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# ИЗУЧЕНИЕ ВАРИАБЕЛЬНОСТИ РИТМА СЕРДЦА У БОЛЬНЫХ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТЬЮ И ХРОНИЧЕСКОЙ ОБСТРУКТИВНОЙ БОЛЕЗНЬЮ ЛЕГКИХ.

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# Study of Heart Rate Variability in Patients with Chronic Heart Failure and Chronic Obstructive Pulmonary Disease

**Резюме**

**Цель.** Изучить вариабельность ритма сердца (ВРС) у больных хронической сердечной недостаточностью (ХСН) и хронической обструктивной болезнью легких (ХОБЛ) во взаимосвязи: с уровнем насыщения крови кислородом, параметрами функции внешнего дыхания (ФВД), концентрацией Nt — proBNP в плазме крови. **Материалы и методы.** Обследовано 128 амбулаторных пациентов обоего пола. Возраст больных составил от 45 до 70 лет. 1 группа — основная (60 больных) с ХСН ишемического генеза II–III функционального класса по NYHA и ХОБЛ GOLD I–III степени ограничения воздушного потока (классификация GOLD 2019) в стадии стойкой ремиссии, 2 группа — контрольная (63 пациента), с изолированной ХСН. Все, включенные в исследование больные с ХСН, перенесли инфаркт миокарда (ОИМ) давностью от 1 года до 5 лет. Статистически значимых различий по тяжести ХСН между 1 и 2 группами не было. **Результаты.** У пациентов с ХСН и ХОБЛ, в отличие от больных с изолированной ХСН, выявлено достоверное преобладание частоты встречаемости гиперсимпатикотонического типа вегетативной регуляции. Достоверно более низкие показатели вариабельности ритма сердца были в группе больных с сопутствующей ХОБЛ в сравнении с пациентами с изолированной ХСН. Выявлены статистически значимые корреляционные связи между показателями ВРС и параметрами ФВД, уровнем насыщения крови кислородом, концентрацией NT-proBNP в крови. При проведении многофакторного регрессионного анализа установлена достоверная зависимость показателей ВРС от параметров ФВД и концентрации NT-proBNP в крови в группе больных с ХСН и ХОБЛ.

***Ключевые слова:*** *хроническая сердечная недостаточность, хроническая обструктивная болезнь легких, вариабельность ритма сердца*

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**Abstract**

**Aim.** To study heart rate variability (HRV) in patients with chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) in relation to: blood oxygen saturation level, parameters of respiratory function (RPF), Nt — proBNP concentration in blood plasma. **Materials and methods.** We examined 128 outpatients of both sexes. The patients' age ranged from 45 to 70 years. Group 1 — main (60 patients) with CHF of ischemic genesis of NYHA functional class II — III and GOLD COPD of I — III degree of airflow restriction (GOLD 2019 classification) in the stage of stable remission, group 2 — control group (63 patients), with isolated CHF. All patients with CHF, who were included in the study, had myocardial infarction (AMI) from 1 to 5 years ago. There were no statistically significant differences in the severity of CHF between groups 1 and 2. **Results.** In patients with CHF and COPD, in contrast to patients with isolated CHF, a significant prevalence of the frequency of occurrence of the hypersympathicotonic type of autonomic regulation was revealed. Significantly lower indicators of heart rate variability were in the group of patients with concomitant COPD in comparison with patients with isolated CHF. Statistically significant correlations were revealed between HRV parameters and RPF, parameters of blood oxygen saturation level, NT-proBNP concentration in blood. Multivariate regression analysis showed a significant dependence of HRV parameters on the parameters of HRV and the concentration of NT-proBNP in the blood in the group of patients with CHF and COPD.

