrial fibrillation, *n* (%)	7 (21.2)	9 (17.0)	0.654

Note. AHI – apnea / hypopnea index (according to polysomnography data), SPO_2av. – average night saturation (according to polysomnography data), FC – functional class, CHF – chronic heart failure, NT-proBNP – N-terminal brain natriuretic peptide precursor, PAH – pulmonary arterial hypertension, SBPav. – average daily systolic blood pressure, DBPav. – average daily diastolic blood pressure, VPB – ventricular premature beats, COPD – chronic obstructive pulmonary disease.

Comparison of the frequencies of adverse events in the groups was carried out using the Kaplan – Meier curves; the log-rank test was used to compare the two curves. To identify predictors of the development of unfavorable endpoints, the univariate analysis was used. To identify independent predictors, the method of multivariate analysis with calculating the odds ratio (OR) was applied. To determine the cutoff predictors of adverse cardiovascular events, the ROC analysis was used with the calculation of the area under the curve (AUC). The critical *p*-value significance level for all analyses was taken equal to 0.05.

RESULTS

Correlation analysis at the stage of inclusion in the study revealed the relationship between AHI and BMI ($r = 0.362$; $p = 0.0006$), left atrial volume ($r = 0.570$; $p < 0.00001$), ΔSRV ($r = –0.527$; $p < 0.00001$), RVSWI ($r = –0.377$; $p = 0.0003$), NT-proBNP ($r = 0.611$; $p < 0.00001$), and 6MWT ($r = –0.511$; $p < 0.00001$).

The main structural and functional EchoCG parameters of the left ventricle (LV) between the groups were comparable. Significant associations of RV performance indicators – ΔSRV ($p = 0.031$) and RVSWI ($p = 0.022$) – with an unfavorable clinical course of CHF were revealed (Table 2).

The therapy received by patients at the time of inclusion in the study was optimal and in line with current recommendations [17]. The groups were comparable in terms of the main groups of drugs used for treatment of hypertension and CHF (Table 3).

Table 2

Echocardiographic characteristics of the patients at the time of inclusion in the study

Parameter	Group 1, $n = 33$	Group 2, $n = 53$	p
Left atrium, mm, *Me* [Q_{25}; Q_{75}]	58 [55; 66]	5.5 [5.3; 6.0]	0.051
LVEF, %, *Me* [Q_{25}; Q_{75}]	58 [51; 66]	58 [52; 62]	0.902
LV EDD, mm, *Me* [Q_{25}; Q_{75}]	62 [56; 69]	58 [55; 63]	0.051
Interventricular septum, mm, *Me* [Q_{25}; Q_{75}]	13 [12; 14]	12 [11; 14]	0.195
Posterior wall of LV, mm, *Me* [Q_{25}; Q_{75}]	11 [10; 12]	11 [10; 12]	0.330
LV myocardial mass index, g / m^2, *Me* [Q_{25}; Q_{75}]	114 [91.5; 134.5]	113 [98; 139]	0.811
Diastolic dysfunction, *n* (%)	17 (51.5)	18 (34.0)	0.107
Left atrial volume, cm^2, *Me* [Q_{25}; Q_{75}]	20.8 [18.8; 22.8]	18.4 [16.2; 22.6]	0.057
ΔSRV, %, *Me* [Q_{25}; Q_{75}]	40 [35; 47]	44 [40; 47]	0.031
RVSWI, *Me* [Q_{25}; Q_{75}]	0.25 [0.22; 0.25]	0.25 [0.24; 0.26]	0.022
RVSP, mm Hg, *Me* [Q_{25}; Q_{75}]	30 [24; 41]	28 [21; 37]	0.321
RV anterior wall thickness, mm, *Me* [Q_{25}; Q_{75}]	5.0 [4.0; 6.0]	4.0 [4.0; 5.0]	0.186
RV EDD, mm, *Me* [Q_{25}; Q_{75}]	26 [21; 36]	29 [20; 33]	0.608

Note. LV – left ventricle, RV – right ventricle, LVEF – left ventricular ejection fraction, EDD – end-diastolic dimension, ΔSRV – fractional area change of the right ventricle, RVSWI – right ventricular myocardial stroke work index, RVSP – systolic pressure in the right ventricle.

