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The relationship between N-terminal pro B-type natriuretic peptide and indicators of daily monitoring of blood pressure in middle-aged hypertensive men with chronic heart failure

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Abstract

Objective. To study the association between N-terminal pro B-type natriuretic peptide (NT-proBNP) and diurnal blood pressure (BP) profile in middle-aged men with arterial hypertension (HTN) and chronic heart failure (CHF). **Design and methods.** We surveyed 550 men from 40 to 50 years, 420 subjects were included in the study and were divided into groups: 1st group — patients with HTN without CHF (n = 180); 2nd group — patients with HTN and CHF (n = 86); 3rd group — patients with CHF without HTN (n = 74). The control group consisted of healthy men with normal BP without CHF (n = 80). NT-proBNP (fmol/ml) and 24-hour BP monitoring were performed in all patients. **Results.** NT-proBNP was lower in patients with HTN 2 and 3 degree in comparison with patients with HTN 1 degree without CHF (group 1). It was not found in hypertensive patients with CHF (group 2). NT-proBNP was higher in patients with HTN 1 degree in the 1st group in comparison with patients with HTN 1 degree in the second group and lower in patients with HTN 2 and 3 degree in the first group, in comparison with patients with HTN 2 and 3 degree in the 2nd group. There was an inverse correlation between NT-proBNP and HTN degree in the 1st group ($r = –0.624$; $p = 0.023$). **Conclusions.** The decrease in plasma level of NT-proBNP in hypertensive patients is associated with the increase in BP. Natriuretic peptides are involved in the circadian rhythm of BP, and their level is associated with the HTN degree and «load pressure». NT-proBNP was the highest in «non-dippers» and «night-peakers» and differed significantly from «over-dippers» and patients with unchanged circadian BP profile.

Key words: arterial hypertension, natriuretic peptides, 24-hour blood pressure monitoring

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Особенности взаимосвязи между N-терминальным промозговым натрийуретическим пептидом и показателями суточного мониторирования артериального давления у мужчин среднего возраста с артериальной гипертензией и хронической сердечной недостаточностью

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Резюме

Цель исследования — определить взаимосвязи между N-терминальным промозговым натрийуретическим пептидом (NT-proBNP) и показателями суточного мониторирования артериального давления (АД) у мужчин среднего возраста с артериальной гипертензией (АГ) и хронической сердечной недостаточностью (ХСН). **Материалы и методы.** Обследованы 550 мужчин от 40 до 50 лет, из них 420 пациентов были включены в исследование и распределены на группы: 1 группа — пациенты с АГ без ХСН (n = 180); 2 группа — пациенты с АГ и ХСН (n = 86); 3 группа — пациенты с ХСН без АГ (n = 74). Группа контроля — здоровые мужчины с нормальным АД, без ХСН (n = 80). Определяли NT-proBNP (фмоль/мл), проводили суточное мониторирование АД. **Результаты.** NT-proBNP был статистически значимо ниже у пациентов со АГ 2-й и 3-й степени в сравнении с лицами с АГ 1-й степени в группе пациентов без ХСН (1 группа). В группе пациентов с АГ и ХСН (2 группа) такой закономерности не наблюдалось. NT-proBNP выше у пациентов с АГ 1-й степени в первой группе по сравнению с пациентами с АГ той же степени во второй группе и статистически значимо ниже у пациентов с АГ 2-й и 3-й степени в первой группе по сравнению с пациентами с АГ той же степени во второй группе. Корреляционный анализ данных в группе 1 показал статистически значимую обратную взаимосвязь NT-proBNP и степени АГ (r = –0,624; p = 0,023). **Заключение.** Снижение плазменного уровня NT-proBNP у пациентов с АГ ассоциировано с повышением ее степени. Натрийуретические пептиды участвуют в формировании суточного ритма АД, и их уровень зависит не только от степени АГ, но и от «нагрузки давлением». NT-proBNP был наиболее высок в группах «non-dipper»,

«night-peaker» и статистически значимо отличался от показателей у пациентов с неизмененным суточным профилем АД и профилем «over-dipper».

Ключевые слова: артериальная гипертензия, натрийуретические пептиды, суточное мониторирование артериального давления

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Introduction

Arterial hypertension (HTN) is still one of the most significant health and social problems. Numerous clinical and epidemiological studies demonstrated the importance of early HTN diagnosis and effective control of blood pressure (BP) for cardiovascular risk reduction [1, 2]. HTN is associated with the development of chronic heart failure (CHF), at least, in 80 % of cases [3]. CHF incidence is increasing by an average of 1.2 per 1,000 per year. The incidence of CHF is higher in men aged from 40 to 59 years and in women aged 70 to 89 years compared to other age groups [4].

