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Assessment of glomerular and tubulointerstitial apparatus state depending on the level of the natriuretic peptide in hypertension patients

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Aim. To assess the state of the glomerular and tubulointerstitial apparatus depending on the level of the N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients with hypertension (HTN).

Material and methods. The study included 119 patients with stage I-II HTN. We determined the cystatin C level, glomerular filtration rate (GFF) using the CKD-EPI equation, neutrophil gelatinase-associated lipocalin (NGAL) and NT-proBNP levels; echocardiography and sphygmoplethysmography was performed. In the first analysis, patients were divided into two groups depending on the NT-proBNP level. Group 1 (n=32) consisted of patients with NT-proBNP level >125 pg/ml, group 2 (n=87) — with NT-proBNP level <125 pg/ml. Empirically, the NT-proBNP cutoff point (75 pg/ml) was found to assess the role of cystatin C. The first group included 41 patients with NT-proBNP level >75 pg/ml, the second group — 78 patients with NT-proBNP level <75 pg/ml.

Results. In the group 1 (NT-proBNP >125 pg/ml) the NGAL concentration was significantly higher than in the group 2: 2,50 [1,90; 2,85] vs 1,30 [0,9; 2,0] ng/ml, respectively (p=0,022). Patients in the groups did not significantly differ in the cystatin C levels and GFR (p=0,099 and p=0,090, respectively). When dividing patients according to the NT-proBNP cutoff point (75 pg/ml), the following data were obtained. The concentration of cystatin C in the first group with NT-proBNP >75 pg/ml was 1041,50 [995,00; 1185,00] vs 964,30 [801,00; 1090,00] ng/ml in the second group (p=0,034). Patients in the groups significantly differed in GFR (p=0,027). A correlation analysis revealed a moderate, direct relationship of NT-proBNP with cystatin C (r=0,32; p<0,005) and NGAL levels (r=0,36; p<0,05), as well as a moderate, inverse relationship with GFR (r=-0,35; p<0,005).

Conclusion. NT-proBNP determination can be used as an integrative risk stratification tool for glomerular and tubulointerstitial injury in HTN patients.

Key words: natriuretic peptide, glomerular and tubulointerstitial apparatus.

Relationships and Activities: not.

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The most important aspect of cardiovascular risk assessment in patients with hypertension (HTN) is the diagnosis of hypertension-mediated organ damage (HMOD). HMOD is defined as structural and/or functional changes in target organs associated with increased BP, such as the heart, arteries, brain, eyes, and kidneys [1, 2].

HTN is the second most important cause of kidney damage after diabetes. In HTN patients, kidney damage is often asymptomatic. In routine practice, renal function changes are usually associated with an increase in serum creatinine [2]. However, recent studies have shown that creatinine and creatinine-based estimated glomerular filtration rate (eGFR) do not accurately reflect the state of glomerular filtration, especially in the early stages [3]. Cystatin C and cystatin C-based eGFR equations are described as more sensitive and early markers of glomerular injury, as well as unfavorable predictors in patients with HTN [3, 4].

One of the debatable issues is the tubulointerstitial assessment in patients with cardiovascular diseases (CVD). The most commonly used markers of tubular dysfunction are neutrophil gelatinase-associated lipocalin (NGAL), tissue inhibitor of metalloproteinases 2 (TIMP-2), kidney injury molecule 1 (KIM-1). NGAL is a member of lipocalin protein family and is highly expressed in the renal tubules, especially after ischemic or nephrotoxic damage. Identification of elevated blood and urine NGAL levels in some kidney diseases can be used as an early marker of tubular damage, including in CVD [5].

It is well known that an increase in N-terminal pro-brain natriuretic peptide (NT-proBNP) level allows not only to diagnose and evaluate the severity of heart failure (HF), but also is associated with HTN and increased BP [6]. It was also described that NT-proBNP levels may increase in patients with GFR decrease [7-9]. However, these studies mainly relate to patients with acute kidney injury and chronic kidney disease, where, first of all, the filtration function was studied, which was assessed by the level of creatinine, creatinine-based eGFR or albuminuria level. The relationship between NT-proBNP and cystatin-associated glomerular damage and tubulointerstitial impairment in patients with CVD and risk factors such as HTN remains poorly understood and debatable. Therefore, the study of this problem is a clinically important and promising area of cardiology, the solution of which will not only allow timely verification of renal dysfunction, but also develop algorithms to prevent kidney damage in patients with HTN and CVD.

The aim of this study was to assess the state of glomerular and tubulointerstitial apparatus depending on NT-proBNP level in HTN patients.

Material and methods

This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The medical ethics committee approved this study. All patients signed informed consent.

