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Correlation of N-terminal pro-B-type natriuretic peptide with clinical parameters in patients with hypertension

Korelacija N-terminalnog pro-B-tipa natriuretskog peptida sa kliničkim parametrima kod bolesnika sa hipertenzijom

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Abstract

Background/Aim. Identification of patients with arterial hypertension and a possible onset of heart failure by determining the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) enables timely intensification of treatment and allows clinicians to prescribe and implement optimal and appropriate care. The aim of this study was to evaluate NT-proBNP in patients with longstanding hypertension and in patients with signs of hypertensive cardiomyopathy. **Methods.** The study involved 3 groups, with 50 subjects each: "healthy" persons (control group), patients with hypertension and normal left ventricular systolic function (group 1) and patients with longstanding hypertension and signs of hypertensive cardiomyopathy with impaired left ventricular systolic function (group 2). We measured levels of NT-proBNP, C-reactive protein and creatinine according to the manufacturer's instructions. All the patients were clinically examined including physical examination of the heart with blood pressure, pulse rate, electrocardiogram (ECG) and echocardiogram. **Results.** Our results showed that the determined parameters generally differed significantly (Student's *t*-test) among the groups. The mean (± SD) values of NT-proBNP in the control group, group 1 and group 2 were: 2.794 (± 1.515) pmol/L, 9.575 (± 5.449) pmol/L and 204.60 (84,93) pmol/L, respectively. NT-proBNP correlated significantly with the determined parameters both in the group 1 and the group 2. In the group 1, the highest correlation was obtained with C-reactive protein (r = 0.8424). In the group 2, the highest correlation was obtained with ejection fraction (r = -0.9111). NT-proBNP showed progressive increase in proportion to the New York Heart Association (NYHA) classification. The patients in the-group 2 who belonged to the II and III NYHA class had significantly higher levels of NT-proBNP than those in the NYHA class I (ANOVA test, $p = 0.001$). **Conclusion.** The obtained results suggest that NT-proBNP is a useful biomarker in the treatment of patients with longstanding hypertension who are at risk for heart failure.

Key words:
natriuretic peptide; biological markers; hypertension; cardiomyopathy, hypertrophic; risk assessment.

Apstrakt

Uvod/Cilj. Identifikacija bolesnika sa arterijskom hipertenzijom kojima preti srčana slabost, pomoću određivanja koncentracije N-terminalnog pro-B-tipa natriuretskog peptida (NT-proBNP) omogućava kliničarima pravovremeno intenziviranje lečenja i propisivanje i sprovođenje optimalne i odgovarajuće nege, jer bolesnici sa hipertenzivnim srčanim oboljenjima imaju povišene koncentracije NT-proBNP. Cilj rada bio je da se izvrši procena razlike u NT-proBNP kod bolesnika sa hipertenzijom i normalnom sistolnom funkcijom i onih sa dugogodišnjom arterijskom hipertenzijom i znacima hipertenzivne kardiomiopatije. **Metode.** U ispitivanje su bile uključene tri grupe, svaka sa po 50 ispitanika: "zdrave" osobe (kontrolna grupa), bolesnici sa arterijskom hipertenzijom i normalnom sistolnom funkcijom leve komore (grupa 1) i bolesnici sa dugogodišnjom arterijskom hipertenzijom i znacima hipertenzivne kardiomiopatije sa oslabljenom sistolnom funkcijom leve komore (grupa 2). Nivoi NT-proBNP, C-reaktivnog proteina i kreatinina određivani su prema uputstvu proizvođača. Svi bolesnici bili su klinički pregledani uključujući fizički pregled srca sa merenjem krvnog pritiska i pulsa, elektrokardiogramom (EKG) i ehokardiogramom. **Rezultati.** Naši rezultati pokazuju da se određivani parametri generalno

