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Risk of heart failure depending on the structure and subclinical target organ damage in patients with hypertension

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Aim. To determine the risk of heart failure (HF) in patients with hypertension (HTN) depending on the structure of subclinical target organ damage (TOD).

Material and methods. The study included 234 patients with HTN without signs of HF. The mean age was 45,96±8,54 years. The patients underwent echocardiography with an assessment of myocardial mass index, ejection fraction, left ventricular diastolic function. Volumetric sphygmoplethysmography with determination of cardio-ankle vascular index (CAVI1) and carotid-femoral pulse wave velocity (PWVcf). Cystatin C blood concentration with the calculation of the glomerular filtration rate (GFR) was performed. NT-proBNP blood levels was also determined. Patients were divided into 4 groups depending on the presence and structure of subclinical TOD. The first group consisted of 74 (31,6%) patients without documented subclinical TOD; the second group — 99 (42,3%) patients with one subclinical TOD; the third group — 42 (18,0%) patients with two TOD; the fourth group — 19 (8,1%) patients with three TOD.

Results. Patients in the groups differed significantly in blood NT-proBNP concentration (p<0,001). As the amount of TOD increased, NT-proBNP increased above the reference value 125 pg/ml (p=0,010). The odds ratio (OR) and relative risk (RR) of HF, determined by NT-proBNP concentration >125 pg/ml, were significantly associated with the TOD structure compared to the group without confirmed TOD (p=0,035, p=0,21, p=0,044, respectively). Correlation analysis revealed direct relationships between the NT-proBNP level and TOD amount (r=0,56; p<0,005), LVH (r=0,33; p<0,005), cystatin C level (r=0,31; p<0,005), CAVI1 and PWVcf (r=0,23; p<0,005 and r=0,26; p<0,005, respectively).

Conclusion. The risk of HF in patients with hypertension depends on the presence and structure of subclinical TOD. With the involvement of one target organ, OR and RR for HF were 4,23 and 3,74, respectively (95% CI for OR, 1,09-19,19; for RR, 1,08-16,03); with the involvement of two target organs — 5,57 (95% CI, 1,23-28,51) and 4,70 (95% CI, 1,21-21,84), respectively; with the multiple TOD — 6,31 (95% CI, 1,4-40,83) and 5,19 (95% CI, 1,04-27,95), respectively.

Key words: heart failure risk, hypertension, target organs.

Relationships and Activities: none.

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According to international and Russian epidemiological studies, hypertensive disease (HD) is one of the main reasons of the development of chronic heart failure (CHF), which takes the lead along with coronary heart disease in the structure of cardiovascular mortality both in the world practice and in the Russian Federation [1].

The main diagnostic criteria for the presence of CHF are typical clinical symptoms and signs, echocardiographic indicators reflecting structural and functional changes in the left heart, and an increase in concentration of natriuretic peptides (NUP) [1, 2].

One of the controversial issues that has been actively discussed recently is asymptomatic CHF, its criteria and risk factors for transformation into clinically significant form [3, 4]. A number of researchers believe that diastolic dysfunction of left ventricle (LV), structural and functional rearrangement of left heart cannot be objective criteria for the CHF preclinical stage due to the fact that various protocols and methods for their diagnosis are used in routine practice.

In this regard, for the verification of CHF preclinical stages and the risk of its development, NUPs are of crucial importance. Thus, according to Gaborit FS, et al. (2020), in patients 60 years and older with 1 or more risk factors for CHF (HD, diabetes mellitus of type 2, chronic kidney disease, atrial fibrillation, vascular disease) with asymptomatic LV dysfunction an increase in concentration of N-terminal fragment of brain natriuretic peptide precursor (NT-proBNP) was associated with an increase in the risk of developing CHF by 49%, the median fragment of NUP — by 77% [5].

There is some evidence that the NT-proBNP level is also associated with subclinical LV dysfunction, including in asymptomatic individuals [6], and is considered as an independent prognostic predictor [7]. Therefore, its definition was recommended not only for CHF diagnosis, but also for assessing the risk of its development.

The literature describes studies that have shown that in some patients, changes in NUP concentration within the range of normal values can be considered as a risk factor for the development of HD itself. It is believed that the brain NUP (BNP) is delivered by ventricular cardiomyocytes as a result of "spontaneous" and "induced" appearance, where the first is largely under genetic control, and the second is stimulated by mechanical stretching, as well as the direct or indirect effects [8]. However, according to some data, a slight increase in NUP in the blood can also be observed in the general population. At the same time, the mechanisms underlying the increase in NUP in healthy subjects are insufficiently studied and have contradictory character [9]. In this manner, the NUP pathophysiological role in the CHF development associated with HD and the possible mechanisms of its formation are also not fully understood and continue to be actively discussed in scientific communities [8].

