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ОЦЕНКА УРОВНЯ NT-PROBNP У ПАЦИЕНТОВ С АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИЕЙ В ВОЗРАСТЕ 80 ЛЕТ И СТАРШЕ В ЗАВИСИМОСТИ ОТ НАЛИЧИЯ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ И СИНДРОМА СТАРЧЕСКОЙ АСТЕНИИ

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Assessment of the Level of NT-proBNP in Patients with Arterial Hypertension Aged 80 Years and Older, Depending on the Presence of Heart Failure and Senile Asthenia Syndrome

Резюме

Цель. Оценить информативность N-концевого промозгового натрийуретического пептида (NT-proBNP) для диагностики хронической сердечной недостаточности (ХСН) в зависимости от наличия синдрома старческой астении (ССА) у пациентов с артериальной гипертензией (АГ) 80 лет и старше. **Материал и методы.** 320 пациентов с АГ в зависимости от наличия ХСН и ССА были распределены в группы: 1А группа — пациенты с АГ, ССА и ХСН (n=84), 1Б группа — пациенты с АГ, ССА без ХСН (n=77), 2А группа — пациенты с АГ, ХСН без ССА (n=84), 2Б группа — пациенты с АГ без ХСН и без ССА (n=75). ССА выявляли по опроснику «Возраст не помеха». Уровень NT-proBNP определяли в сыворотке крови иммуноферментным методом. Для определения порогового значения маркеров применили ROC-анализ. **Результаты**. У пациентов с АГ и ССА без ХСН концентрация NT-proBNP в крови выше в 2,3 раза (p=0,003) по сравнению с пациентами с АГ без ССА и без ХСН, что свидетельствует о влиянии ССА на уровень NT-proBNP. У пациентов с АГ и ХСН без ССА уровень NT-proBNP в 4,3 раза выше в сравнении с пациентами с АГ без ССА и без ХСН (p<0,001), у которых концентрацию NT-proBNP отмечали ниже порогового уровня (106,2 пг/мл). У пациентов с АГ и ССА и ХСН регистрировали наибольшие значения концентрации NT-proBNP, которые в 2,9 раза (p<0,001) выше, чем у «хрупких» пациентов с АГ без ХСН и в 1,5 раза выше чем у «крепких» пациентов с АГ и ХСН (p<0,001). Рассчитан новый пороговый уровень NT-proBNP для диагностики ХСН у пациентов с АГ и ССА в возрасте 80 лет и старше — 365,9 пг/мл. **Заключение.** Для диагностики ХСН у пациентов с АГ 80 лет и старше без ССА маркер NT-proBNP является информативным, так как, согласно полученным данным, его уровень не зависел от возраста пациентов. При применении NT-proBNP для выявления ХСН у пациентов с АГ и ССА 80 лет и старше следует использовать рассчитанный пороговый уровень маркера (365,9 пг/мл), поскольку у этих пациентов концентрация NT-proBNP повышена, независимо от наличия ХСН.

Ключевые слова: *хроническая сердечная недостаточность, синдром старческой астении, возраст 80 лет и старше, NT- proBNP*

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Abstract

Objectives. To evaluate the informativeness of the N-terminal brain-promoting natriuretic peptide (NT-proBNP) for the diagnosis of chronic heart failure (CHF), depending on the presence of senile asthenia syndrome (SSA) in patients with arterial hypertension (AH) 80 years and older. **Materials and Methods.** 320 patients with hypertension, depending on the presence of CHF and SSA, were divided into groups: group 1A — patients with hypertension, SSA and CHF (n=84), group 1B — patients with hypertension, SSA without CHF (n=77), group 2A — patients with hypertension, CHF without SSA (n=84), group 2B — patients with hypertension without CHF and without SSA (n=75). The CSA was identified by the questionnaire "Age is not a hindrance". The level of NT-proBNP was determined in blood serum by enzyme immunoassay. ROC analysis was used to determine the threshold value of markers. **Results.** In patients with hypertension and SSA without CHF, the concentration of NT-proBNP in the blood is 2.3 times higher (p=0.003) compared with patients with hypertension without SSA and without CHF, which indicates the effect of SSA on the level of NT-proBNP. In patients with hypertension and CHF without SSA, the level of NT-proBNP is 4.3 times higher compared with patients with hypertension without SSA and without CHF (p<0.001), in whom the concentration of NT-proBNP was noted below the threshold level (106.2 pg/ml). In patients with hypertension and SSA and CHF, the highest concentrations of NT-proBNP were recorded, which are 2.9 times (p<0.001) higher than in "fragile" patients with hypertension without CHF and 1.5 times higher than in "strong" patients with hypertension and CHF (p<0.001). A new threshold level of NT-proBNP has been calculated for the diagnosis of CHF in patients with hypertension and SSA aged 80 years and older — 365.9 pg/ml. **Conclusion.** For the diagnosis of CHF in patients with hypertension 80 years and older without CSA, the NT-proBNP marker is informative, since, according to the data obtained, its level did not depend on the age of the patients. When using NT-proBNP to detect CHF in patients with hypertension and SSA 80 years and older, the calculated threshold marker level (365.9 pg/ml) should be used, since in these patients the concentration of NT-proBNP is increased, regardless of the presence of CHF.