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značajno razlikuju (Studentov *t*-test) među grupama. Srednje (± SD) vrednosti NT-proBNT u kontrolnoj grupi, grupi 1 i grupi 2 bili su: 2,794 (± 1,515) pmol/L, 9,575 (± 5,449) pmol/L i 204,60 (84,93) pmol/L, redom. NT-proBNT značajno koreliše sa određivanim parametrima u grupi 1 i u grupi 2. U grupi 1, najviša korelacija dobijena je sa C-reaktivnim proteinom (r = 0,8424). U grupi 2, najviša korelacija dobijena je sa ejekcionom frakcijom leve komore (r = -0,9111). Utvrđeno je progresivno povećanje NT-proBNT u odnosu na klasifikaciju *New York Heart Association* (NYHA). Bolesnici u grupi 2 koji su pripadali NYHA klasi II i III imali su značajno više vrednosti NT-proBNP od bolesnika u NYHA klasi I (ANOVA test, p = 0,001). **Zaključak.** Rezultati istraživanja ukazuju na to da je NT-proBNP koristan biomarker u lečenju bolesnika sa dugogodišnjom arterijskom hipertenzijom kojima preti zastojna srčana slabost.

Ključne reči:
natriuretski peptidi; biološki pokazatelji; hipertenzija; kardiomiopatija, hipertrofička; rizik, procena.

Introduction

Like other natriuretic peptides, N-terminal pro-B-type natriuretic peptide (NT-proBNP) is secreted from the heart in response to cardiac hemodynamic stress mediated by volume and/or pressure overload [1]. The identification of patients with arterial hypertension with the onset of heart failure by determining the concentration of NT-proBNP, enables timely intensification of treatment and allows physicians to prescribe and implement optimal and appropriate therapy [2–4]. The increase of NT-proBNP is related to the left ventricular mass index, left ventricular hypertrophy and diastolic left ventricular dysfunction. Concentrations of NT-proBNP in the serum were not significantly increased in hypertensive patients with the normal left ventricular geometry compared to normotensive individuals [5, 6].

Heart failure is characterized by a dysfunctional natriuretic peptide system. Natriuretic peptides are semiquantitative markers of cardiac stress and heart failure, and thus related to the extent of atrial, ventricular, and valvular dysfunction [1]. Diagnosis of heart failure in the primary stage using only clinical criteria in 50% of cases gives false positive results [7, 8]. Heart failure, especially in its early stages, is difficult to diagnose. The most commonly applied method of investigation to confirm the diagnosis of heart failure is echocardiography, which offers structural and functional information about the heart. However, assessment of cardiac function by echocardiography requires considerable time and is expensive to use in daily practice. For clinicians there is a legitimate medical requirement for a biomarker that would be a reliable and objective test to identify hypertensive patients with the onset of heart failure [9–15].

Inflammatory markers are increased in chronic heart failure, including C-reactive protein (CRP) [16]. Additionally, CRP predicts morbidity and mortality in patients with established heart failure [17–19].

NT-proBNP has a principal effect on the kidney, promoting tubular natriuresis and diuresis. As with heart failure evaluation, knowledge of the cardiac and noncardiac factors that influence the NT-proBNP concentration is necessary. Therefore, proper study of the evaluation of heart failure must include the estimation of glomerular filtration rate or determination of creatinine [20].

The aim of this study was to compare the concentrations of NT-proBNP with the parameters of clinical examination and biomarkers (systolic blood pressure, diastolic blood pressure, ejection fraction, CRP and creatinine) in patients with hypertension, and to determine the relationship between NT-proBNP and the New York Heart Association (NYHA) classification in patients with longstanding hypertension with signs of hypertensive cardiomyopathy.

Methods

We measured all the biomarkers according to the manufacturer's instructions. The analytical performance of the methods has been evaluated and described elsewhere [21]. The study included three groups, each with 50 subjects: "healthy" persons (control group), patients with hypertension and normal systolic left ventricular function (group 1) and patients with longstanding hypertension and signs of hypertensive cardiomyopathy with impaired systolic function of the left ventricle (group 2). The control group included healthy adults of both sexes subjected to the routine systematic health examination at the Institute of Occupational Medicine, Military Medical Academy in Belgrade, Serbia and voluntary blood donors at the Institute of Transfusion, Military Medical Academy in Belgrade, Serbia. The patients of the group 1 and group 2 were treated at the Clinic of Cardiology, Military Medical Academy and had the diagnosis of these diseases. These patients were clinically examined including physical examination of the heart with blood pressure, pulse rate, electrocardiogram (ECG) and echocardiogram. Left ventricular ejection fraction (EF) was derived from 2-dimensional echocardiography. Blood samples were taken from all the subjects and the serum was separated from cells within 60 minutes of collection and centrifuged at 2028g (4000 rpm) for 10 min. We measured all the biomarkers in a single batch at the Institute of Medical Biochemistry, Military Medical Academy. The study was approved by the institutional Ethics Committee, in compliance with the Helsinki criteria. All the study participants gave written informed consent.