One of the main tasks in the last decade is the search of universal and accessible screening laboratory and instrumental predictors of CHF in HTN patients without clinical evidence of heart failure. Natriuretic peptides (NUP) play an important role in the regulation of structure and function of the cardiovascular system and cardiovascular risk. Brain NUP (BNP) and its precursor (NT-proBNP), being the markers of myocardial stress, are recommended by the European Society of Cardiology (ESC) and the Russian Society of Cardiology (RSC) [5, 6] for the CHF screening. However, their pathophysiological role in the development of HTN and CHF with preserved left ventricular ejection fraction (LVEF) is not fully understood [7–9].

The purpose of our study was the evaluation of the relationship between NT-proBNP and indicators of ambulatory BP monitoring in middle-aged men with HTN and CHF.

Design and methods

The study was performed at the Department of Internal Medicine, Samara State Medical University. Our own clinical and laboratory data of HTN in-patients were analysed. All patients provided written informed consent to participate in the study.

In accordance with the recommendations for diagnosis and treatment AH and CHF developed by the RSC and the National Society of cardiovascular failure [6, 10, 11], we examined 550 men aged 40–50 years, who were admitted to the Center of Hypertension and Cardiology Department of the private clinic "Road Hospital at the Railway Station Samara of the Joint Stock Company "Russian Railways"" within the period from October 2007 to December 2013.

We included 420 patients divided into three groups: Group 1 — HTN patients without CHF (n = 180); Group 2 — patients with HTN and CHF (n = 86); Group 3 — patients with CHF without HTN (n = 74). The control group included age-matched healthy normotensive men without CHF (n = 80).

Clinical characteristics of the patients and echocardiography (EchoCG) data are presented in Table 1. Data are presented as mean and error of the mean (M ± m). Groups were matching by gender and age. Patients in group 2 had longer duration of HTN than patients in the 1st group. Treatment was comparable in both groups.

We included patients with HTN, CHF with preserved left ventricular ejection fraction (LVEF > 50 %), CHF stage I I–II functional class (FC), who signed informed consent to participate in the study.

Exclusion criteria were: age under 35 years and older than 60 years; secondary HTN; ST-elevation myocardial infarction, acute ischemic stroke, cardiovascular interventions within 3 months before the inclusion; cardiomyopathy; atrial fibrillation; significant valvular heart disease (congenital or acquired); LVEF less than 50 %; CHF II–III stage, CHF FC III and IV; thyroid disease; cirrhosis of the liver; chronic kidney