Table 3

Therapy received by patients at the time of inclusion in the study, *n* (%)

Group of drugs	Group 1, $n = 33$	Group 2, $n = 53$	p
ACE inhibitors	20 (60.6%)	33 (62.3%)	0.581
Beta-blockers	22 (66.6%)	32 (60.4%)	0.472
Diuretics	16 (48.5%)	26 (49%)	0.748
Calcium antagonists	14 (42.4%)	20 (37.7%)	0.665
AT^2-receptor antagonists	17 (51.5%)	25 (47.2%)	0.678

Note. ACE – angiotensin-converting enzyme.

According to the univariate analysis, ΔSRV (OR 2.51; 95% CI 2.42–3.24; $p = 0.0009$), NT-proBNP (OR 1.92; 95% CI 1.32–2, 78; $p = 0.003$), and AHI (OR 3.93; 95% CI 2.87–4.11; $p = 0.018$) were predictors of an unfavorable course of CHF, while RVSWI (OR 2.53; 95% CI 1.98–4.08; $p = 0.0009$) turned out to be an insignificant predictor (OR 1.08; 95% CI 0.98–1.17; $p = 0.082$).

According to the ROC analysis, the cutoff point characterizing the unfavorable course of CHF, was the AHI value ≥ 33.5 episodes per hour (sensitivity 75.8%, specificity 67.9%, AUC – 0.732; $p < 0.0001$), ΔSRV ≥ 18.6% (sensitivity 75.8%, specificity 54.7%, AUC – 0.62; $p = 0.047$), and NT-proBNP ≥ 311 pg / ml (sensitivity 63.6%, specificity 73.6%, AUC – 0.645; $p < 0.0001$). When comparing the ROC curves, AHI remained the most significant predictor of CHF progression ($p = 0.007$), as opposed to NT-proBNP and ΔSRV (Fig. 1).

To identify the association of a higher AHI with an unfavorable course of CHF, the Kaplan – Meier analysis was carried out. The patients were divided according to the cutoff level: group A ($n = 38$) – less than 33.5, group B ($n = 48$) – more than 33.5. According to the results of the Kaplan – Meier analysis (Fig. 2), it was found that the frequency of the unfavorable course of CHF in the groups was statistically significantly different ($p = 0.014$). It was shown that AHI was associated with higher frequency of CHF progression during 12 months of follow-up.

According to the multivariate analysis with the inclusion of risk factors for CHF progression (BMI, weight, LVEF, carbohydrate metabolism disorders,

NT-proBNP levels, etc.), the AHI remained an independent predictor of an unfavorable course of CHF (OR 3.49; 95% CI 2.17–11.73; $p = 0.0008$), while the addition of NT-proBNP significantly improved risk stratification for an unfavorable course of CHF (OR 4.66; 95% CI 3.87–13.11; $p < 0.0001$).