All the biomarkers were measured according to the manufacturer's instructions. The analytical performance of the methods has been evaluated and described elsewhere [21]. Levels of NT-proBNP were measured by a one-step enzyme immunoassay based on electrochemiluminescence technology on the Elecsys® 2010 platform (Roche Diagnostics). The reference range, as reported by the manufacturer, was < 14.75 pmol/L. Levels of CRP were measured using the Behring BN II Nephelometer (Dade Behring/Siemens Medical Solutions

Diagnostics). The reference range, as reported by the manufacturer, was < 3 mg/L. Creatinine concentrations were measured by the kinetic alkaline picrate method (improved Jaffe reaction) on a Dimension RxL Max analyzer (Dade Behring/Siemens Medical Solutions Diagnostics). The reference range, as reported by the manufacturer, was 53–115 μmol/L (71–115 μmol/L for men and 53–88 μmol/L for women).

Adherence to Gaussian distributions was assessed using the Kolmogorov-Smirnov test. The mean, standard deviation (SD), Student's *t*-test and Pearson's test were used for statistical analysis. All the probabilities were two tailed and $p < 0.05$ was regarded as significant. The 95% confidence interval (CI) was also shown in reported data. The data were statistically analysed with the MedCalc®, Ver. 11.3.3.0 package (MedCalc Software, Mariakerke, Belgium).

Results

The control group included 25 women and 25 men aged 50–65 years ($\bar{x}$ ± SD, 56.3 ± 4.20 years). The group 1 included 19 women and 31 men aged 50–65 years ($\bar{x}$ ± SD, 57.7 ± 4.57 years), and in the group 2 there were 17 women and 33 men aged 50–65 years ($\bar{x}$ ± SD, 58.1 ± 4.82 years). Clinical and echocardiographic examinations were performed in all patients in order to evaluate the NYHA-class and the left ventricular EF.

The mean (SD) values of NT-proBNP, creatinine, CRP, systolic blood pressure, diastolic blood pressure and in the control group, group 1 and group 2 were presented in Tables 1–3. Comparison studies showed that levels of NT-proBNP and systolic blood pressure were significantly higher in the group 1 and the group 2 than in the control group, and also higher in the group 2 than in the group 1. EF values were significantly lower in the group 1 and in the group 2 than in the control group, and also lower in the group 2 than in the group 1. Levels of creatinine and diastolic blood pressure did not differ significantly between the groups 1 and 2, while CRP levels did not differ between the control group and the group 1 (Tables 1–3, Figure 1).

In the group 2, the patients were divided into three subgroups according to the NYHA classification. The number of patients in the group 2 in different NYHA classes was: I (n = 29.58%), II (n = 16.32%) and III (n = 5.10%). The group 2 subjects that belonged to the NYHA class II and III had significantly higher levels of NT-proBNP than those in the NYHA class I (ANOVA test, $p = 0.001$). The levels of NT-proBNP were also significantly higher in the NYHA class I than in the control group (Tables 4–5, Figure 2).

The distribution of data in all the groups was generally normal, so the Pearson's test was used for correlation analysis. The values for the correlation coefficient (r), the confidence interval for r (95% CI) and *p* are given in Tables 6 and 7.

Table 1

Comparison analysis data for the determined parameters between the control group and the group 1

Parameter	Control group	Group 1	*p* value
NT-proBNP (pmol/L)	2.794 (1.515)	9.575 (5.449)	< 0.0001*
Creatinine (μmol/L)	85.5 (12.4)	90.9 (13.7)	0.0414*
CRP (mg/L)	2.64 (1.02)	2.73 (1.07)	0.6609
Systolic blood pressure (mm/Hg)	126.9 (9.5)	146.3 (9.4)	< 0.0001*
Diastolic blood pressure (mm/Hg)	81.2 (4.9)	92.2 (5.0)	< 0.0001*
EF (%)	63.2 (4.5)	60.8 (5.3)	< 0.0001*

Data are presented as means (± SD); * statistically significant difference (Student's *t*-test); NT-proBNP–N–terminal pro B-type natriuretic peptide; CRP – C-reactive protein; EF – ejection fraction.