It is known that the activation of neurohumoral systems in patients with HD leads to the target organ damage (TOD). In connection with the wider use of various imaging study methods, the detection of TOD is becoming more and more obvious both in patients with HD and in the preclinical stages of CHF [10]. However, while such an approach is effective, it is often time consuming and expensive. Therefore, the search for a universal TOD marker and the associated risk of developing CHF is of great clinical interest. In this regard, the NT-proBNP indicator may be of great diagnostic value, since it correlates with the LV myocardial mass index (LVMMI), is associated with aortic stiffness, and its level increases in patients with nonterminal chronic kidney disease [11, 12].

As can be seen from the above, the search for universal and easily accessible markers for assessing the risk of developing asymptomatic CHF in patients with HD with TOD is an relevant cardiological task.

The study's goal was to determine the risk of developing asymptomatic CHF, estimated by NT-proBNP concentration, in patients with HD, depending on the presence and subclinical TOD structure.

Material and methods

The study was carried out in accordance with the Good Clinical Practice standards and the principles of the Helsinki Declaration. The study protocol was approved by the Ethics Committee. All participants received written informed consent before enrollment.

The study enrolled 234 patients of employable age, suffering from HD, working at one of the enterprises of Perm. The median age was 45,96±8,54 years. The average duration of HD is 4,11 [2;6] years. Among the examined 139 (59,4%) men and 95 (40,6%) women.

The HD diagnosis was verified in accordance with the Russian (2020) and European Recommendations on Arterial Hypertension (2018).

The criteria for enrollment were HD of I-II disease state, any degree of increase in blood pressure without CHF clinical symptoms and signs.

The criteria for non-enrollment were: HD of III disease state, secondary arterial hypertension; symptoms and signs that make it possible to suspect CHF; verified diagnosis of CHF; oncological and other diseases that require specific treatment and monitoring; acute inflammatory and infectious dis-

Table 1

Clinical and anamnestic characteristics of patients depending on NT-proBNP level (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
Gender, abs. m/w	32/42	63/36	27/15	11/8	0,050
Age, years	44,65±7,65	47,95±7,39	45,10±9,85	44,25±9,41	0,047
Smoking, abs./%	17/22,97	23/23,23	10/23,81	6/31,58	1,000
HD duration	3,04 [2,0;4,0]	7,78 [3,0;7,0]	4,57 [2,0;6,0]	4,5 [3,0;5,0]	<0,001
DM, abs./%	3/4,05	9/9,09	5/11,91	3/15,79	0,378
COPD, abs./%	2/2,70	3/3,03	1/2,38	1/5,26	1,000
BMI, kg/m^2	28,08±3,81	28,52±3,96	28,80±5,19	29,47±4,47	0,663
WC, cm	92,22±10,61	95,58±11,09	96,17±13,38	97,81±11,96	0,116
SBD, mmHg	132,76±9,93	138,83±14,27	139,38±14,31	140,09±13,59	0,020
DBP, mmHg	86,91±8,64	91,70±10,98	91,04±12,80	93,47±9,89	0,022
HR, beats/min	68,52±10,66	67,91±9,24	67,00±11,08	68,87±9,77	0,941

Abbreviations: HD — hypertension disease, DBP — diastolic blood pressure, BMI — body mass index, WC — waist circumference, SBD — systolic blood pressure, DM — diabetes mellitus, COPD — chronic obstructive pulmonary disease, HR — heart rate.

Table 2

Characteristics of drug therapy in patients depending on NT-proBNP level (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
ACE inhibitors, abs./%	39/52,70	57/57,58	20/47,62	9/47,37	0,918
AIIRA, abs./%	35/47,30	42/42,42	22/52,38	10/52,63	0,918
BB, abs./%	21/28,38	39/39,40	19/45,24	9/47,37	0,268
Calcium antagonists, abs./%	19/25,68	35/35,35	12/28,57	7/36,84	0,709
Diuretics, abs./%	17/22,97	29/29,29	13/30,95	6/31,58	0,993
Statins, abs./%	45/60,81	51/51,52	22/52,38	11/57,89	0,880
Antiplatelet agents, abs./%	4/5,41	11/11,11	8/19,05	5/26,32	0,041

Abbreviations: ACE inhibitors — angiotensin-converting enzyme inhibitors, AIIRA — angiotensin II receptor blocker, BB — β-adrenergic blockers.

eases; mental illnesses that prevent the signing of informed consent and further adequate contact with the patient during the examination.