**Key words:** *chronic heart failure, chronic obstructive pulmonary disease, heart rate variability.*

**Conflict of interests**

The authors declare no conflict of interests

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CHF — chronic heart failure, COPD — chronic obstructive pulmonary disease, CCP — chronic cor pulmonale, HRV — heart rate variability, AMI — acute myocardial infarction, ANS — autonomic nervous system, PFT — pulmonary function test

## Introduction

Chronic heart failure (CHF) and chronic obstructive pulmonary disease (COPD) are common diseases in clinical practice. CHF in COPD can be associated with both concomitant cardiac disease (in particular, coronary heart disease) and decompensation of chronic cor pulmonale (CCP) [1].

The prevalence of CHF among COPD patients is on average 10–20%. The incidence of COPD in CHF is 9–13%. CHF worsens the prognosis and increases the frequency of hospitalizations in patients with COPD. On the other hand, the prevalence of CHF and cardiovascular complications increases as the severity of COPD increases. Cardiovascular events are one of the main, if not the primary, reasons for the hospitalization of patients with COPD [2].

In COPD, a chronic inflammatory process in the tracheobronchial tree is observed due to the toxic effects of inhaled pathogenic particles or gases, leading to microhemocirculation disorders, increased endothelial dysfunction, the elevation of C-reactive protein, development of atherosclerosis, regression of capillary networks, blood stasis and tissue hypoxia [3, 4].

Hypoxia, inflammation, oxidative stress, activation of neurohumoral systems (renin-angiotensin-aldosterone (RAAS) and sympathoadrenal (SAS)systems) are associated with direct and indirect cytotoxic effects that contribute to CHF and aggravation of its clinical course [1, 2 ].

As a result of the cascade of pathophysiological reactions, the activity of the sympathetic and parasympathetic components of the autonomic nervous system (ANS) changes. A number of studies described a decrease in heart rate variability (HRV) and the predominance of the sympathetic nervous system activity, both in patients with CHF and patients with COPD [5–9].

However, we did not see any studies of heart rate variability in relation to blood oxygen saturation, the severity of airway obstruction, and blood NT-proBNP level in patients with CHF and COPD.

**The aim of the study** was to assess heart rate variability in patients with CHF and COPD in relation to blood oxygen saturation, pulmonary function test (PFT) results, and plasma NT-proBNP level.

## Materials and Methods

Our prospective, open-label, controlled study included 123 outpatients, both men and women. Group 1 — main (60 patients), NYHA II–III CHF of ischemic genesis and GOLD I–III (GOLD classification 2019) COPD in the stage of stable remission; group 2 — control (63 patients), isolated CHF. All enrolled patients with CHF had a history of myocardial infarction (AMI) in the past 1–5 years. The age of participants ranged from 45 to 70 years.