The study included patients meeting the following inclusion criteria: the presence of stage I-II GB without symptoms and signs of chronic heart failure (CHF), continuous antihypertensive and lipid-correcting therapy at the time of inclusion, signing of informed consent. Stage III patients with secondary hypertension, with oncological and other diseases requiring specific ongoing treatment and monitoring, acute inflammatory and infectious diseases were n.

The study included 119 working-age patients with HTN: 72 (60,5%) men and 47 (39,5%) women. The mean age was 45,96±8,54 years. The mean duration of HTN was 4,17 [2; 6] years.

HTN was established in accordance with Russian (2010) and European (2018) guidelines.

Inclusion criteria were stage I-II HTN without symptoms and signs of heart failure (HF), continuous antihypertensive and lipid-lowering therapy at the inclusion, signed informed consent. There were following exclusion criteria: stage III or secondary HTN; cancer and other diseases requiring specific permanent treatment and monitoring, acute inflammatory and infectious diseases; mental disorders.

To assess cardiac stress, we determined the blood NT-proBNP concentration using an enzyme-linked immunosorbent assay (ELISA) and Vector-Best (Russia) reagent kit on the Expert Plus microplate reader (Biochrom, UK). NT-proBNP >125 pg/ml were considered diagnostic criterion for asymptomatic HF.

To assess renal filtration function, serum creatinine levels was determined by ELISA, and GFR was estimated using creatinine-based SKD-EPI equation; serum cystatin C levels were determined by ELISA using the BioVendor (Czech Republic) reagent kit on the IMMULITE® 1000 system (DPC, USA), and GFR was also estimated using cystatin C-based CKD-EPI equation. The reference values of serum cystatin C concentration were 1043,1±107,5 ng/ml.

To assess the condition of renal tubules, serum NGAL levels was determined by ELISA using the BioVendor (Czech Republic) reagent kit on the IMMULITE® 1000 system (DPC, USA). Reference values of NGAL were 1,2-2,6 ng/ml.

To assess the cardiac structure and function, echocardiography was performed according to the guidelines of American Society of Echocardiography and European Association of Cardiovascular Imaging using the Vivid S5 ultrasound system (General

Table 1

Glomerular and tubulointerstitial parameters in patients depending on NT-proBNP level (n=119)

Parameter	Patients with NT-proBNP >125 pg/ml, (n=32)	Patients with NT-proBNP <125 pg/ml, (n=87)	p
Cystatin C, ng/ml	1039,50 [990,00;1170,00]	970,00 [851,90;1090,00]	0,099
Cystatin C-based eGFR, ml/min/1,73 m^2	74,00 [63,00;89,00]	82,00 [69,00;106,00]	0,090
Serum creatinine, μmol/L	74,75 [72,85;82,90]	71,85 [63,60;80,95]	0,400
Creatinine-based eGFR, ml/min/1,73 m^2	94,85 [85,35;106,40]	100,00 [87,60;107,85]	0,744
NGAL, ng/ml	2,50 [1,90;2,85]	1,30 [0,9;2,0]	0,025

Abbreviations: NT-proBNP — N-terminal pro-brain natriuretic peptide, GFR — glomerular filtration rate, NGAL — neutrophil gelatinase-associated lipocalin.

Electric, USA). Left ventricular ejection fraction (LVEF) (Simpson's biplane) and LV diastolic function were assessed.

To assess the artery condition, sphygmoplethysmography was performed on the VaSeraVS-1000 (Fucuda Denshi, Japan). Cardio-ankle vascular index (CAVI1) in the range from 7,4±0,63 to 8,0±0,67 and ankle-brachial index (ABI) <0,9 were considered criterion for arterial damage.

To assess the condition of glomeruli and tubules depending on the NT-proBNP concentration, all patients were divided into 2 groups. The first group consisted of 32 (26,9%) patients with NT-proBNP >125 pg/ml, the second group — 87 (73,1%) patients with NT-proBNP <125 pg/ml.

Statistical processing was carried out using the software package STATISTICA 10.0. For normally distributed quantitative traits, the mean (M) ± standard deviation (SD) were calculated; for non-normally traits — the median with lower and upper quartiles (Me [LQ;UQ]). For qualitative traits, the absolute manifestation frequency and manifestation frequency percentage (%) or 95% confidence interval (CI) were calculated. An analysis of distribution type was carried out using the Shapiro-Wilk and Kolmogorov-Smirnov tests. Most of the traits were non-normally distributed, and for their statistical analysis, nonparametric statistics were used: for quantitative traits — the Mann-Whitney test; for qualitative traits — chi-squared test. Student's t-test and chi-squared test were used for normally distributed quantitative and qualitative traits, respectively. The differences were considered significant at p<0,05. To study the relationship between the parameters of glomeruli and tubules and NT-proBNP concentration, 2x2 contingency tables were compiled and Yates's chi-squared test, odds ratios (OR), relative risk (RR) and 95% CI for OR and RR were determined.