Table 1

GROUP CHARACTERISTICS

Parameter	Control	Group 1	Group 2	Group 3
Number of patients, n	80	180	86	74
Age, years	44.23 ± 1.85	40.93 ± 1.08	48.02 ± 0.50	45.10 ± 2.11
BMI, kg/m^2	24.72 ± 2.03	23.22 ± 4.02$^{\#\&}$	31.06 ± 3.02$^{*\#\&}$	25.22 ± 4.05$^{*\#\&}$
SBP mm Hg	116.93 ± 1.88	156.15 ± 1.61$^{*\&}$	160.08 ± 1.88$^{*\&}$	115.55 ± 1.94
DBP, mm Hg	73.89 ± 1.40	97.99 ± 0.99$^{*\&}$	97.55 ± 0.97$^{*\&}$	74.70 ± 1.62
PP mm Hg	43.04 ± 1.26	56.94 ± 1.65$^{*\&}$	62.99 ± 1.39$^{*\#\&}$	41.95 ± 1.92
HR, min	66.20 ± 9.68	67.01 ± 8.75	66.85 ± 8.11	69.32 ± 9.79
Cholesterol, mmol/l	3.31 ± 1.13	4.73 ± 1.35	4.67 ± 1.25	4.56 ± 1.16
β-PL, mmol/l	3.73 ± 1.35	4.63 ± 1.53*	4.47 ± 1.39*	3.84 ± 1.07
TG, mmol/l	1.34 ± 0.68	1.49 ± 0.79	1.54 ± 0.67	1.43 ± 0.46
GFR, ml / min / 1.73 m^2	129.33 ± 12.88	103.8 ± 23.47$^{\#}$	87.62 ± 17.31$^{*\#}$	93.17 ± 16.15*
HTN duration, years	–	3.04 ± 0.46	6.33 ± 0.41	–
HTN duration, % 1st 2nd 3rd	 – – –	 34% 36% 30%	 25% 40% 35%	 – – –
6-MWT, m	675.17 ± 8.08	613.14 ± 6.33	468.17 ± 6.15	422.13 ± 9.15
CHF duration, years	–	–	4.79 ± 0.34	3.27 ± 0.82
CHF FC, % I II	 – –	 – –	 69% 31%	 53% 47%
FW, %	66.67 ± 5.05	63.11 ± 5.17	55.38 ± 5.03	56.52 ± 6.04
iEDD, cm / m^2	2.70 ± 0.04	2.67 ± 0.03	2.73 ± 0.03	2.76 ± 0.09
LVMMI, g / m^2	93.38 ± 2.42	106.59 ± 2.64*	143.58 ± 3.65$^{*\&}$	111.71 ± 4.49*
LVM, g	180.03 ± 6.56	212.68 ± 5.61$^{*\#}$	293.54 ± 8.05$^{*\#\&}$	212.97 ± 10.35*
RTI	0.33 ± 0.00	0.34 ± 0.01$^{\#}$	0.38 ± 0.01$^{\#\&}$	0.34 ± 0.01
E max, m/s	75.20 ± 3.19	65.11 ± 1.77**	46.66 ± 0.98$^{**\&\#}$	57.55 ± 3.71**
A max, m/s	44.67 ± 1.51	45.33 ± 0.71$^{\&\#}$	55.25 ± 1.34$^{**\&}$	54.45 ± 3.26$^{**\&}$
E / A	1.68 ± 0.08	1.45 ± 0.04*	0.96 ± 0.05*	1.08 ± 0.08*
DT, mc	205.12 ± 3.08	210.11 ± 2.12	235.19 ± 4.15**	228.32 ± 3.08**

Note: BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; PP — pulse pressure; HR — heart rate; LDL — cholesterol; LA — left atrium; TG — triglycerides; GFR — glomerular filtration rate; AH — hypertension; Test 6-MWT — six-minute walk test; CHF — congestive heart failure; FC — functional class; iEDD — indexed end-diastolic dimension; LVMMI — left ventricular myocardial mass index; LVM — left ventricular mass; IRT — relative thickness thickness; E/A — ratio of early diastolic filling velocity and filling during atrial systole; DT — deceleration time of early diastolic blood flow of left ventricular filling; * — significant differences ($p < 0.05$) between the control group and the studied groups; # — significant difference ($p < 0.05$) between the 1st and 2nd groups; & — significant difference ($p < 0.05$) in comparison with the third group.

disease stages 3–5; body mass index ≥ 35 kg / m^2; diabetes mellitus.

HTN was the main cause of CHF (n = 86, 100%) in 1st group, while CHD was the main cause in group 3 (n = 74, 100%) — non-ST-elevation myocardial infarction, stable angina (verified by coronary angiography).

NT-proBNP was evaluated by enzyme immunoassay (Biomedica, Austria) in fmol / ml, the recommended diagnostic threshold was > 4.8 fmol / ml.

EchoCG study was performed in accordance with the recommendations of the American Society of Echocardiography (ASE), in a prone position, after 10 minute of rest. Additional indicators were calculated as following [12]: 1) left ventricular myocardial stress (MS, g / cm^2): MS = 0.334 × P (ED) / LVPWT (1 + LVPWT / ED), where

MS — myocardial stress during systole (MSsist) or diastolic (MSdiast), P — systolic or diastolic blood pressure, respectively, ED — end-systolic or diastolic LV dimension, respectively, LVPWT — posterior wall thickness of the left ventricular myocardium (regardless of local contractility disturbances); 2) the midwall fractional shortening/end-systolic stress (MFS %): MFS= ([EDD + IVSTD / 2 + LVPWT / 2] — [ESD + inner shell]) / (EDD + IVSTD / 2 + TLVPW / 2] × 100 %, where the EDD — end-diastolic dimension, IVSTD — interventricular septum thickness in diastole; LVPWT — posterior wall thickness of left ventricular myocardium during diastole, the inner "shell" = [(the EDD IVSTD + / 2 + LVPWTd / 2)^3 — EDD^3 + ESD^3]$^{1/3}$ — ESD.