***Table 1**. Characteristics of the patients included in the study, Me [Q25; Q75]*

| Variable | 1st group (main) | Group 2 (control) | p |
|---|---|---|---|
| Number of patients, n | 60 | 63 | p >0,05 |
| Average age, years | 64 [60; 68] | 62 [58; 69] | p >0,05 |
| Men, n (%) | 48 (80,0) | 53 (84,1) | p >0,05 |
| Women, n (%) | 12 (20,0) | 10 (15,8) | p >0,05 |
| BMI | 29,7 [26,1; 34,2] | 30,4 [26,5; 33,3] | p >0,05 |
| AHA, % | 100 | 100 | p >0,05 |
| SBP, mm Hg | 130 [120; 140] | 130 [120; 130] | p >0,05 |
| DBP, mm Hg | 80 [75; 80] | 80 [75; 80] | p >0,05 |
| Heart rate, beats / min | 67 [60; 72] | 64 [59; 71] | p >0,05 |
| CHF duration, years | 2 [1; 4] | 2 [1; 5] | p >0,05 |
| FC, years | 2,0 [2,0; 3,0] | 2,0 [2,0; 3,0] | p >0,05 |
| NT-proBNP, fmol /ml | 231,7 [187,2; 383,0] | 227,1 [164,4; 300,8] | p >0,05 |
| LVEF, % | 48,5 [42,0; 54,5] | 52,0 [44,0; 57,0] | p >0,05 |
| HFpEF,% | 45,0 | 58,0 | p >0,05 |
| HFmrEF, % | 38,3 | 29,0 | p >0,05 |
| HFrEF, % | 16,7 | 13,0 | p >0,05 |
| LA, mm | 38,0 [36,0; 43,0] x 55,0 [54,0; 56,0] | 37,0 [35,0; 41,0] x 54,0 [50,0; 57,0] | p >0,05 |
| RA, mm | 37,0 [35,0; 41,0] x 56,0 [48,0; 62,0] | 35,0 [34,0; 37,0] x 51,0 [45,0; 54,0]* | p <0,05 |
| RV, mm | 39,0 [36,0; 41,5] | 28,0 [27,0; 34,0]* | p <0,05 |
| EDD, mm | 54,0 [48,0; 58,0] | 52,0 [47,0; 57,0] | p >0,05 |
| LVDS, mm | 37,0 [35,0; 42,0] | 35,0 [32,0; 40,0] | p >0,05 |
| ICH, years | 30 [0; 40] | 15 [0; 27,5]* | p <0,05 |
| $SpO_2$, % | 96% [95; 97] | 97% [96; 98]* | p <0,05 |
| FVC, % | 58,0 [45,0; 71,0] | 85,0 [76,0; 89,0]* | p <0,05 |
| $FEV_1$, % | 52,0 [41,0; 64,0] | 90,0 [83,0; 95,0]* | p <0,05 |
| VC, % | 68,0 [55,0; 77,0] | 88,0 [78,0; 93,0]* | p <0,05 |
| $FEV_1$/FVC, % | 65,0 [59,0; 67,0] | 88,0 [84,0; 93,0]* | p <0,05 |
| MEF 25% | 39,0 [25,0; 52,0] | 94,0 [72,0; 109,0]* | p <0,05 |
| MEF 50% | 31,0 [20,0; 41,0] | 93,0 [77,0; 106,0]* | p <0,05 |
| MEF 75% | 34,0 [24,0; 43,0] | 78,0 [70,0; 103,0]* | p <0,05 |
| Enalapril, mg /day | 5,0 [5,0; 10,0] | 5,0 [5,0; 10,0] | p>0,05 |
| Bisoprolol, mg /day | 2,5 [2,5; 5,0] | 5,0 [2,5; 5,0] | p>0,05 |
| Veroshpiron, mg /day | 25,0 | 25,0 | p >0,05 |
| Torasemide, mg / day | 2,5 | 2,5 | p >0,05 |
| Atorvastatin, mg /day | 20 [10,0; 20,0] | 20 [10,0; 20,0] | p >0,05 |
| Acetylsalicylic acid, mg /day | 100 [75; 100] | 100 [75; 100] | p >0,05 |
| Isosorbide mononitrate, mg | 40 [20,0;40,0] | 40 [20,0;40,0] | p >0,05 |
| Ivabradine, %; mg /day | 7,6%; 5,0 [5,0; 7,5] | 6,3%; 6,2 [5,0; 7,5] | p >0,05 |
| Ipratropium bromide, mcg /day | 140,0 [100,0;160,0] | - | |
| Budesonide+formoterol, mcg /day | 160,0/4,5 мкг/сут.; | - | |
| Olodaterol hydrochloride+ tiotropium bromide, mcg /day | 2.5 мкг/2.5 мкг сут | - | |

**Note:** * p< 0,05, BMI — body mass index, AHA — arterial hypertension, SBP — systolic blood pressure, DBP — diastolic blood pressure, HFpEF — Heart failure with preserved ejection fraction, HFmrEF — Heart failure with midrange ejection fraction, HFrEF — heart failure with reduced ejection fraction, FC — functional class of CHF, NT-proBNP — terminal fragment of cerebral natriuretic peptide, LVEF — left ventricular ejection fraction, LA — left atrium, RA — right atrium, RV — right ventricle, EDD — end diastolic size of the left ventricle, CSR — terminal systolic size of the left ventricle, ICH — index of a smoking person, FVC% — forced vital capacity of the lungs, $FEV_1$% — forced expiratory volume in the first second, VC% — vital capacity of the lungs, $FEV_1$ / FVC% — Tiffno index, MEF 25% — instantaneous volumetric expiratory flow rate of 25% FVC, MEF 50% — instantaneous expiratory flow rate of 50% FVC, MEF 75% — instantaneous expiratory flow rate of 75% FVC