Table 2

Comparison analysis data for the determined parameters between the control group and the group 2

Parameter	Control group	Group 2	*p* value
NT-proBNP (pmol/L)	2.794 (1.515)	204.60 (84.93)	< 0.0001*
Creatinine (μmol/L)	85.5 (12.4)	90.9 (14.3)	0.0464*
CRP (mg/L)	2.64 (1.02)	4.17 (1.03)	< 0.0001*
Systolic blood pressure (mm/Hg)	126.9 (9.5)	150.5 (6.3)	< 0.0001*
Diastolic blood pressure (mm/Hg)	81.2 (4.9)	95.5 (11.0)	< 0.0001*
EF (%)	63.2 (4.5)	48.0 (6.0)	< 0.0001*

Data are presented as means (± SD); * statistically significant difference (Student's *t*-test); NT-proBNP–N–terminal pro B-type natriuretic peptide; CRP – C-reactive protein; EF – ejection fraction.

Table 3

Comparison analysis data for the determined parameters between the group 1 and the group 2

Parameter	Group 1	Group 2	*p* value
NT-proBNP (pmol/L)	9.575 (5.449)	204.60 (84.93)	< 0.0001
Creatinine (μmol/L)	90.9 (13.7)	90.9 (14.3)	1.000
CRP (mg/L)	2.73 (1.07)	4.17 (1.03)	< 0.0001
Systolic blood pressure (mm/Hg)	146.3 (9.4)	150.5 (6.3)	0.0099
Diastolic blood pressure (mm/Hg)	92.2 (5.0)	95.5 (11.0)	0.0558
EF (%)	60.8 (5.3)	48.0 (6.0)	< 0.0001

Data are presented as means (± SD); * statistically significant difference (Student's t-test); NT-proBNP–N–terminal pro B-type natriuretic hormone; CRP – C-reactive protein; EF – ejection fraction.