National recommendations on heart failure management of the Russian Society of Cardiology and Society of Heart Failure (fourth revision, 2013) and comments were used to assess CHF stage [6].

Asymptomatic left ventricular dysfunction (corresponds to I CHF stage):

• symptoms of CHF at rest and under usual load are absent (see the definition of stage I);

• systolic dysfunction: LVEF ≤ 45 % and / or end-diastolic dimension of LV> 5.5 cm (indexed EDDLV > 3.3 cm / m^2);

• diastolic dysfunction: IVST + LVPWT / 2 > 1.3 cm and / or LVPWT > 1.2 cm, and / or hypertrophic type Doppler spectrum transmitral flow (E / A < 1.0), where IVST — interventricular septum thickness, LVPWT — left ventricular posterior wall thickness.

The index of the relative thickness (IRT) ≥ 0.42 and sphericity index < 0.70.

Adaptive remodeling (corresponds to CHF stage IIA):

• CHF symptoms (see the definition of the CHF stage II);

• systolic dysfunction (see description of CHF stage I.);

• diastolic dysfunction (see the description of CHF stage I and / or type of spectrum pseudonormal transmitral Doppler flow — E / A ≥ 1.1 and ≤ 2.0.);

• IRT ≥ 0.30 and <0.42, and the index of sphericity > 0.70.

Maladaptive remodeling (corresponds to CHF IIB stage):

• CHF symptoms (see the definition of the CHF IIB stage);

• systolic dysfunction (see the description of CHF I stage);

• diastolic dysfunction (see the description of CHF I stage and restrictive type of transmitral Doppler flow spectrum — E / A> 2.0);

• IRT < 0.30 and a sphericity index > 0.80.

A 6-minute walk test should be used to estimate CHF functional class (6-MWT, m) [6]:

• 426 to 550 m — 1 CHF FC;

• 300 to 425 m — 2 CHF FC;

• 150 to 300 m — 3 CHF FC;

• less than 150 m — 4 CHF FC.

Ambulatory BP monitoring was performed by oscillometric method (BPLab, Nizhny Novgorod, Russia). These devices were tested according to the protocol of the European Society of Hypertension (ESH) in 2001 and are recommended by the European experts. BP monitoring started between 9 and 11 am, and lasted for at least 24 hours (24.3 ± 0.7 hours). Daytime and nighttime intervals were considered from 6:00 to 22:00 and from 22:00 to 6:00, respectively. During daytime the intervals between measurements (from 7 to 23 hours) were 30 minutes, and at night (from 23 to 7 hours) BP was measured every 60 minutes. We analyzed the degree of nocturnal BP reduction as a percentage of the nighttime and daytime indicators. The ratio was calculated by the formula (BPday — BPnight) × 100 % / BPday. Based on the results the following groups were formed: "dipper" (normal physiological BP reduction in the range 10–20 %), "non-dipper" (BP reduction 0–10 %), "night-peaker" (overnight increase of BP), "over-dipper" (blood pressure reduction over 20 %).

The database was created using spreadsheet «MS Excel 7.0». Data analysis was performed using the statistical package «Statistica 7.0» and «SPSS 11.5». Statistical analysis was performed using the methods of parametric and nonparametric statistics [13]. The variable distribution was evaluated, and most of the studied indicators were distributed normally. In case of non-normal distribution ranking method was applied. Quantitative indicators in several groups were compared using ANOVA and Kruskal-Wallis test. U — test of Mann-Whitney-Wilcoxon was used to compare 2 groups. Associations between parameters were assessed using Pearson and