The study was conducted in accordance with the ethical principles set forth in the World Medical Association Declaration of Helsinki (2008), the ICH Harmonised Tripartite Guideline on Good Clinical Practice (ICH-GCP), and Basics of Health Protection of the Citizens in the Russian Federation. The study was approved by the regional ethics committee (protocol No. 001-2019, expert opinion No. 002/5).

Patients who participated in the study were comparable on the main clinical and demographic characteristics, the severity of CHF signs, as well as the dose regimens of the CHF treatment used. All patients with CHF and concomitant COPD in our study received baseline treatment of COPD with long-acting drugs: predominantly M-anticholinergics (tiotropium bromide) or a combination of tiotropium bromide and long-acting β2-agonist olodaterol (double bronchodilation); a number of patients (20%) took combined drugs (long-acting β2-agonist (formoterol) + inhalation GCS (budesonide)). Six patients occasionally used short-acting bronchodilators during the observation period, but in all cases, these drugs (ipratropium bromide and fenoterol hydrobromide) were withdrawn 3–4 days before the study. Patients with diabetes mellitus were not included in the study.

Clinical and demographic characteristics of patients are presented in Table 1.

HRV was studied using the Poly-Spectrum-Rhythm software module (Poly-Spectrum-8/E (Russia)). Short-term (five-minute) electrocardiogram recordings in the supine position of the patient were evaluated [10].

HRV was recorded in a state of complete rest. Before the exam, the patients were lying down for ten minutes. Then HRV data were recorded in the supine position. Time-series analysis was evaluated by the following indices: SDNN — standard deviation of all analyzed *R-R* intervals, pNN50 (%) — the percentage of consecutive NN intervals; RMSSD (ms) — the root mean square of differences of the values of successive pairs of NN intervals. Changes in RMSSD and pNN50 were used to assess the parasympathetic nervous system shift. The minimum and maximum R-R interval (R-R min and R-R max) were also determined.

To assess the tension of regulatory systems, we evaluated the stress index (SI) and tension index (TI). TI was calculated as follows [11]:

$$TI = AMo/Mo \times 2 \times (R\text{-}R\ max — R\text{-}R\ min)$$

Spectral Analysis was used to determine the contribution of periodic components to the changes in heart rate (TP — the total power of the HRV spectrum; LF/HF — the vagosympathetic balance ratio; ULF% — ultra-low-frequency component of variability as % of the total oscillation power; VLF % — very low-frequency component of variability as % of the total oscillation power; LF % — low-frequency component of variability as % of the total oscillation power; HF % — high-frequency component of variability as % of the total oscillation power) [10].

PFT was performed according to the generally accepted technique on the SPIROSOFT FUKUDA 3000 device (Japan).

$SpO_2$ was assessed using laser Doppler flowmetry (LDF) with spectral analysis of blood flow fluctuations using the LAKK — OP device.

The plasma level of the N-terminal fragment of brain natriuretic peptide (NT-proBNP) was evaluated using ELISA (NT-proBNP, Bio-medica, Slovakia). The data obtained were reported in fmol/ml. For the methods used, a concentration of 150 fmol/ml was considered the upper limit for NT-proBNP.

The results are presented as Me [Q25; Q75], where Me is the median, Q25 and Q75 are 25th and 75th percentiles, respectively. Data were processed using the STATISTICA 10.0 software. When analyzing the results of independent samples, we used the Mann—Whitney test (estimation of quantitative indices) and the Fisher exact test (for qualitative indices). The differences between studied groups were considered significant at $p < 0.05$.