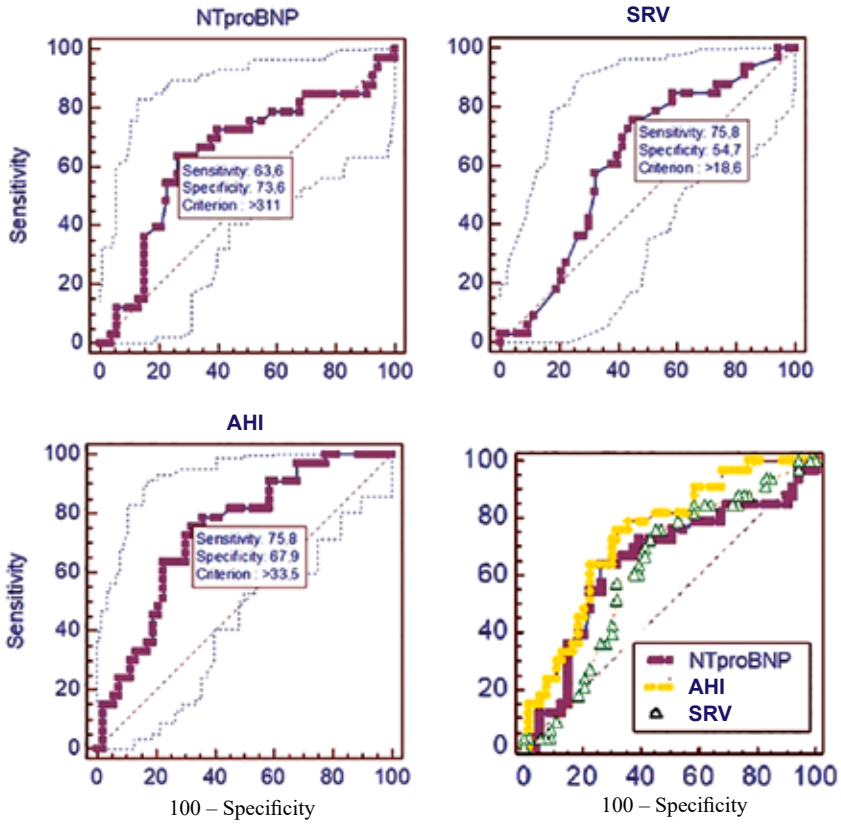

Fig. 1. Predictors of an adverse course of chronic heart failure (ROC-analysis): AHI – the apnea / hypopnea index (according to polysomnography), NT-proBNP – the N-terminal brain natriuretic peptide precursor, ΔSRV – fractional area change in the right ventricle (here and in Fig. 2)

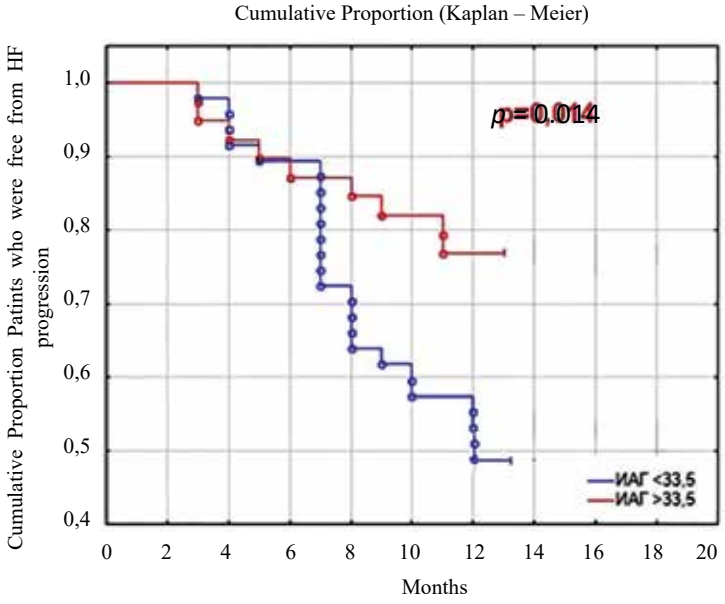

Fig. 2. Analysis of the frequency of an adverse course of CHF depending on the apnea / hypopnea index (Kaplan – Meier)

DISCUSSION

The study revealed the presence of a relationship between the severity of obstructive breathing disorders during sleep, assessed by AHI and echocardiographic (ΔSRV, RVSWI) parameters of right ventricular dysfunction, and the level of NT-proBNP. On the contrary, no significant correlations of the above-mentioned indicators with the severity of nocturnal hypoxemia (SPO_2av.) were found. This may indicate a key pathogenetic role of a prolonged excessive increase in intra-abdominal and intra-thoracic pressure during repeated apnea episodes in the development of right ventricular dysfunction in OSAS.

From this point of view, it is the frequency of apnea episodes, and not blood oxygenation, that seems to be the main factor determining right ventricular dysfunction and the clinical course of the disease in general. The importance of chronic nocturnal hypoxemia as a factor forming the mechanism of persistent pulmonary hypertension fades into the background. This is consistent with the data of a number of already published studies [18, 19].

As the analysis of the obtained data showed, the severity of obstructive breathing disorders during sleep, the main parameter of which is AHI, significantly correlates with the unfavorable clinical course of CHF with preserved ejection fraction. The most unfavorable course was observed in patients with severe OSAS (AHI > 33.5 per hour according to the Kaplan – Meier analysis). This association is probably determined by the commonality of a number of pathogenetic links in OSAS and the pathogenesis of the classic cardiovascular continuum: hyperactivation of the sympathetic nervous system, oxidative stress, and triggering of systemic inflammatory responses. Along with this, statistical analysis did not reveal significant correlations between the severity of nocturnal hypoxemia (SPO_2av.) and the course of CHF in the studied patients, which again may indicate a secondary role of nocturnal hypoxemia caused by obstructive apnea in the formation of right ventricular dysfunction in these patients.