Figure 1. NT-proBNP levels in the studied groupsпп

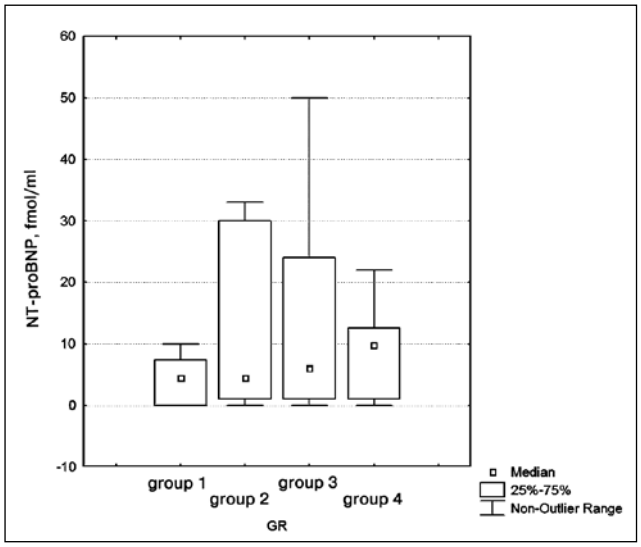
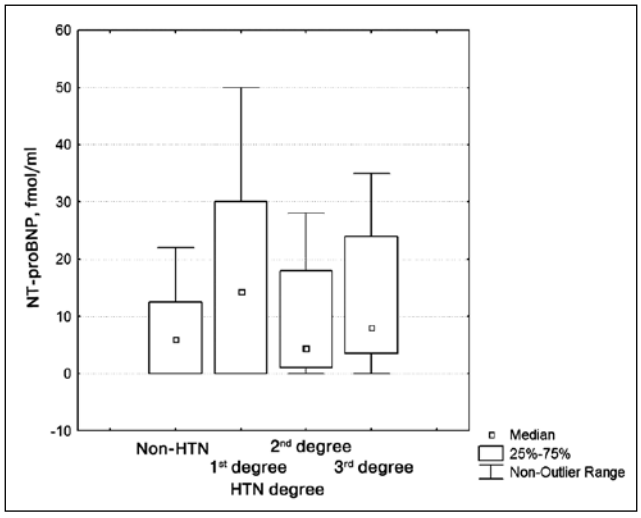


Figure 2. Plasma NT-proBNP level depending on the degree of hypertension



Note: HTN — hypertension.

Spearman correlation analysis. The differences and correlations were considered significant at p-level 0.05.

Results and discussion

Plasma levels of NT-proBNP were the greatest in group 3 (Fig. 1) in comparison with the control group (p = 0.046), group 1 (p = 0.037) and group 2 (p = 0.046).

Inter-group comparison showed no difference in plasma NT-proBNP level in patients of groups 1 and 2 (p = 0.615) and the control group (p = 0.351).

The HTN duration did not impact on plasma NT-proBNP level (r = 0.186; p = 0.537). NT-proBNP level correlated with CHF duration (r = 0.287; p = 0.037) and CHF FC (r = 0.304; p = 0.027).

There was no difference in plasma NT-proBNP level depending on the HTN (Fig. 2) between the groups.

We compared NT-proBNP levels in patients in groups 1 and 2 with comparable HTN degree. The results are presented in Table 2 [medians and interquartile span, Me (25%; 75%)]. Plasma NT-proBNP level was significantly lower in patients with HTN 2nd and 3rd degree, compared to subjects with HTN 1st degree among patients without CHF (Group 1), as oppoased to the group of patients with HTN and CHF (Group 2), where such association was not found. NT-proBNP was higher in patients with HTN 1st degree in the first group compared to patients with comparable HTN degree in the second group and was significantly lower in patients with HTN 2nd and 3rd degree in

Table 2

NT-proBNP LEVELS DEPENDING ON THE HYPERTENSION DEGREE

Hypertension degree	Group 1 (n = 180)	Group 1 (n = 86)	p1–2
1	30.00* (4.50; 35.60) n = 61	2.75 (0.00; 27.75) n = 22	0.003
2	1.75* (0.50; 5.50) n = 65	4.50 (1.00; 21.00) n = 34	0.034
3	3.20* (0.00; 5.00) n = 54	9.20 (4.7; 34.02) n = 30	0.044

Note: * — significant differences with the group of people with hypertension 1st degree.

the first group compared with patients with comparable HTN degree in the second group. In the group 1, an inverse relationship between NT-proBNP and HTN degree was found (r = –0.624; p = 0.023). In group 2, there was no correlation between these parameters (r = 0.151; p = 0.294). In the group 2, NT-proBNP weakly correlates with CHF FC (r = 0.215; p = 0.049).

Figures 3 and 4 show the diagnostic value of NT-proBNP changes for the diagnosis of HTN 1st degree compared to HTN 2–3rd degree in patients without CHF. At the cut-off 3.85 the sensitivity was 83 %, specificity — 71 %. The area under the curve (ROC) was 0.81; model quality was very good.