To assess the CHF development risk, the NT-proBNP concentration in the blood serum was determined using an enzyme immunoassay using a reagent from the company Vector-Best (Russia) on the analyzer Expert Plus Microplate Reader (Biochrom, UK). The NT-proBNP concentration in the blood serum >125 pg/ml was considered as an indicator corresponding to one of the CHF diagnostic criteria.

To assess the presence of LV hypertrophy (LVH) as a target organ in HD, echocardiography was carried out according to the standard method recommended by the American and European Society of Echocardiography on a Vivid S5 ultrasound scanner (General Electric, USA). LVH was confirmed for overweight and obese patients with LVMMI for men >50 g/m^{2,7}, for women >47 g/m^{2,7}; for patients with normal body weight with LVMMI in men >115 g/m^2, in women >95 g/m^2. To assess the LV functional state, the LV systolic function was determined according to LV ejection fraction, assessed by the Simpson method, LV diastolic function based on the determination of speed indicators of transmitral diastolic flow and tissue visualization of mitral valve annulus fibrosus ring movement.

To verify kidney damage as a target organ in HD, the filtration function was evaluated by determining the serum cystatin level with the enzyme immunoassay method, and the glomerular filtration rate (GFR) was calculated using the formula CKD-EPIcys (Chronic Kidney Disease Epidemio-

Table 3

Structure of target organ damage in groups (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
LVH, abs./%	0/0	65/65,66	37/88,10	19/100,00	p<0,001
LVDD, abs./%	0/0	6/6,06	4/9,52	3/15,79	0,038
LV EF, %	62,13±7,28	61,12±9,21	60,19±8,65	59,99±9,43	0,606
Increase in cystatin C >1000 pg/ml, abs./%	0/0	14/14,14	12/28,57	19/100,00	p<0,001
CAVI1 >9, abs./%	0/0	6/6,06	9/21,43	7/36,84	p<0,001
FSC >10 m/s, abs./%	0/0	14/14,14	26/61,91	12/63,16	p<0,001

Abbreviations: LVH — left ventricular hypertrophy, LVDD — left ventricular diastolic dysfunction, cfPWV — carotid-femoral pulse wave velocity, LV EF — left ventricular ejection fraction, CAVI1 — cardiovascular-ankle-vascular index.

Table 4

NT-proBNP level in patients, depending on TOD (n=234)

Indicator	Patients without target organ damage (n=74)	Patients with 1 target organ damage (n=99)	Patients with 2 target organs damage (n=42)	Patients with 3 target organs damage (n=19)	p_{mg}
Intermediate level NT-proBNP, pg/ml	0,007 [0,004;0,009]	0,009 [0,006;3,640]	31,15 [11,70;75,00]	231,65 [146,35;367,20]	<0,001
Occurrence frequency of elevated NT-proBNP levels >125, pg/ml, abs./%	3/4,05	15/15,15	8/19,05	5/31,58	0,009

Abbreviation: NT-proBNP — N-terminal fragment of brain natriuretic peptide precursor.

logy Collaboration Cystatin-Based). Signs of kidney damage in HD were considered to be an increase in concentration of cystatin C in blood >1000 ng/ml and/or a decrease in GFR according to the formula CKD-EPIcys 60 ml/min/1,73 m^2.

To assess arterial damage, volumetric sphygmoplethysmography was carried out on a VaSeraVS-1000 device (Fucuda Denshi, Japan) with determination of cardio-ankle-vascular index (CAVI1) and pulse wave velocity in carotid-femoral segment (PWVcf). Signs of arterial damage in HD were considered to be an increase in CAVI1 >9 and/or PWVcf >10 m/s.

To determine the relationship between HD and TOD with the risk of developing CHF, patients were divided into 4 groups. The first group consisted of 74 (27,6%) patients without confirmed TOD, the second group enrolled 99 patients with signs of subclinical lesions of one target organ, the third group consisted of 42 patients with lesions of two target organs, the fourth group enrolled 19 patients with confirmed subclinical lesions of three target organs.