Key words: *chronic heart failure, senile asthenia syndrome, age 80 years and older, NT-proBNP*

Conflict of interests
Co-author of the article Chesnikova A.I. is a member of the editorial board of the journal «The Russian Archives of Internal Medicine». The article passed the journal's peer review procedure. Chesnikova A.I. was not involved in the decision to publish this article. The authors did not declare any other conflicts of interest

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Conformity with the principles of ethics
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AH — arterial hypertension, NUP — natriuretic peptides, FS — frailty syndrome, CCF — chronic cardiac failure, NT-proBNP — N-terminal pro brain natriuretic peptide

Introduction

Chronic cardiac failure (CCF) is one of the most relevant problems of the modern healthcare. It is worth mentioning that the incidence of CCF increases with age. Elderly people (65 years old and over) make 80 % of patients with CF [1]. CCF in elderly people worsens prognosis significantly, and 1-year and 5-year mortality rates in people over 80 years old are 19.5 % and 24.4 %, respectively [2]. Early identification of adverse events in patients with CVDs, including CCF development and decompensation, is essential. However, diagnosis of cardiac insufficiency in elderly patients can be challenging due to low specificity of symptoms, and special attention should be paid to ECG results and blood cardiac markers [3]. Currently, measurement of natriuretic peptide (NUP) levels in included into the diagnostic algorithms for CCF and is an essential test method to make a diagnosis; and their high value in prognosis and risk classification in patients with CF has been repeatedly proven in numerous clinical trials [4,5]. Of note, besides a number

of advantages (easy and accessible tests, high prognostic significance), NUPs have drawbacks, such as highly variable values, which depend on sex, age and comorbidities [6]. Also, the use of NUP in elderly people with CCF is challenging because of higher biomarker levels due to comorbidities and ageing with a number of geriatric syndromes. Patients with CCF are more susceptible to senile asthenia (SA) than the general population; SA is an independent predictor of re-hospitalisations and mortality in this category of patients. Approximately 20 % of patients with CCF have senile asthenia syndrome, while 50 % have pre-asthenia [7]. SA diagnosis can become an integral component of the management plan for elderly and old patients with CCF. Strategies of CCF diagnosis and prognosis, clinical symptoms, as well as structural and functional heart re-modelling in patients with AH depending on the presence or absence of FS, remain understudied.

The objective of this study was to evaluate the informative value of N-terminal pro brain natriuretic peptide (NT-proBNP) in diagnosis of CCF depending on the presence of frailty syndrome (FS) in patients with arterial hypertension (AH), who are 80 years old and over.

Materials and Methods

This study was a cross-sectional study. The study meets the standards and principles of the Declaration of Helsinki. The study was approved by the Ethics Committee at the Federal State Budgetary Educational Institution of Higher Education Rostov State Medical University of the Ministry of Health of Russia (minutes No. 13/19 dated 05/09/2019). The patients were enrolled in the study after they signed a written voluntary informed consent form. Patients were recruited in outpatient settings in Rostov-on-Don. The total number of subjects was 320 patients with AH aged at least 80 years old (56.9 % were women and 43.1 % were men); the mean age was 85.8 ± 4.5 years.

Inclusion criteria: age of at least 80 years old; AH, grade IIA–IIB CCF and FC II–IV. Exclusion criteria: haemodynamically significant heart diseases, implanted electrocardiostimulator, a history of ischaemic heart disease (absence of typical clinical presentation, past medical history, ST segment depression or elevation on ECG and Holter ECG, area of hypo- and akinesia on Echo CG), acute cerebrovascular accident or transient ischaemic attack within past 6 months, malignancies, severe liver condition (transaminase levels 3xUNL or more) or severe kidney condition (GFR ≤ 30 mL/min).

Depending on the presence of CCF and FS, all patients were divided into four clinical groups: group 1A — patients with AH, FS and CCF (n = 84), group 1B — patients with AH, FS and without CCF (n = 77), group 2A — patients with AH, CCF and without FS (n = 84), group 2B — patients with AH and without CCF and FS (n = 75).

AH was diagnosed on the basis of the past medical history and results of office blood pressure (BP) measured under the method developed by S. N. Korotkov.

CCF was diagnosed on the basis of symptoms and clinical signs, cardiac failure marker (NT-proBNP) levels and ECG findings in accordance with the national clinical guidelines for CCF diagnosis and management [4]

FS was diagnosed with the help of the "Age is no disqualification" questionnaire; patients who scored ≥ 3 points underwent a brief battery of physical function tests [8].

Serum NTproBNP levels in study subjects were measured with ELISA test.

A form was filled out for each patient, specifying risk factors, comorbidity, current therapy, physical examination results, laboratory and instrumental test results, as well as scale and questionnaire scores.

Study results were statistically processed using STATISTICA 12.0 (StatSoft Inc., USA), SPSS 21.0, MedCalc (version 9.3.5.0).