Figure 3. Prediction model (ROC-curve) of hypertension 1st degree compared to hypertension 2-3 degree in patients without chronic heart failure

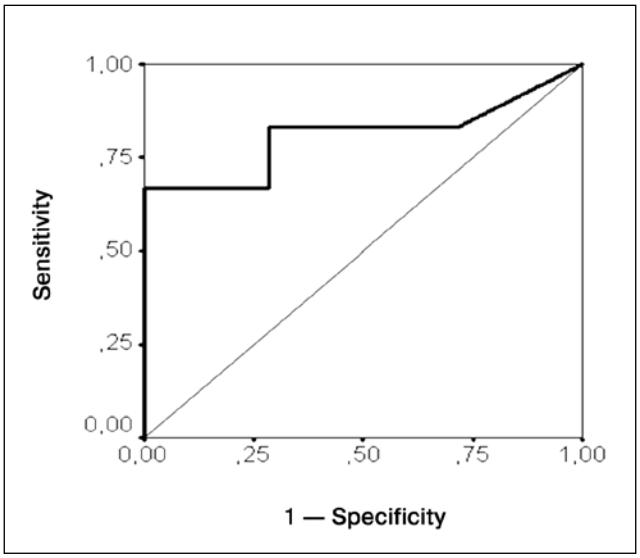
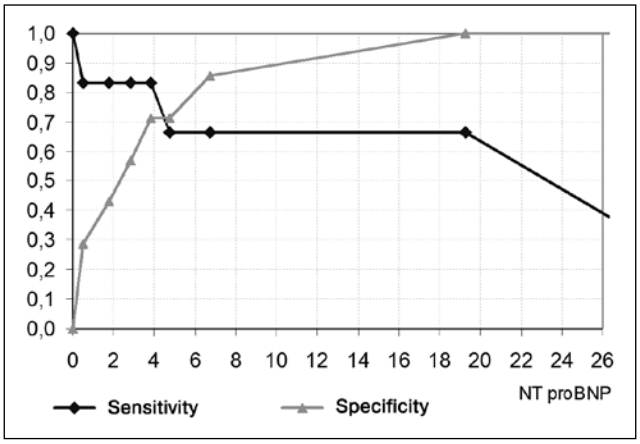


Figure 4. Sensitivity and specificity of NT-proBNP change for the diagnosis of hypertension 1st degree compared to hypertension 2-3 degree in patients without chronic heart failure



Hyperactivation of tissue and circulating neurohormonal systems is a crucial mechanism for compensation at the certain stage of the cardiovascular continuum. The role of neurohormones can be represented as the balanced scales, reflecting the balance of neurohormonal systems leading to "positive" (nitric oxide, NUP, prostacyclin, bradykinin and others) and "negative" (rennin-angiotensin-aldosterone system and sympathoadrenal systems, endothelin, vasopressin) effects. Data in the role of NUP in HTN are contradictory. No reliable data exist on the difference in BNP levels in hypertensive and normotensive patients. BNP level was higher in presence of left ventricular hypertrophy: BNP directly correlated with LV myocardial mass, relative left ventricular myocardial wall thickness, IVST and posterior wall thickness. Moreover, in patients with HTN and diastolic dysfunction BNP levels were increased: EchoCG indices of LV diastolic function correlated with NUP levels [14–17].

Belluardo P. 2006 challenged the common view that the LV hypertrophy is associated with increased NUP levels in HTN. He showed that the NUP production decreases at the early stages of HTN [18].

In addition, the importance of ANP and BNP in BP regulation and increased risk of HTN has recently been confirmed by C. Newton-Cheh (2009). In this population-based study genetic variants of the ANP and BNP gene were studied, in particular those associated with increased concentration of plasma ANP and / or BNP and lower BP and reduced HTN risk. These findings are consistent with previous experimental studies, which demonstrated the development of HTN and LV hypertrophy in ANP and NPR-A knockout mice [19].

Ramachandran C. M. has followed initially normotensive men and women (1081 people) for 4 years. As a result, increased BP of various degree was reported in 36.2 % of men and 33.1 % women. HTN stages were defined according to the classification of the Joint National Committee (Joint National Committee, JNC) VI. HTN occurred in 16.4 % men and 15.5 % women. After adjustment for known risk factors, there was a weak but statistically significant association between increased plasma BNP levels and the likelihood of BP elevation in men: odds ratio of

Table 3

CIRCADIAN PROFILE IN PATIENTS WITH ARTERIAL HYPERTENSION

CI BP	Group	"dipper" %	"non-dipper" %	"night-peaker" %	"over-dipper" %
SBP	Group 1 (n = 180)	80 (n = 144)	20 (n = 36)	–	–
	Group 2 (n = 86)	33 (n = 28)	44 (n = 38)	2 (n = 2)	21 (n = 18)
DBP	Group 1 (n = 180)	80 (n = 144)	20 (n = 36)	–	–
	Group 2 (n = 86)	21 (n = 18)	51 (n = 44)	14 (n = 12)	14 (n = 12)

Note: CI BP — circadian index of blood pressure; SBP — systolic blood pressure; DBP — diastolic blood pressure.