Statistical processing of the obtained results was carried out using the program STATISTICA 10.0. For continuous characters, the arithmetic mean (M) ± standard deviation (SD) or the median with the lower and upper quartile (Me [LQ;UQ]) were calculated. For qualitative signs, the absolute frequency of the sign, the sign frequency as a percentage (%) or the 95% confidence interval (CI) were calculated. To test statistical hypotheses about distribution type, the Shapiro-Wilk and Kolmogorov-Smirnov criteria were used. The distribution of most features did not correspond to the law of normal distribution. In the multi-group comparison of quantitative indicators, the Kruskall-Wallis criterion was used, and for qualitative characteristics, the χ^2 criterion was used. Statistically significant when comparing the four independent groups were the differences in indicators at p<0,012. To study the relationship between the indicators reflecting TOD and the concentration of NT-proBNP, 2x2 conjugacy tables were compiled, χ^2 was calculated with the calculation of achieved significance level for them with the Yates correction for continuity, the odds ratio (OR), relative risk (RR) and 95% CI for OR and RR were determined. At p<0,05, the differences were considered statistically significant. The study of relationship between features was carried out on the basis of Spearman's rank correlation coefficients.

The funding was made from the authors' own funds.

All manipulations related to development of study design, obtaining informed consent, collecting biological material, conducting diagnostic tests, interpreting the results and their statistical processing are carried out by the authors themselves.

Results

Patients in the groups did not significantly differ in age, gender, cardiovascular risk factors, structure of concomitant pathology, antihypertensive and other drug therapy, and clinical characteristics (Tables 1, 2). The groups differed in HD duration and TOD frequency (Tables 1, 3).

All patients, according to echocardiography, had a preserved LV ejection fraction without statistically significant differences between the groups. 121 patients (51,71%) had LVH signs (0% of patients — in group 1, 65,66% of patients — in group 2, 88,10% — in group 3 and 100,00% — in group 4). In 5,12% of patients, LV diastolic dysfunction was detected without significant differences between the groups.

When assessing the arterial wall state, it turned out that arterial stiffness, estimated by CAVI1 index, was increased in 22 patients (9,40%), while in patients of group 1 there was no increase in CAVI1 (0%), in group 2 it was observed in 6,06% of patients, in group 3 — in 21,43% of patients, in group 4 — in 36,84% of patients.

PWVcf >10 m/s was detected in 52 patients (22,22%): in group 1, there were no patients with an increase in PWVcf, in group 2, an increase in PWVcf was found in 14,14% of patients, in group 3 — in 61,91% of patients, in group 4 — in 63,16% of patients.

When assessing the kidneys state, it was revealed that impaired renal filtration function with a level of cystatin C >1000 ng/ml was observed in 45 patients (19,23%), while the level of cystatin C was normal in group 1, an increase in the level of cystatin C was observed in 14,14% of patients in group 2, in group 3 — in 28,57% of patients, in group 4 — in all 100% of patients. GFR in all patients was >60 ml/min/1,73 m^2.

Patients in the groups differed significantly in the mean NT-proBNP concentration ($p<0,001$) (Table 4). As the number of TODS increased, NT-proBNP increased significantly ($p<0,001$). Also, as the number of TODS increased, an increase in the frequency of NT-proBNP increases >125 pg/ml ($p=0,010$) was detected. Among patients of group 1 without TOD, the incidence of elevated NT-proBNP was 4,05%, among patients of group 2 — 15,15%, among patients of group 3 — 19,05%, among patients of group 4 — 31,58%.

The correlation analysis revealed the relationship of NT-proBNP level with number of TOD ($r=0,56$; $p<0.005$), LVH ($r=0,33$; $p<0,005$), the concentration of cystatin C in blood ($r=0,31$; $p<0,005$), CAVI1 and PWVcf ($r=0,23$; $p<0,005$ and $r=0,26$; $p<0,005$, respectively).

When assessing the OR and RR of CHF development, the following data were obtained. The OR and RR values were statistically significant ($p=0,035$) and were 4,23 and 3,74, respectively (95% CI for OR =1,09-19,19; for RR =1,08-16,03). The OR of CHF development in damage of two target organs increased more than 5 times in comparison with the group without TOD (OR 5,57, 95% CI 1,23-28,51), and RR of its development was 4.70 (95% CI 1,21-21,84, $p=0,021$). An increase in the NT-proBNP level is also statistically significantly associated with damage to three target organs ($p=0,044$). In the presence of multiple organ damage, the chance of developing CHF increased more than 6 times (OR 6,31, 95% CI 1,04-40,83), and RR of its development was 5,19 (95% CI 1,04-27,95).

Discussion

Our work shows that the CHF risk assessed by increasing the NT-proBNP concentration in patients with CHF depends on the presence and structure of subclinical TOD.

It was shown that as the number of TOD increases in patients with HD, the NT-proBNP concentration increases as a criterion for preclinical CHF stages.