The representative sample size, characterising the general population in terms of FS rates, was calculated as follows:

$$n= (z_{\alpha}^2\, p*q)/\Delta^2, \text{ where}$$

n is the number of observations in the sample; z_{α} is type I error (at a = 0.05); p is the incidence of the attribute in the population; q is the reverse event rate; D is the margin of sampling error

The incidence of all test parameters was checked for normality using Shapiro — Wilk test. Since the incidence of test parameters in the sample was both normal and other than normal, then the data were presented using both mean selective value, error of mean (M±σ) and median and interquartile range (Me [Q1; Q3]). Qualitative variables are presented as absolute (n) and relative (%) values. Groups were compared using Yates corrected χ2 for qualitative attributes and Mann — Whitney U test for quantitative attributes for two independent groups. The four groups of patients were compared using Kruskal — Wallis ANOVA. The critical significance level of the zero statistical hypothesis was $p_{mg} < 0.05$. Evaluations of the diagnostic efficiency of the methods and identification of the diagnostic cut-off were performed using ROC-analysis with calculation of sensitivity and specificity, odds ratio, as well as ROC-curve plotting and area under ROC-curve evaluation.

Results

Clinical characteristics of subjects are presented in Table 1. All patients in the clinical groups had a very high cardiovascular risk; AH duration exceeded 20 years.

A comparative analysis of CCF stage distribution demonstrated the lack of any statistically significant difference between patients, irrespective of FS (p> 0.05).

Table 1. *Clinical characteristics of the patients included in the study*

Indicator \ Group	1A group (AH + CHF + SAS, n=84)	1B group (AH + SAS without CHF, n=84)	2A group (AH + CHF without SAS, n=77)	2B group (AH without SAS and without CHF, n=75)	Pairwise comparison of groups	$p_{мг}$/ p_{mg}
Age, years	84,9±4,8	84,2±4,1	85,7±5,9	86,4±5,7	p_1=0,937 p_2=0,848 p_3=0,839 p_4=0,962	0,852
Gender (f/m), n (%)	44/40 (52,4/47,6)	41/43 (48,8/51,2)	38/39 (49,4/50,6)	38/37 (50,7/49,3)	p_1=0, 953 p_2=0,871 p_3=0, 639 p_4=0,597	0,872
HTN stage II, n (%)	-	6 (7,1)	-	4 (5,3)	p_4=0,861	-
HTN stage III, n (%)	84 (100)	78 (92,9)	77 (100)	71 (94,7)	p_1=0,634 p_2=0,739 p_4=0,906	0,945
Left ventricular ejection fraction, %	44,0 [42,4;47,3]	52,8 [50,6;55,4]	59,2 [57,8;60,5]	62,2 [60,6;63,9]	p_1<0,001 p_2=0,813 p_3=0,002 p_4=0,009 p_5=0,092	0,004
CHF stage IIA, n (%)	73 (86,9)	-	71 (92,2)	-	p_3=0,314	-
CHF stage IIB, n (%)	11 (13,1)	-	6 (7,8)	-	p_3= 0,428	-
CHF II FC, n (%)	24 (28,6)	-	32 (41,6)	-	p_3=0,041	-
CHF III FC, n (%)	52 (61,9)	-	35 (45,5)	-	p_3=0,036	-
CHF IV FC, n (%)	8 (9,5)	-	10 (12,9)	-	p_3=0,382	-
Anemia, n (%)	20 (23,8)	9 (10,7)	12 (15,6)	10 (13,3)	p_1=0,033 p_2=0,172 p_3=0,237 p_4=0,341	0,193
Atrial fibrillation, n (%)	42 (50,0)	25 (29,8)	19 (24,7)	13 (17,3)	p_1=0,003 p_2=0,313 p_3<0,001 p_4=0,082	<0,001
Chronic kidney disease, n (%)	56 (66,67)	48 (57,14)	31 (40,26)	24 (32)	p_1=0,203 p_2=0,293 p_3<0,001 p_4=0,001	<0,001
Type 2 diabetes mellitus, n (%)	26 (31)	15 (17,9)	19 (24,7)	12 (16)	p_1=0,042 p_2=0,199 p_3=0,386 p_4=0,778	0,089
BMI, kg/m^2	23,4 ± 2,1	28,2±0,4	32,1 ± 2,0	30,3±0,4	p_1=0,062 p_2=0,319 p_3=0,029 p_4=0,823	0,481
Obesity, n (%)	8 (9,88)	14 (16,67)	18 (23,37)	11 (14,66)	p_1=0,236 p_2=0,563 p_3=0,032 p_4=0,206	0,582
Dyslipidemia, n (%)	47 (55,95)	58 (69,05)	46 (59,74)	55 (73,33)	p_1=0,076 p_2=0,079 p_3=0,614 p_4=0,571	0,080
Hemoglobin, g/L	110±14*•	123±6	122±9	125±8	p_1=0,020 p_2=0,452 p_3=0,034 p_4=0,547	0,013

Table 1. (The end)