1.15 for the transition to each stage according to the JNC classification (p = 0.046). In women, such associations were not observed (p = 0.82) [20].

Our results confirm the data by Holditch S. J. et al. (2015) who showed that the decline in NUP levels is associated with the HTN progression and increased cardiovascular risk in HTN patients [9].

The increase in plasma NT-proBNP level is strongly correlated with the severity of CHF and is caused by both the deterioration of intracardiac hemodynamics and increased activity of the renin-angiotensin-aldosterone and sympathoadrenal systems. Our findings indicate a direct correlation between CHF severity and NT-proBNP levels in group 2, and greater NT-proBNP in higher CHF FC (r = 0.215; p = 0.049).

We assessed the ABPM parameters, including systolic BP daily index (SBP) and diastolic blood pressure (DBP), the time index, measurement index, hypertension square index. The majority of patients in group 1 had biphasic rhythm (so called "dipper" pattern) of both SBP and DBP (Table 3). However, 20 % subjects demonstrated insufficient nocturnal decline of SBP and DBP ("non-dipper").

In group 2, according to the daily BP profile the distribution was the following: based on SBP pattern 33 % subjects were "dippers" and 44 % patients were "non-dippers". Up to 21 % subjects demonstrated excessive nocturnal fall in BP ("over-dippers"), while 2 % subjects were "night-peakers". The predominant patterns were "non-dippers" (51 %) and "dippers" (21 %). "Over-dippers" and "night-peakers" were presented equally (14 %).

The natural circadian BP rhythm changes under the effects of exogenous and endogenous factors. The exogenous factors include smoking, alcohol consumption and high sodium consumption. Daily fluctuations in BP caused by endogenous rhythms are modulated by physical and mental activity in accordance with sleep-wake cycle, are age-dependent (in elderly persons over 70 years old nocturnal BP reduction disappears or becomes less evident) [21].

Along with the HTN progression nocturnal BP drop becomes less pronounced, specific evening-and-night and evening variants of circadian BP rhythm develop. Pathogenesis of insufficient nocturnal BP reduction is unclear. The leading role is attributed to the sympathetic overactivity and increase in blood volume due to circulation redistribution. There is a linear correlation between cardiovascular mortality and the degree of nocturnal BP reduction: increase of ratio night / day (for SBP or DBP) for each 5 % is associated with increased risk of death by 20 %. Such association is still observed when average 24-hour BP levels are within normal values [22]. A number of long-term prospective studies have confirmed that insufficient nocturnal BP reduction leads to the organ damage: increased LV myocardial mass index, severity of microalbuminuria and greater incidence of cerebrovascular events [23].

Correlation analysis of circadian BP profile and EchoCG parameters showed a statistically significant relationship between SBP circadian profile and the left atrium (r = –0.307; p = 0.050), LV myocardium mass index (r = –0.332; p = 0.039), MSsist/iEDV (r = 0.349; p = 0.034), the MFS

(r = 0.392; p = 0.013), E (r = 0.385; p = 0.047); circadian DBP pattern and left atrium (r = –0.361; p = 0.022), LV myocardium mass index (r = –0.323; p = 0.044), the right ventricle (r = –0.326; p = 0.040), MFS (r = 0.390; p = 0.014), MSsyst / iESV (r = 0.329; p = 0.047), where MSsyst — systolic myocardial stress; iESV — indexed end-systolic volume, the MFS — the midwall fractional shortening / end-systolic stress.

Several neurohormonal systems are involved in circadian BP pattern formation, confirmed by the correlations between BP level and plasma renin activity, levels of norepinephrine and angiotensin II. The role of vasoactive hormones is undoubtedly important for BP elevation in the early morning.