The absence of reliable associations between the severity of pulmonary hypertension and the clinical course of the disease is worth noting. This is possibly determined by the method for assessing the degree of pulmonary hypertension chosen for this study. The assessment was carried out by calculation according to the degree of tricuspid regurgitation. At the same time, the degree of tricuspid regurgitation could be mediated to a certain extent with right ventricular dysfunction itself, and to clarify the value of pulmonary hypertension as a marker of the clinical course of OSAS, it is necessary to consider, apparently, another, more accurate variant of assessing this parameter.

At the same time, the results of the study demonstrated that the ΔSRV echocardiographic parameter of right ventricular dysfunction and the NT-proBNP laboratory marker are independent predictors of an unfavorable clinical course of CHF with preserved EF and OSAS. Considering the pathogenetic concept of the initial lesion of the right heart [20], which is currently available in the works of most researchers, the facts obtained in this study seem quite logical. The appearance of structural and functional disorders in the work of the right heart may indicate a previous pathogenetic effect of OSAS, significant in time and strength, and be accompanied by appropriate clinical presentation, or indicate its imminent emergence. In this case, the markers of right ventricular dysfunction can appear much earlier than the corresponding disorders in the left ventricle and serve as a criterion for the severity of the syndrome and an important prognostic sign.

A number of studies showed the prognostic significance of various forms of pulmonary hypertension as a marker of an unfavorable prognosis of cardiovascular mortality in patients with cardiovascular diseases, such as acquired heart defects, coronary artery disease, and CHF [20, 21]. However, at this point in time, the formation of chronic pulmonary hypertension and right ventricular dysfunction against the background of OSAS, as well as the prognostic role of these disorders are poorly understood. Data on the epidemiology and prevalence of pulmonary hypertension in OSAS both in Russia and in economically developed countries are very contradictory [18, 19, 22, 23].

A number of researchers consider an increase in the pulmonary artery pressure in the development of OSAS during the rapid eye movement (REM) sleep phase, regardless of the degree of arterial hypoxemia, a proven fact [24]. In addition, some researchers believe that OSAS induces the development of pulmonary hypertension mainly or exclusively in patients with COPD or in OSAS associated with primary pulmonary hypertension [25–27].

In practical terms, the emergence of the markers of right ventricular dysfunction can be useful in choosing a treatment strategy for these patients, as a signal for more aggressive treatment tactics with an earlier

decision on starting continuous positive airway pressure (CPAP) therapy. At the same time, the severity of nocturnal hypoxemia did not show such significant associations either with the markers of right ventricular dysfunction or with the clinical course of the disease. It is obvious that hypoxemia was mediated by OSAS and was secondary in nature.

From this point of view, when determining the treatment strategy, the preferred choice is CPAP therapy rather than prolonged oxygen inhalation, which is consistent with existing clinical guidelines and consensus documents [28, 29]. Undoubtedly, for clarifying the prognostic role of individual parameters of right ventricular dysfunction as well as for a more detailed study of the pathogenesis of cardiovascular complications in OSAS, it seems promising to evaluate these echocardiographic parameters at runtime with a longer follow-up period for this category of patients.

CONCLUSION

In the study, significant correlations between the severity of obstructive breathing disorders during sleep and echocardiographic and laboratory markers of developing right ventricular dysfunction in patients with OSAS were found, which may indicate an important pathogenetic role of these disorders in development of cardiovascular complications in the studied pathology. Evaluation of the clinical course of the disease revealed the relationship between the echocardiographic (ΔSRV) parameters of right ventricular dysfunction and the laboratory (NT-proBNP) markers with an adverse clinical course in this category of patients.

The data obtained make it possible to evaluate these markers as independent predictors of an adverse clinical course of the disease. In the future, they can be used to stratify the clinical risk of heart failure with preserved left ventricular ejection fraction and determine the treatment strategy in patients with OSAS.

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