Group / Indicator	1A group (AH + CHF + SAS, n=84)	1B group (AH + SAS without CHF, n=84)	2A group (AH + CHF without SAS, n=77)	2B group (AH without SAS and without CHF, n=75)	Pairwise comparison of groups	p_{MG}/ p_{mg}
Red blood cells, $\times10^{12}$/ L	4,1±0,8	4,2±0,6	4,0±0,5	4,5±0,7	p_1=0,620 p_2=0,492 p_3=0,716 p_4=0,937	0,482
Glycemia, mmol/L	5,2±0,31	5,1±0,26	5,3±0,28	5,0±0,35	p_1=0,784 p_2=0,592 p_3=0,847 p_4=0,286	0,981
Urea, mmol/L	5,7±0,21	6,1±0,37	5,9±0,42	6,0±0,36	p_1=0,482 p_2=0,291 p_3=0,582 p_4=0,637	0,934
Creatinine, μmol/L	126±0,79	110±0,83	104±0,94	101±0,77	p_1=0,691 p_2=0,482 p_3=0,593 p_4=0,791	0,158
Estimated glomerular filtration rate, ml/min/1.73m^2	54,4±2,13*•	72,3±2,37	75,7±2,08	73,6±2,68	p_1=0,027 p_2=0,491 p_3=0,041 p_4=0,285	0,031
Uric acid, μmol/L	393,2±4,39*	370,3±4,67	380,5±4,0	369,6±4,63	p_1=0,015 p_2=0,782 p_3=0,451 p_4=0,991	0,113
ALT, U/L	22±2,7	23± 3,3	21± 2,1	22± 1,9	p_1=0,835 p_2=0,621 p_3=0,423 p_4=0,815	0,729
AST, U/L	27±3,2	24±2,8	25±3,1	23±2,5	p_1=0,581 p_2=0,371 p_3=0,514 p_4=0,148	0,725
Total bilirubin, mmol/L	13±1,5	15±1,8	15±1,4	14±1,7	p_1=0,571 p_2=0,491 p_3=0,281 p_4=0,623	0,381

Note: AH — arterial hypertension, HTN — hypertension, BMI — body mass index, SAS — senile asthenia syndrome, CHF — chronic heart failure;
p_1 — differences between groups 1A and 1B; p_2 — differences between groups 2A and 2B; p_3 — differences between groups 1A and 2A; p_4 — differences between groups 1B and 2B;
p_5 — differences between groups 1B and 2A; p_{mg} — multi-group comparison; * — p — differences between groups 1A and 1B, p <0,05; • — p — differences between groups 1A and 2A, p <0,05; the differences are statistically significant when p <0,05.

The evaluation of CCF FC in the study groups showed a higher incidence of FC III CCF with FS (by 16.4 %, p = 0.036) and FC II CCF in patients without FS (by 13 %, p = 0.041). The lowest LV EF was observed in frail patients with AH and CCF; the values were statistically different from the same parameter in frail patients with AH without CCF (p < 0.001) and non-frail patients with AH and CCF (p = 0.002). CCF duration was 8.4 ± 3.6 years.

An analysis of the clinical characteristics demonstrated that frail patients with AH and CCF had concomitant AFib (by 29.3 %, p = 0.003), anaemia (by 13.1 %, p = 0.033) and type 2 DM (by 17.6 %, p = 0.042) more often that frail patients with AH and without CCF.

It is worth noting that patients with AH, CCF and FS had twice as high rates of AFib (p < 0.001) and 26.4 % more CCF (p < 0.001) as compared to patients with AH and CCF and without FS. Non-frail patients with AH and CCF, on the other hand, had a higher BMI vs. frail patients with AH and CCF (p = 0.029), and 2.4-fold number of obese patients (p = 0.032). Also, frail patients without CCF had more cases of CKD (by 25.14 %) (p = 0.001) vs. non-frail patients without CCF.

An analysis of laboratory values showed that frail patients with AH and CCF (subgroup 1A) had higher levels of uric acid (p = 0.015) vs. frail patients with AH and without CCF (subgroup 1B) and statistically lower levels of GFR and Hb vs. frail patients without

CCF (p = 0.027, p = 0.020) and non-frail patients with CCF (subgroup 2A) (p = 0.034, p = 0.041), respectively (Table 1). It can be a result of a comorbidity, particularly CCF, and the effect of FS, which is associated with reduced active muscle body weight and reduced intensity of metabolic processes. There were no intergroup differences in biochemistry parameters (p > 0.05). Mean biochemistry values were within reference ranges, indicating compensated somatic functions.

Statistically significant differences (p_{mg} < 0.001) (Table 2) were demonstrated by an intergroup comparison of NT-proBNP concentrations in the study groups.

Of note, non-frail patients with AH and without CCF had lower serum NT-proBNP concentrations, with the mean values being below the threshold level of 125 pg/mL (Fig. 1).

When non-frail patients with AH (group 2A) had CCF, they also had expectedly higher NT-proBNP levels (4.3-fold, p < 0.001) vs. non-frail patients with AH and without CCF (group 2B).

An evaluation of FS effects on NT-proBNP levels included an intergroup comparison of values of patients with AH in groups 1B and 2B, i.e. with or without FS, respectively. It has been established that in patients with AH and FS and without CCF (group 1B), blood NT-proBNP concentrations were 2.3 times higher (p = 0.003) than in patients with AH and without CCF and FS (group 2B), making it possible to see the FS effects on the levels of this marker.

Results of an intergroup analysis of NT-proBNP concentrations in patients with AH and CCF, but without FS (group 2A) and AH and FS, but without CCF (group 1B) indicate statistically higher effects of CCF on NT-proBNP levels (460.2 pg/mL vs. 244.5 pg/mL, p < 0.001) as compared to effects of FS.