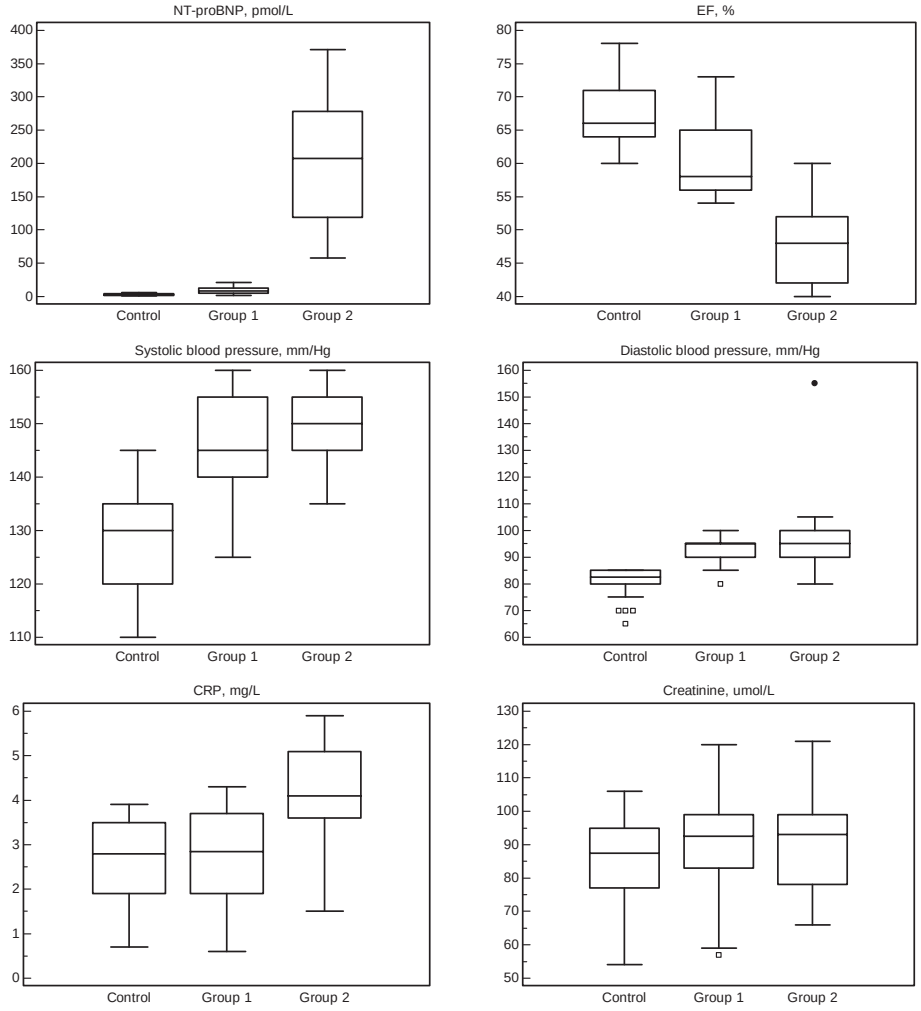

Fig. 1 – Distribution of N–terminal pro B-type natriuretic peptide (NT-proBNP), ejection fraction (EF), systolic and diastolic blood pressure, creatinine and C-reactive protein (CRP) value in the control group, the group 1 and the group 2

Table 4

Comparison analysis data for the determined parameters in the group 2 in regard to the New York Heart Association (NYHA) classes

Parameter	*p* values	NYHA	
		class	mean
NT-proBNP (pmol/L)	< 0.001*	I	147.4 (II) (III)
		II	367.2 (I)
		III	336.4 (I)
Creatinine (μmol/L)	0.447	I	89.5
		II	91.2
		III	98.4
CRP (mg/L)	< 0.001*	I	3.69 (II) (III)
		II	4.60 (I) (III)
		III	5.58 (I) (II)
Systolic blood pressure (mm/Hg)	0.004*	I	148.3 (II) (III)
		II	152.5 (I)
		III	157.0 (I)
Diastolic blood pressure (mm/Hg)	0.251	I	93.4
		II	97.5
		III	101.0
EF (%)	< 0.001*	I	52.1 (II) (III)
		II	43.1 (I)
		III	40.0 (I)

The numbers in brackets [(I), (II), (III)] indicate a NYHA class which was significantly different from the present NYHA class; * statistically significant difference (ANOVA test); NT-proBNP–N–terminal pro B-type natriuretic peptide; CRP – C-reactive protein; EF – ejection fraction.

Table 5

Comparison analysis data for the determined parameters between the control group and the NYHA I subgroup in the group 2

Parameter	Control group	NYHA I	*p* values
NT-proBNP (pmol/L)	2.794 (1.515)	147.30 (49.58)	< 0.0001*
Creatinine (μmol/L)	85.5 (12.4)	89.5 (15.9)	0.2197
CRP (mg/L)	2.64 (1.02)	3.69 (0.85)	< 0.0001*
Systolic blood pressure (mm/Hg)	126.9 (9.5)	148.3 (6.2)	< 0.0001*
Diastolic blood pressure (mm/Hg)	81.2 (4.9)	93.4 (6.3)	< 0.0001*
EF (%)	63.2 (4.5)	52.1 (4.0)	< 0.0001*

Data are presented as means (± SD); * statistically significant difference (Student's t-test); NT-proBNP–N–terminal pro B-type natriuretic peptide; CRP – C-reactive protein; EF – ejection fraction.