The role of the central mechanisms is confirmed by the loss of circadian BP rhythm in stroke survivors, as well as the strong relationship between daily BP fluctuations and sleep-wake cycle in shift-workers. The sympathetic nervous system, in addition vasoconstriction of resistance vessels resulting in an increase in total peripheral resistance and increase in cardiac output, also leads to spasm of renal blood vessels and RAAS activation. NUP are physiological RAAS antagonists, and due to their natriuretic and vasodilator effects they are considered as "unloading" factors [24].

We assessed NUP level in 1st and 2nd groups with various BP circadian patterns (Table 4, 5).

NUP level was the highest in "non-dippers", "night-peakers" and differed from patients with normal circadian BP profile and "over-dippers" (for both SBP and DBP). There was an inverse relationship between NT-proBNP and circadian SBP pattern (r = –0.498; p = 0.035).

No "night-peakers" or "over-dippers" were registered in group 1, we evaluated NUP levels in patients with the same type of circadian BP pattern in groups 1 2 (Tables 5, 6).

NT-proBNP was reduced in "non-dippers" in group 1 compared to patients in group 2 and compared to "dippers".

Conclusions

1. NUP levels are useful for personalised diagnosis and cardiovascular prognosis in patients with hypertension and heart failure: decreased plasma NT-proBNP levels in HTN patients are associated with higher HTN degrees and increased risk of target organ damage. In CHF patients, regardless of the HTN degree, increased NUP indicates the degree of myocardial dysfunction and CHF severity.

2. Clear relationship between plasma NT-proBNP levels and LV structural parameters (left ventricular myocardial mass index, relative wall thickness) and diastolic LV filling (NT-proBNP and E: r = 0.252, p = 0.050; E / A: r = 0.347, p = 0.018) allows us to consider NT-proBNP as a marker of left ventricular remodeling and diastolic dysfunction in HTN.

Table 4

NT-proBNP LEVELS IN PATIENTS WITH HYPERTENSION DEPENDING ON THE CIRCADIAN INDEX OF SYSTOLIC BLOOD PRESSURE

Parameter	"dipper" (n = 172)	"non-dipper" (n = 74)	"night-peaker" (n = 2)	"over-dipper" (n = 18)
NT-proBNP, fmol / ml	10.52 ± 2.44*	30.54 ± 14.31*	45.41 ± 3.47*	4.22 ± 1.34*

Note: * — significant differences (p < 0.05) between the groups.

Table 5

NT-proBNP LEVEL IN PATIENTS WITH HYPERTENSION DEPENDING ON THE CIRCADIAN INDEX OF DIASTOLIC BLOOD PRESSURE

Parameter	"dipper" (n = 162)	"non-dipper" (n = 80)	"night-peaker" (n = 12)	"over-dipper" (n = 12)
NT-proBNP, fmol / ml	29.50 ± 5.44*	32.71 ± 14.3*	44.35 ± 5.64*	2.47 ± 0.88*

Note: * — significant differences (p < 0.05) between the groups.

Table 6

NT-proBNP THE FIRST AND SECOND GROUPS IN PATIENTS WITH THE SAME DAILY PROFILE OF SYSTOLIC BLOOD PRESSURE

Parameter	"dipper"		"non-dipper"		p1–2	p1'-2'
	Group 1 (n = 144)	Group 2 (n = 28)	Group 1 (n = 36)	Group 2 (n = 38)		
NT-proBNP, fmol / ml	9.45 ± 1.07	3.13 ± 1.51	3.2 ± 1.01	40.46 ± 4.39	0.038	0.001

Note: p1–2 — the difference between 1st and 2nd groups with the daily profile "dipper"; P1'–2' — differences between the 1st and 2nd groups with the daily profile "non-dipper".

Table 7

NT-proBNP LEVELS IN THE FIRST AND SECOND GROUPS IN PATIENTS WITH THE SAME PROFILE OF DIASTOLIC BLOOD PRESSURE

Parameter	"dipper"		"non-dipper"		p1–2	p1'–2'
	Group 1 (n = 144)	Group 2 (n = 18)	Group 1 (n = 36)	Group 2 (n = 44)		
NT-proBNP, fmol / ml	13.33 ± 3.06	18.24 ± 4.45	2.8 ± 1.01	29.24 ± 3.76	0.051	0.006

Note: p1–2 — the difference between 1st and 2nd groups with the daily profile "dipper"; P1'–2' — differences between the 1st and 2nd groups with the daily profile "non-dipper".

3. NUP are involved in the formation of circadian BP pattern, and their plasma levels depend both on HTN degree and the "load pressure".

Conflict of interest
The authors declare no conflict of interest.

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