It is worth noting that a combination of FS and CCF in patients with AH (group 1A) was associated with the highest NT-proBNP concentrations, which were 2.9 times higher (p < 0.001) than the same parameter in the group of patients with AH and FS, but without CCF (group 1B), and 1.5 times higher than the marker levels in patients with AH and CCF, but without FS (group 2A) (p < 0.001).

A gender analysis of serum NT-proBNP concentrations demonstrated no statistically significant differences between men and women in each group (p > 0.05) (Table 3).

Table 2. *Analysis of NT-proBNP serum levels in patients included in the study*

Group / Marker	1A group (AH + CHF + SAS, n=84)	1B group (AH + SAS without CHF, n=84)	2A group (AH + CHF without SAS, n=77)	2B group (AH without SAS and without CHF, n=75)	Pairwise comparison of groups	$p_{мг}$/ p_{mg}
NT-proBNP, pg/ml	697,9 [606,2 — 837,3]	244,5 [187,2– 300,2]	460,2 [341,2–531,7]	106,2 [55,7–173,8]	p_1<0,001 p_2<0,001 p_3<0,001 p_4=0,003 p_5<0,001	<0,001

Note: AH — arterial hypertension, SAS — senile asthenia syndrome, CHF — chronic heart failure; NT-proBNP N-terminal propeptide of B-type natriuretic hormone; p_1 — differences between groups 1A and 1B; p_2 — differences between groups 2A and 2B; p_3 — differences between groups 1A and 2A; p_4 — differences between groups 1B and 2B; p_5 — differences between groups 1B and 2A; p_{mg} — multi-group comparison; the differences are statistically significant when p <0,05.

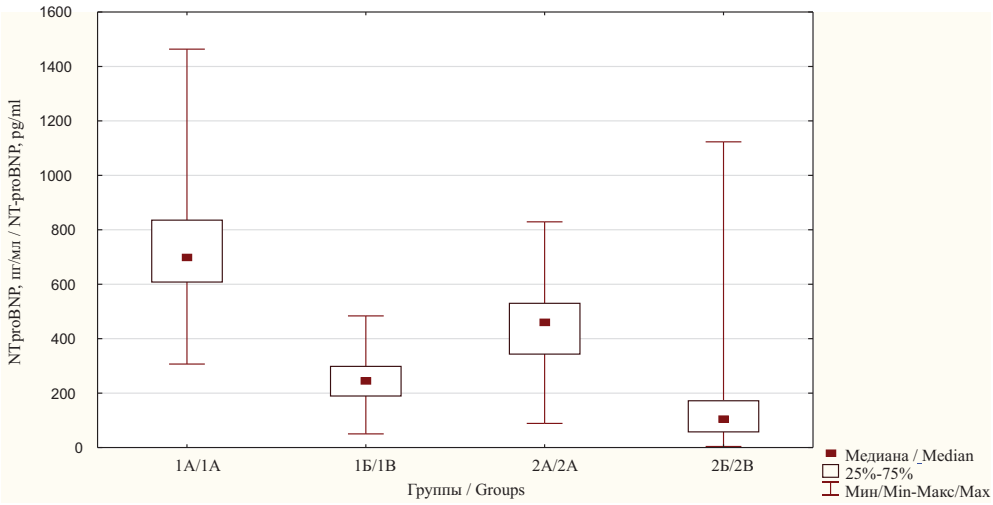

Figure 1. *Median, interquartile range and range of NT-proBNP concentration in blood serum in patients of the studied groups*

Note: NT-proBNP — N-terminal propeptide of the B-type natriuretic hormone

Table 3. *Analysis of NT-proBNP serum levels in patients included in the study, depending on gender*

1A group (n=84)			
Gender/Marker	Women (n=44)	Men (n=40)	$p_{1A\ wom\ -1A\ men}$
NT-proBNP, pg/ml	793,0 [643,0 — 988,2]	658,3 [539,4 — 792,1]	0,92
1B group (n=84)			
Gender/Marker	Women (n=43)	Men (n=41)	$p_{1B\ wom\ -1B\ men}$
NT-proBNP, pg/ml	281,4 [216,1 — 320,2]	215,7 [161,5 — 267,3]	0,90
2A group (n=77)			
Gender/Marker	Women (n=38)	Men (n=39)	$p_{2A\ wom\ -2A\ men}$
NT-proBNP, pg/ml	474,1 [416,2 — 554,5]	428,6 [264,1 — 511,4]	0,91
2B group (n=75)			
Gender/Marker	Women (n=37)	Men (n=38)	$p_{2B\ wom\ -2B\ men}$
NT-proBNP, pg/ml	71,2 [51,4 — 191,3]	126,4 [83,9 — 163,3]	0,89
	$p_{1A\ wom\ -1B\ wom} < 0,001$ $p_{1A\ wom\ -2A\ wom} < 0,001$ $p_{1B\ wom\ -2B\ wom} < 0,001$ $p_{2A\ wom\ -2B\ wom} < 0,001$ $p_{1A\ wom\ -2B\ wom} < 0,001$	$p_{1A\ men\ -1B\ men} < 0,001$ $p_{1A\ men\ -2A\ men} < 0,001$ $p_{1Б\ men\ -2B\ men} = 0,004$ $p_{2A\ men\ -2B\ men} = 0,002$ $p_{1A\ men\ -2Б\ men} < 0,001$	
$p_{мг}$ / p_{mg}	$p_{mg\ wom} < 0,001$	$p_{mg\ men} < 0,001$	