## Results

There was a significant decrease in the following parameters in patients of the main group: SDNN, ms (33.5 [19.0; 47.0] vs 35.0 [27.0; 55.0]), CV % (3.1 [2.0; 5.1] vs 3.8 [2.7; 5.6]) and TP, $ms^2$ (1,185.0 [520.0; 1,863.0] vs 1,364.0 [750.0; 3,312.0]), in comparison with the control group patients. This may suggest the predominance of the sympathetic nervous system effects in comorbid patients. A significant low pNN50% value (1.1 [0.0; 5.6] vs 2.7 [0.9; 14.4]) in the group of patients with CHF and COPD indicates a decrease in the activity of the parasympathetic nervous system.

The significant predominance of the sympathetic nervous system activity in the 1st group, compared to the 2nd group, contributes to the tension of regulatory systems, which is confirmed by a significant increase in SI, c.u. (229.7 [96.7; 528.5] vs 138.9 [79.3; 265.1]), and TI, c.u. (161.7 [81.4; 435.1] vs 134.8 [58.9; 220.7]). Results are shown in Table 2.

The assessment of HRV in the study groups revealed a significant increase in the incidence of patients with hypersympathicotonia (51% vs 34.5%). The obtained data confirm the predominance of sympathetic nervous system activity in the patients of the main group and, consequently, the tension of regulatory systems, along with a decrease in the activity of the parasympathetic nervous system. Results are shown in Table 3.

***Table 2.*** *Indicators of heart rate variability of the patients in the study*

| Indicator | 1st group (CHF+COPD) | Group 2 (CHF isolated) | p |
|---|---|---|---|
| SDNN, ms | 33,5 [19,0; 47,0] | 35,0 [27,0; 55,0]* | p <0,05 |
| SDNN <50, n (%) | 73,3% | 70,0% | p >0,05 |
| CV, % | 3,1 [2,0; 5,1] | 3,8 [2,7; 5,6]* | p <0,05 |
| TP, ms$^2$ | 1185,0[520,0;1863,0] | 1364,0[750,0; 3312,0]* | p <0,05 |
| LF/ HF, u.e. | 0,7 [0,48;1,3] | 0,8 [0,5; 1,3] | p >0,05 |
| ULF, % | 15,4 [9,4; 26,5] | 18,4 [8,2; 31,9] | p >0,05 |
| VLF, % | 13,8 [9,0; 26,8] | 17,2 [9,7; 28,6] | p >0,05 |
| LF, % | 23,9 [17,8; 33,0] | 25,6 [18,0; 33,4] | p >0,05 |
| HF, % | 35,8 [18,4; 51,3] | 28,9 [15,7; 46,0] | p >0,05 |
| (SI), u.e. | 229,7 [96,7; 528,5] | 138,9 [79,3; 265,1]* | p <0,05 |
| pNN50, % | 1,1 [0,0; 5,6] | 2,7[0,9; 14,4]* | p <0,05 |
| RMSSD, ms | 25,0 [13,0; 59,0] | 22,0 [15,0; 49,0] | p >0,05 |
| RMSSD <20, n (%) | 40,3% | 34,6% | p >0,05 |
| IN, c.e. | 161,7 [81,4; 435,1] | 134,8 [58,9; 220,7]* | p <0,05 |

**Notes:** * Differences between groups are significant (p <0,05). SDNN is the standard deviation of all analyzed R — R intervals; CV % — coefficient of variation; TP — total power of HRV spectrum; LF/HF — vagosympathetic balance coefficient; ULF% — ultra-low-frequency component of variability in% of the total oscillation power; VLF% — very low-frequency component of variability in% of the total oscillation power; LF% — low-frequency component of variability in% of the total oscillation power; HF% — high-frequency component of variability in% of the total oscillation power; SI — stress index of regulatory systems; pNN50,% — percentage of consecutive NN intervals; RMSSD — square root of the mean square of the differences in the values of consecutive pairs of NN intervals; IN — stress index