Results

Patients in the groups were comparable in age, gender, cardiovascular risk factors, HTN duration, achievement of target BP, heart rate (HR) at rest, comorbidities and antihypertensive therapy.

According to echocardiography, LVEF was preserved in all patients an d 30,3% of patients had LV hypertrophy, estimated by LV mass index; 8,4% of patients had LV diastolic dysfunction (LV DD). There were no significant differences between the groups with respect to parameters of cardiac structure and function.

By CAVI1, arterial damage was detected in 57,1% of patients, by ABI — in 5,9%. The groups did not significantly differ in the frequency and severity of arterial changes.

Table 1 shows that patients, depending on the NT-proBNP concentration, did not significantly differ in the creatinine and cystatin C levels, creatinine-based and cystatin C-based eGFRs.

The NGAL level in group 1 was significantly lower than in group 2, and amounted to 1,30 [0,9; 2,0] and 2,50 [1,90; 2,85] ng/ml (p=0,022), respectively. The OR and RR of the tubular damage, assessed by NGAL, in NT-proBNP >125 pg/ml were 3,25 and 1,91, respectively (95% CI for OR=1,30-8,20; for RR=1,17-2,88). Sensitivity and specificity were 64,3% and 74,4%, respectively.

A correlation analysis revealed a moderate direct relationship of NT-proBNP with cystatin C (r=0,32; p<0,005) and NGAL levels (r=0,36; p<0,05), as well as a moderate inverse relationship with cystatin C-based eGFR (r=-0,35; p<0,005).

To assess the NT-proBNP effect on the filtration function, the NT-proBNP cutoff point was found empirically and amounted to 75 pg/mg. The distribution of patients in groups depending on the NT-proBNP cutoff point was as follows: group 1 — 41

Table 2

Glomerular and tubulointerstitial parameters in patients depending on NT-proBNP cut-off point (n=119)

Parameter	Patients with NT-proBNP >75 pg/ml, (n=32)	Patients with NT-proBNP <75 pg/ml, (n=87)	p
Cystatin C, ng/ml	1041,50 [995,00;1185,00]	964,30 [801,00;1090,00]	0,034
Cystatin C-based eGFR, ml/min/1,73 m^2	73,00 [63,00;84,50]	83,00 [69,00;106,00]	0,027
Serum creatinine, μmol/L	74,75 [72,30;89,10]	71,85 [64,10;80,60]	0,400
Creatinine-based eGFR, ml/min/1,73 m^2	94,85 [84,70;101,60]	100,00 [89,50;107,90]	0,744
NGAL, ng/ml	2,40 [1,50;2,70]	1,30 [0,9;2,0]	0,056

Abbreviations: NT-proBNP — N-terminal pro-brain natriuretic peptide, GFR — glomerular filtration rate, NGAL — neutrophil gelatinase-associated lipocalin.

patients (34,5%) with NT-proBNP >75 pg/ml, group 2 — 78 patients (65,5%) with NT-proBNP level <75 pg/ml.

Patients in the groups did not significantly differ in clinical, anamnestic and routine laboratory parameters, comorbidities and antihypertensive therapy. According to echocardiography, the groups were comparable in cardiac structure and function and, according to sphygmoplethysmography — in artery condition.

Table 2 presents the data on glomerular and tubular assessment in the groups. There were significant differences between group 1 and 2 in the cystatin C level (1041,50 [995,00; 1185,00] ng/ml vs 964,30 [801,00; 1090,00] ng/ml (p=0,034), respectively) and cystatin C_2-based eGFR (73,00 [63,00; 84,50] ml/min/1,73 m^2 vs 83,00 [69,00; 106,00] ml/min/1,73 m^2 (p=0,027), respectively). According to cystatin C concentration, the OR and RR of glomerular dysfunction at NT-proBNP >75 pg/ml increased 3 times (OR=3,1, 95% CI=1,27-7,31) and 2 times (RR=2,0 95% CI=1,17-3,31), respectively. Sensitivity and specificity were 64,1% and 82,2%, respectively.

There were following study limitations: small sample size; to confirm tubular damage more accurately, 2 or more methods for determining tubular dysfunction are required; to determine NT-proBNP predictor value for kidney damage in HTN patients more accurately, a ROC analysis should be performed in a larger population.

Discussion

It is well known that NT-proBNP can act not only as a biomarker of myocardial injury in HF. Its relationship with target organ damage, in particular the kidneys, in patients with HTN, chronic kidney disease, and type 2 diabetes without symptoms and signs of HF [9]. In studies, conventionally, kidney damage is assessed by the concentration of serum creatinine, creatinine-based eGFR and/or albuminuria level. However, earlier markers of glomerular and tubulointerstitial kidney damage are not evaluated. It was suggested that, using more accurate and earlier markers of renal dysfunction, assessing the effect of NT-proBNP levels on glomerular and tubular damage in HTN patients will predict the dysfunction in the early stages.