Note: NT-proBNP — N-terminal propeptide of natriuretic hormone B-type; p — differences between women and men of groups 1A, 1B, 2A, 2B; p_{mg} — multi-group comparison; p_{mg} of women, p_{mg} of men — confidence probability of multiple comparison of groups 1A, 1B, 2A, 2B among women and men, accordingly, using the analysis of variance and the Kraskell-Walis criterion

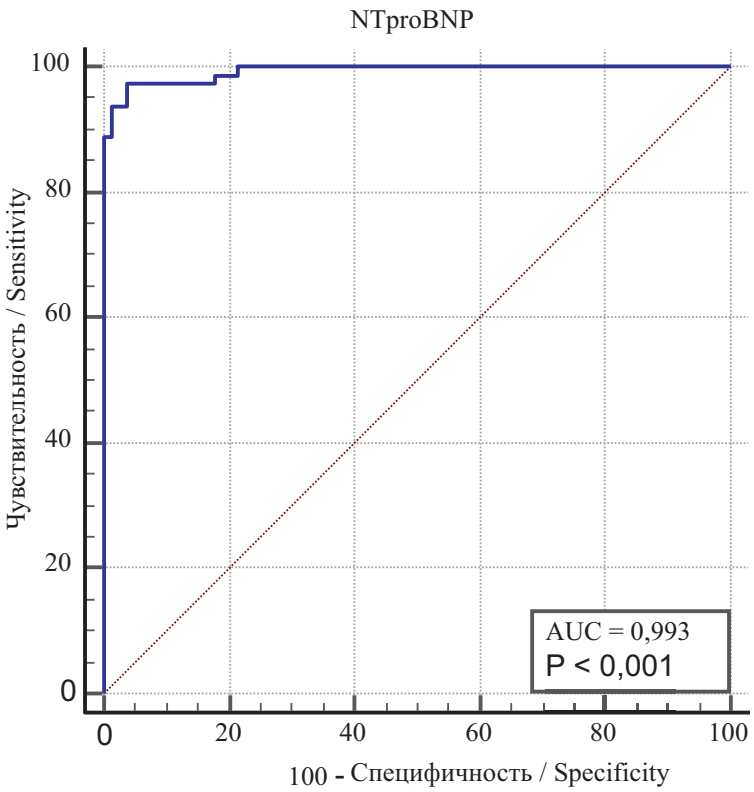

Figure 2. *ROC-curve of compliance of diagnostic sensitivity and specificity of NT-proBNP concentration for the diagnosis of CHF in patients with hypertension and senile asthenia syndrome*

Note: AH — arterial hypertension, SAS — senile asthenia syndrome, CHF — chronic heart failure; NT-proBNP N-terminal propeptide of B-type natriuretic hormone

However, both frail women with CCF and frail men with CCF had highest NT-proBNP values vs. both frail women and frail men without CCF and non-frail women and non-frail men with CCF ($p_{mg\ women} < 0.001$, $p_{mg\ men} < 0.001$).

ROC-analysis was used to identify the threshold value. Diagnostic sensitivity and diagnostic specificity values were used to plot a performance curve (ROC-curve). An important aspect of the ROC-analysis was identification of the cut-off point. In addition to visual assessment of ROC-curve location of the plot, the area under ROC-curve (AUC) was calculated for the unbiased identification of the diagnostic efficiency of the method. The closer the AUC value to one, the higher the diagnostic test ability to identify a disease [9].

Given that frail patients with AH and without CCF had higher NT-proBNP levels, the focus of the study was on the determination of the threshold value of NT-proBNP for CCF diagnosis in patients with AH and FS. Its blood concentration, corresponding to the highest values of diagnostic sensitivity and specificity (cut-off point) in the diagnosis of CCF with presence/absence of FS, was 365.9 pg/mL. When this level is achieved and exceeded, a diagnostic decision on CCF is taken with 97.5 % sensitivity and 96.2 % specificity ($p < 0.001$).

AUC value for NT-proBNP in patients with AH and FS for CCF diagnosis was 0.993 ± 0.004 (CI: 0.965–1.0) ($p < 0.001$), indicating the excellent quality of the model (Fig. 2).

Discussion

It is well known that NTproBNP concentrations increase with age, both in men and women. At the same time, the level of this hormone in elderly people over 75 years of age (especially in women) can be 4 times higher than in younger patients [10]. It is associated both with comorbidities (diabetes mellitus, arterial hypertension, chronic obstructive pulmonary disease, atrial fibrillation) and impaired renal function [11].

In some patients, no adequate increase in NUP values is observed, despite increased filling pressure in the left heart. To the contrary, obese patients have significantly lower blood NT-proBNP concentrations vs. patients with lower body weight [12].

It has been reported that, in patients with CCF and preserved LF EF, NTproBNP levels can remain within the normal range, and it is observed approximately in three–four patients with verified CCF and preserved LF EF out of ten [13].

Of note, in this study, non-frail old patients with AH had the mean NT-proBNP level within the normal range (< 125 pg/mL), irrespective of sex and age. A higher level of this marker in elderly and old patients with CCF in works by other researchers can be explained by the fact that no evaluation of FS presence was performed. In this study, this is FS that impacts NT-proBNP levels in patients over 80 years old with AH and without CCF.