***Table 3.*** *The background state of the autonomic nervous system*

| Type of vegetative tone | Group 1 (CHF+COPD) | Group 2 (CHF isolated) | p |
|---|---|---|---|
| Wagotonia (IN <30), % | 9,0 | 16,3 | p >0,05 |
| Eutonia (IN=30-90), % | 27,3 | 27,4 | p >0,05 |
| Sympathicotonia (IN=90-160), % | 12,7 | 21,8 | p >0,05 |
| Hypersympathicotonia (IN >160), % | 51 | 34,5* | p <0,05 |

**Notes:** *p <0,05

In patients with CHF and COPD, significant correlations were established between VC % and TI, c.u., ($r = -0.27$; $p < 0.05$); VC % and SDNN, ms ($r = 0.24$; $p < 0.05$); VC % and CV % ($r = 0.20$; $p < 0.05$); VC % and RMSSD, ms ($r = 0.26$; $p < 0.05$); VC % and ULF % ($r = -0.28$; $p < 0.05$). Significant correlations were also revealed between $FEV_1$/FVC % and VLF % ($r = -0.19$; $p < 0.05$), $FEV_1$/FVC % and LF % ($r = 0.20$; $p < 0.05$). These correlations indicate a reliable relationship between the main HRV and PFT parameters. The activation of the sympathetic center of the medulla oblongata, which has a vasoconstrictive and cardiostimulating effect, could be closely associated with an increase in the degree of airway obstruction.

Blood oxygen saturation also significantly correlated with an increase in the activity of the sympathetic nervous system. Significant correlations were revealed between $SpO_2$% and VLF % ($r = 0.16$; $p < 0.05$), $SpO_2$% and LF % ($r = 0.19$; $p < 0.05$).

CHF progresses with airway obstruction and increasing hypoxia, as evidenced by the significant correlation between NT-proBNP level, fmol/ml, and SI, c.u. ($r = 0.35$; $p < 0.05$), NT-proBNP, fmol/ml, and TI, c.u. ($r = 0.30$; $p < 0.05$), NT-proBNP, fmol/ml, and SDNN, ms ($r = -0.32$; $p < 0.05$), NT-proBNP, fmol/ml, and CV % ($r = -0.28$; $p < 0.05$), NT-proBNP, fmol/ml and TP, ms$^2$ ($r = -0.36$; $p < 0.05$), NT-proBNP, fmol/ml, and VLF % ($r = 0.34$; $p < 0.05$), NT-proBNP, fmol/ml, and RMSSD, ms ($r = -0.23$; $p < 0.05$).

A multivariate regression analysis was performed to determine the contribution of the PFT parameters, $SpO_2$ and NT-proBNP in the development of HRV dysfunction. The data are presented in Table 4.

According to the results of the multivariate regression analysis, VC % ($p < 0.05$) contributes the most to the development of autonomic dysfunction (LF/HF). The degree of influence of VC % on LF/HF was 40%.

Based on the data obtained, it can be assumed that the progression of bronchial obstruction in patients with CHF and COPD significantly changes the vegetative balance due to the predominance of the sympathetic activity.

A significant effect of blood NT-proBNP on VLF % was also revealed. The degree of influence of blood NT-proBNP on VLF % was 40%. Accordingly, a high level of NT-proBNP, indicating the CHF progression, significantly changes the vegetative balance causing hypersympathicotonia.

*Table 4. Multivariate regression analysis of the influence of the parameters of HRV, $SpO_2$, NT-proBNP on HRV parameters*