The obtained data can be justified from a physiological point of view. In TOD pathogenesis, activation of renin-angiotensin-aldosterone (RAAS) and sympatho-adrenal systems (SNS) play an important role. In the early stages of HD, BNP functions as a compensating agent that reduces the activity of these systems [6]. With disease progression, the RAAS and SNS activation increases, there is an imbalance of the NUP system and, despite high levels, endogenous NUP become resistant, and are no longer able to compensate for neurohumoral activation. At this stage, an increase in delivery and BNP and NT-proBNP concentration is considered not as a compensatory mechanism, but as a violation of the altered organ function. In addition, the BNP delivery, which is more associated with positive and compensatory effects, is under genetic control, and with an increase in the RAAS and SNS activity, it is stimulated by mechanical stretching of cardiomyocytes — myocardial stress. Therefore, the final NT-proBNP and BNP concentration in serum is determined by the balance between their production, degradation, and renal clearance. Therefore, TOD can affect the BNP concentration in serum, increasing it.

TOD, as well as their various combinations, play an important role both in the progression of CHF itself and in determining the risk of its development.

Thus, there are well-known studies in the literature that have shown that NPS blood concentrations, in particular NT-proBNP and BNP, are directly related to LVH [13]. Increased NUP delivery by cardiac myocytes into the bloodstream may be the result of increased LV wall tension, the development of its hypertrophy or volume overload. There is also evidence that the NT-proBNP level can be an independent and prognostic marker of LVH risk in patients without CHF, since it reflects a subclinical pathological process, including inflammation, myocardial fibrosis, and subsequently heart remodeling [14]. In our study, a correlation was obtained between NT-rroBNP and LVH, and the CHF development risk was shown depending on this parameter. However, the LVH contribution to the CHF development risk has not been assessed separately in the TOD structure and requires further study.

We have shown that the frequency of increased CAVI1 >9 and PWVcf >10 m/s were connected with the risk of asymptomatic CHF development. It is understood that an increase in arterial stiffness leads to a decrease in elasticity of peripheral arteries and a change in reflected wave. With an increase in arterial stiffness, the reflected wave returns to aorta during late systole, which leads to an increase in afterload on heart and a decrease in coronary perfusion. This process may trigger the development of diastolic heart dysfunction and LVH [15]. Having said so, the stretching of cardiomyocytes is an important stimulus for the NUP production [9]. Nah E-H, et al. (2019) suggested that a higher NT-proBNP level may be associated not so much with LV diastolic dysfunction as with initial preclinical structural changes in cardiomyocytes [16].

In our study, the presence of an increase in the cystatin C level in blood was considered as a kidney damage in HD. An increase in cystatin C was observed with an increase in the NT-proBNP level and, accordingly, with an increase in the TOD number. The literature describes the association of NT-proBNP with TOD, in particular, in the kidneys, including in patients with HD without CHF symptoms and signs [11]. Also, according to some studies, an increase in the cystatin C level correlates with concentric LV remodeling [17]. Consequently, in patients with HD in the presence of LV structural rearrangement, the risk of glomerular renal dysfunction increases, which, in turn, leads to a high tension of myocardial stress and an increased CHF development risk. However, the mechanism of increasing the NT-proBNP level in patients with TOD, including chronic kidney disease, is more complex, remains not fully understood and requires further study.

The study limitations are as follows: in patients with HD, the diagnostic criterion for the CHF development risk was considered to be the NT-proBNP concentration >125 pg/ml, while the "gray" area of this indicator was not taken into account; indicators reflecting increased collagen formation and fibrosis were not used to diagnose TOD in patients with HD; the study does not present the rating of each TOD separately in assessing the CHF development risk.

Conclusion

The results indicate that the CHF development risk in patients with HD, determined by the NT-proBNP concentration in blood, depends on the presence and structure of subclinical TOD. As the number of TOD increases, not only the average level of NT-proBNP increases, but also the frequency of occurrence of an increase in NT-proBNP above the diagnostic value of 125 pg/ml increases. In case of one target organ damage, OR and RR of CHF development were 4,23 and 3,74, respectively (95% CI for OR =1,09-19,19; for RR =1,08-16,03), in case of two target organs — 5,57 (95% CI 1,23-28,51) and 4,70 (95% CI 1,21 — 21,84), respectively, in case of multiorgan lesion — 6,31 (95% CI 1,04-40,83) and 5,19 (95% CI 1,04-27,95), respectively.

Relationships and Activities: none.

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