According to our study, in HTN patients without HF symptoms, NT-proBNP >125 pg/ml was associated with kidney damage. In study by Takahama H, et al., it was shown that NT-proBNP increase is a predictor of kidney damage in patients with acute decompensated HF [8]. Moreover, NT-proBNP levels were significant in patients who had HTN-related HF.

Glomerular damage, assessed by cystatin C level, was recorded in our study at a lower NT-proBNP level (75 pg/ml). The obtained data can be explained by the fact that BNP increases GFR in the kidneys by relaxing mesangial cells and inhibits fractional sodium reabsorption. This enhances natriuresis and decreases BP. BNP also reduces vascular resistance by relaxing smooth muscle cells. Therefore, many studies showed that lower initial concentrations of BNP and NT-proBNP in HTN patients are associated with a higher risk of HF and target organ damage [10, 11]. Nevertheless, there is no doubt that renin-angiotensin-aldosterone system (RAAS) and sympathoadrenal system (SAS) play an important role in the pathogenesis of target organ damage. But BNP acts as a compensator only in the early stages by reducing the activity of these systems [10]. As the disease progresses, RAAS and SAS activity increases, and there is imbalance in BNP system, and despite high levels, endogenous BNP becomes resistant and is no longer able to compensate it. Then an increase

in release and level of BNP and NT-proBNP is already considered not as compensatory mechanisms, but as a dysfunction of the changed organ, including tubular and glomerular damage. It should be noted that BNP release, which is more associated with positive and compensatory effects, is under genetic control, and with an increase in RAAS and SAS activity, it is stimulated by mechanical stretching of cardiac myocytes, i.e., myocardial stress. Therefore, the final serum concentration of NT-proBNP and BNP is specified by the balance between production, degradation and renal clearance. Changes in cardiac, arterial, and renal function associated with HTN can affect serum BNP concentration.

In our study, NT-proBNP >75 pg/ml was associated with cystatin C increase. Some studies showed that changes in circadian BP profile in HTN patients and nondecrease of nocturnal BP compared with daytime values are closely related to kidney damage, assessed by the cystatin C concentration, as well as to the progression of its dysfunction [12]. Therefore, it can be assumed that NT-proBNP level may reflect an increase of nighttime BP, which leads to impaired renal filtration function and cystatin C increase. In our study, 24-hour BP profile was not evaluated, and this hypothesis requires further study. Another confirmation of the relationship between cystatin C and NT-proBNP is the fact that cystatin C correlates with left ventricular (LV) concentric remodeling in patients with chronic kidney disease [13]. Therefore, in patients with HTN, LV remodeling leads to myocardial stress even in normal NT-proBNP values for HF, which, in turn, leads to glomerular dysfunction. Thus, observed NT-proBNP increase >75 pg/ml can be considered as an additional predictor of glomerular damage.

We also obtained data on tubulointerstitial damage in HTN patients with NT-proBNP >125 pg/ml. The data obtained can also be explained by the fact that when the compensatory effect of BNP on the renal function is reduced, it becomes resistant and all positive effects are withdrawn. But given the evidence that BNP is localized in the distal tubules [10], it can be assumed that BNP and NT-proBNP increase can reflect tubular dysfunction.

There is literature evidence that NGAL is not only a marker of decreased tubular function, but can be a predictor of cardiovascular events in patients with chronic kidney disease [5]. Recent studies have also shown that NGAL level associated with NT-proBNP was a predictor of cardiovascular events and mortality in patients with HF [14]. At the same time, studies showed that the level of NGAL was higher in HTN patients.

Шn the study by Kim IY, et al., it was shown that NGAL is an independent predictor of LV hypertrophy and LV DD in patients with chronic kidney disease [15].

Conclusion

The results obtained indicate that NT-proBNP can be used for risk stratification of glomerular and tubulointerstitial damage in HTN patients without symptoms and signs of HF. The OR and RR of the tubular lesion, assessed by NGAL, with an increase in NT-proBNP >125 pg/ml were 3,25 and 1,91, respectively (95% CI for OS=1,30-8,20; for RR=1, 17-2,88). The OR and RR of glomerular dysfunction, estimated by cystatin C concentration, with NT-proBNP >75 pg/ml, were 3,1 and 2,0, respectively (95% CI for OR=1,27-7,31; 95% CI for RR=1,17-3,31). Therefore, an early glomerular and tubulointerstitial changes in HTN patients occurs not only due to an increase and inadequate control of BP, but may also be due to myocardial stress, which is reflected in NT-proBNP levels even in the normal range.

Relationships and Activities: not.

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