| Indicator | | β | | b | | t(95) | p |
|---|---|---|---|---|---|---|---|
| | | M | SE | M | SE | | |
| SDNN, ms | member | | | 385,06 | 219,80 | 1,75 | 0,08 |
| | $SpO_2$,% | -0,25 | 0,14 | -4,37 | 2,39 | -1,82 | 0,07 |
| | NT-proBNP, fmol /ml | -0,23 | 0,13 | -0,03 | 0,02 | -1,77 | 0,08 |
| CV, % | member | | | 46,04 | 27,56 | 1,67 | 0,10 |
| | $SpO_2$, % | -0,25 | 0,14 | -0,55 | 0,30 | -1,83 | 0,07 |
| | $FEV_1$/FVC, % | 0,32 | 0,17 | 0,15 | 0,08 | 1,79 | 0,07 |
| TP, $ms^2$ | member | | | 2590,38 | 12329,84 | 0,21 | 0,83 |
| | NT-proBNP, fmol /ml | -0,24 | 0,13 | -2,21 | 1,23 | -1,80 | 0,07 |
| LF/ HF, u.e. | member | | | -3,88 | 8,35 | -0,46 | 0,64 |
| | VC, % | -0,40 | 0,19 | -0,02 | 0,01 | -2,06 | 0,04* |
| VLF, % | member | | | -156,41 | 95,06 | -1,64 | 0,10 |
| | $SpO_2$, % | 0,25 | 0,13 | 1,93 | 1,03 | 1,86 | 0,06 |
| | NT-proBNP, fmol /ml | 0,40 | 0,12 | 0,03 | 0,00 | 3,21 | 0,002* |
| RMSSD, ms | member | | | 530,70 | 403,00 | 1,31 | 0,19 |
| | ЖЕЛ, % | 0,34 | 0,18 | 1,06 | 0,58 | 1,81 | 0,07 |

**Notes:** * p <0,05, SE — is the standard error; β — is the standardized equivalent of the coefficient b; b — is the regression coefficient; p — is the exact value for each regression coefficient, member — constant

## Discussion

The results of the study can be explained by morphological changes in the myocardium after acute myocardial infarction with the formation of denervated areas and a secondary violation of the autonomous regulation of heart rhythm, an increase in catecholamines, as well as the progression of hypercapnia and hypoxia [5, 12].

Complex pathogenetic interactions create a vicious circle with an increased cardiac load and aggravation of CHF. Hypoxemia, hypercapnia, and acid-base imbalance increase the electrical heterogeneity of the myocardial tissue that can lead to life-threatening arrhythmias. Hypoxemia is an important factor in the pathophysiology of autonomic neuropathy and is considered the main cause of autonomic dysfunction, manifesting in the hyperactivation of the sympathetic nervous system [5, 13].

A significant increase in the stress index and tension index of regulatory systems, as well as hypersympathicotonia revealed in patients with CHF and COPD are independent predictors of the risk of sudden death and general mortality. In turn, a sharp decrease in PNN50 (which is determined by the predominant effect of the parasympathetic system) indicates a decrease in vagal activity and imbalance of autonomic influences on the sinus rhythm, which is an unfavorable sign and correlates, the same as SDNN, with an increased risk of sudden death [5, 7, 9, 14].

Reliable correlation between HRV parameters and blood oxygen saturation, parameters of PFT, and plasma NT-proBNP level confirms the inextricable relationship between pathophysiological changes occurring in concomitant CHF and COPD.

Hypoxia and hyperactivity of the sympathetic ANS trigger vasoconstriction, which exacerbates CHF and leads to complications that contribute to an unfavorable outcome in comorbid patients.

Due to the increase in airway obstruction, significantly lower blood oxygen saturation, decreased heart rate variability, and the predominance of hypersympathicotonia, patients with CHF and COPD are more difficult to manage than patients with isolated CHF; and they have a higher risk of sudden death from cardiovascular complications.

## Conclusions

1. Significantly lower values of heart rate variability were observed in patients with CHF and COPD compared with patients with isolated CHF. The hypersympathicotonic type of autonomic regulation was significantly more common in the group of patients with CHF and COPD compared with patients with CHF without COPD.

2. Reliable correlations between HRV and PFT parameters, $SpO_2$ and blood NT-proBNP level were established in patients with CHF and COPD. An increase in the activity of the sympathetic nervous system in patients with CHF and COPD is accompanied by an increase in the blood NT-proBNP concentration, a decrease in the pulmonary function and blood oxygen saturation.

3. Multivariate regression analysis showed that VC and the blood level of NT-proBNP contribute the most to the development of autonomic dysfunction in patients with CHF and COPD.

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