Available data coincide with the results of the study by Yao S et al., which demonstrated the association between higher plasma NUP levels and a higher risk of FS and pre-asthenia in elderly people [14].

This study shows that in frail patients over 80 years of age with AH, but without CCF, the mean NT-proBNP concentration was above 125 pg/mL, and it enabled us to see FS effects on the marker concentration.

Inflammation is known to play an essential part in the development not only of cardiovascular diseases, but it also contributes to pathogenesis of senile asthenia. Patients with senile asthenia have higher levels of such markers of inflammation as WBC, interleukin 6, C-reactive protein, blood coagulation factor VIII, fibrinogen, D-dimer, and tumour necrosis factor-α [15]. The inflammatory nature of senile asthenia has also been proven in Women's Health and Ageing I and II study, where a higher risk of senile asthenia with an increase in the number of inflammatory diseases [16] was reported. It should also be noted that the rate of increase in proinflammatory mediator concentrations correlates with NT-proBNP levels [4].

Another connecting mechanism between senile asthenia and a higher NT-proBNP concentration can be endothelial dysfunction. Results of Toledo Study for Healthy Ageing showed that patients with FS had impaired endothelial function when evaluated on the basis of asymmetric dimethyl arginine [17]. Also, the results correlate with results from the study by Y. Wang et al., where endothelial dysfunction was associated with higher NT-proBNP levels, larger left atrium (myocardium remodelling) and fibrosis [18].

A higher NT-proBNP concentration (> 125 pg/mL) was reported both in non-frail patients with CCF and frail patients without CCF. However, a comparative analysis demonstrated statistically higher effect of CCF on increased NT-proBNP levels vs. effects of FS.

Non-frail patients with CCF had higher NT-proBNP concentrations (> 125 pg/mL), similar to younger patients.

A combination of CCF and FS in old patients with AH was associated with the highest NT-proBNP concentration among the groups, indicating potentiation of CCF and FS effects.

Given higher NUP concentrations in patients with FS, the NT-proBNP level was calculated, which reliably shows the presence of CCF in patients over 80 years of age with AH and FS. In patients with AH and FS, higher NT-proBNP levels of over 365.9 pg/mL enable confirming CCF.

A gender analysis of serum NT-proBNP concentrations in the study groups demonstrated the lack of statistically significant differences between men and women.

Conclusions

The results allow drawing a conclusion that, in diagnosing CCF in patients over 80 years of age with AH, but without FS, NT-proBNP is an informative marker, because the results show that its concentrations were independent of the patient age. When using NT-proBNP for identification of CCF in patients over 80 years of age with AH and FS, the calculated threshold level (365.9 pg/mL) should be used, since these patients have an elevated NT-proBNP concentration, with or without CCF.

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Contribution of the authors:

All the authors made a significant contribution to the preparation of the work, read and approved the final version of the article before publication
Safronenko V.A.: concept and design development, data collection, analysis and interpretation, justification and writing of the manuscript, final approval for publication, the author is responsible for all aspects of the work

A.I. Chesnikova: concept and design development, data collection, analysis and interpretation, verification of critical intellectual content, final approval for publication, the author is responsible for all aspects of the work

Список литературы/References:

1. Котовская Ю.В., Розанов А.В., Курашев Д.Х. и др. Сердечная недостаточность и синдром старческой астении. Медицинский Совет. 2018; 16: 72–79. doi: 10.21518/2079-701X-2018-16-72-79.
   Kotovskaya Yu.V., Rozanov A.V., Kurashev D.Kh. and others. Heart failure and senile asthenia syndrome. Medical Advice. 2018; 16: 72–79 doi: 10.21518/2079-701X-2018-16-72-79 [In Russian].
2. Орлова Я.А., Ткачёва О.Н., Арутюнов Г.П. и др. Особенности диагностики и лечения хронической сердечной недостаточности у пациентов пожилого и старческого возраста. Мнение экспертов Общества специалистов по сердечной недостаточности, Российской ассоциации геронтологов и гериатров и Евразийской ассоциации терапевтов. Кардиология. 2018; 58(12S): 42–72. doi: 10.18087/cardio.2560.
   Orlova Y.A., Tkacheva O.N., Arutyunov G.P. and others. Features of diagnosis and treatment of chronic heart failure in elderly and senile patients. Expert opinion from the Society of Heart Failure Specialists, the Russian Association of Gerontologists and Geriatricians and the Eurasian Association of Therapists. Cardiology. 2018; 58(12S): 42–72. doi: 10.18087/cardio.2560 [In Russian].
3. Алиева А.М., Резник Е.В., Гасанова Э.Т. и др. Клиническое значение определения биомаркеров крови у больных с хронической сердечной недостаточностью. Архивъ внутренней медицины. 2018; 8(5): 333-345. doi: 10.20514/2226-6704-2018-8-5-333-345.
   Alieva A.M., Reznik E.V., Gasanova E.T. et al. Clinical significance of determining blood biomarkers in patients with chronic heart failure. The Russian Archives of Internal Medicine. 2018;8(5):333-345. doi: 10.20514/2226-6704-2018-8-5-333-345 [In Russian].
4. Терещенко С.Н., Галявич А.С., Ускач Т.М. и др. Хроническая сердечная недостаточность. Клинические рекомендации 2020. Российский кардиологический журнал. 2020; 25(11): 4083 doi: 10.15829/29/1560-4071-2020-4083.
   Tereshchenko S.N., Galyavich A.S., Uskach T.M. et al. 2020 Clinical practice guidelines for Chronic heart failure. Russian Journal of Cardiology. 2020; 25(11): 4083. doi: 10.15829/1560-4071-2020-4083 [In Russian].
5. Медведева Е.А., Суркова Е.А., Лимарева Л.В. и др. Молекулярные биомаркеры в диагностике, стратификации риска и прогнозировании хронической сердечной недостаточности. Российский кардиологический журнал. 2016; (8): 86-91. doi: 10.15829/1560-4071-2016-8-86-91.
   Medvedeva E.A., Surkova E.A., Limareva L.V. et al. Molecular biomarkers in diagnosis, risk stratification and prognosis of chronic heart failure. Russian Journal of Cardiology. 2016; (8): 86-91. doi: 10.15829/1560-4071-2016-8-86-91 [In Russian].
6. Ларина В.Н. Хроническая сердечная недостаточность. В помощь врачу амбулаторного звена: монография. Москва: Издательство РАМН. 2019; 168 с.
   Larina V.N. Chronic heart failure. To help outpatient doctors: monograph. Moscow: RAMS Publishing House. 2019; 168 p. [In Russian].
7. Kojima G. Prevalence of Frailty in Nursing Homes: A Systematic Review and Meta-Analysis. J.Am. Med. Dir. Assoc. 2015; 16(11): 940–945. doi: 10.1016/j. jamda.2015.06.025.
8. Ткачева О.Н., Котовская Ю.В., Рунихина Н.К. и др. Клинические рекомендации «Старческая астения». Российский журнал гериатрической медицины. 2020; (1): 11–46. doi: 10.37586/2686-8636-1-2020-11-46.
   Tkacheva O.N., Kotovskaya Yu.V., Runikhina N.K. et al. Clinical guidelines on frailty. Russian Journal of Geriatric Medicine. 2020; (1): 11–46. doi: 10.37586/2686-8636-1-2020-11-46 [In Russian].
9. Hand D.J., Till R.J. A simple generalisation of the area under the ROC curve for multiple class classification problems. Machine Learning. 2001; 45: 171–86. doi: 10.1023/A:1010920819831.
10. Luchner A., Behrens G., Stritzke J. et al. Long-term pattern of brain natriuretic peptide and N-terminal pro brain natriuretic peptide and its determinants in the general population: contribution of age, gender, and cardiac and extra-cardiac factors. Eur J Heart Fail. 2013; 15: 859-867. doi: 10.1093/eurjhf/hft048.
11. Anwaruddin S., Lloyd-Jones D., Baggish A. et al. Renal Function, Congestive Heart Failure and Amino-Terminal Pro-Brain Natriuretic Peptide Measurement. Results From the ProBNP Investigation of Dyspnea in the Emergency Department (PRIDE) Study. J Am Coll Cardiol. 2006; 47: 91-97. doi: 10.1016/j.jacc.2005.08.051.
12. Драпкина О.М., Шепель Р.Н. Хроническая сердечная недостаточность и «парадокс ожирения». Журнал Сердечная Недостаточность. 2016; 17(6): 398-404. doi: 10.18087/rhfj.2016.6.2263.
   Drapkina O.M., Shepel R.N. Chronic heart failure and the "obesity paradox." Journal of Heart Failure. 2016; 17(6): 398-404. doi: 10.18087/rhfj.2016.6.2263 [In Russian].
13. Verbrugge F., Omote K., Reddy Y. et al. Heart failure with preserved ejection fraction in patients with normal natriuretic peptide levels is associated with increased morbidity and mortality. Eur Heart J. 2022; 43(20): 1941-1951. doi: 10.1093/eurheartj/ehab911.
14. Yao S., Guo J., Shi G. et al. Association of BNP with frailty in elderly population: rugao longevity and ageing study. J Nutr Health Aging. 2018; 22(5): 601-607. doi: 10.1007/s12603-018-1112-7.
15. Walston J., McBurnie M.A., Newman A. et al. Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities: results from the Cardiovascular Health Study. Arch Intern Med. 2002; 162: 2333–2341. doi: 10.1001/archinte.162.20.2333.
16. Chang S., Weiss C., Xue Q-L. et al. Association between inflammatory-related disease burden and frailty: results from the Women's Health and Aging Studies (WHAS) I and II. Arch Gerontol Geriatr. 2012; 54: 9–15. doi: 10.1016/j.archger.2011.05.020.
17. Alonso-Bouzon C., Carcaillon L., Garcia-Garcia F.J. et al. Association between endothelial dysfunction and frailty: the Toledo Study for Healthy Aging. AGE. 2014; 36: 495-505. doi: 10.1007/s11357-013-9576-1.
18. Neubauer S., Kolm P., Ho C. et al. Distinct Subgroups in Hypertrophic Cardiomyopathy in the NHLBI HCM Registry. J Am Coll Cardiol. 2019; 74(19): 2333-2345. doi: 10.1016/j.jacc.2019.08.1057.

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