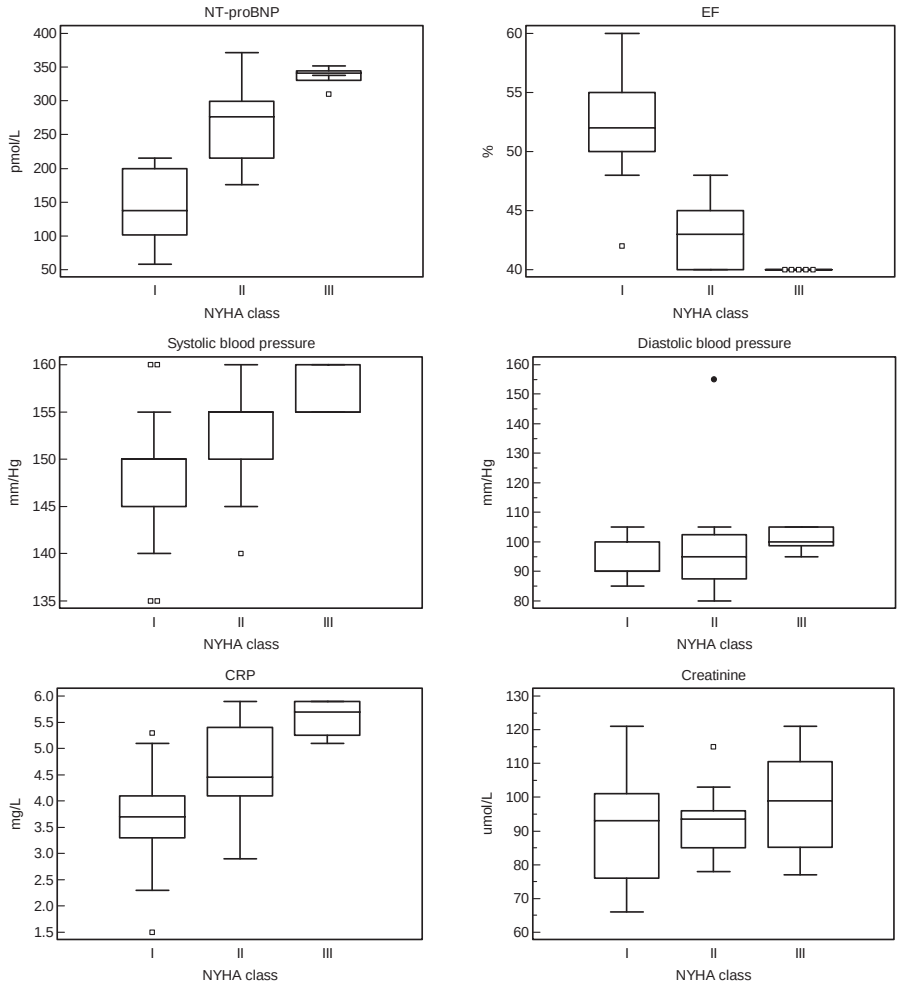

Fig. 2 – Distribution of N–terminal pro B-type natriuretic peptide (NT-proBNP), ejection fraction (EF), systolic and diastolic blood pressure, creatinine and C-reactive protein (CRP) value in the group 2 according to the NYHA classification

In the group 1, NT-proBNP correlated significantly with all the determined parameters (Table 6). The highest correlation was obtained between NT-proBNP and CRP (r = 0.8424, 95% CI 0.7369–0.9079). In the group 2, NT-proBNP also correlated significantly with all the parameters, except with creatinine (Table 7). The highest correlation was obtained between NT-proBNP and EF (r = -0.9111, 95% CI -0.9489 – -0.8478).

Table 6

The correlation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations and the values of determined parameters in the group 1 (n = 50)

Parameter	NT-proBNP (pmol/L)		
	r	95%CI	*p* values
Creatinine	0.3379	0.0657–0.5633	0.0164*
CRP	0.8424	0.7369–0.9079	< 0.0001*
Systolic blood pressure	0.7213	0.5542–0.8325	< 0.0001*
Diastolic blood pressure	0.4282	0.1701–0.6313	0.0019*
EF	-0.7390	-0.8438 – -0.5800	< 0.0001*

*** statistically significant correlation (Pearson's test); CRP – C-reactive protein; EF – ejection fraction.**

Table 7

The correlation of N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations and the values of determined parameters in the group 2 (n = 50)

Parameter	NT-proBNP, pmol/L		
	r	95%CI	*p* values
Creatinine	0.1737	-0.1100–0.4312	0.2276
CRP	0.6650	0.4745–0.7960	< 0.0001*
Systolic blood pressure	0.4856	0.2396–0.6730	0.0004*
Diastolic blood pressure	0.3989	0.1355–0.6095	0.0041*
EF	-0.9111	-0.9489 – -0.8478	< 0.0001*

*** statistically significant correlation (Pearson's test); CRP – C-reactive protein; EF – ejection fraction.**

Discussion

Elevated blood pressure causes left ventricular hypertrophy as an independent factor for the development of arrhythmias, heart failure and sudden death. NT-proBNP now appears to be an indicator of asymptomatic cardiac organ damage in patients who eventually develop left ventricular hypertrophy, left arterial dilation, atrial fibrillation, and left ventricular systolic dysfunction [22, 23].

This study aimed to assess the characteristics of NTproBNP, CRP, creatinine and the parameters of clinical examination (systolic blood pressure, diastolic blood pressure) in patients with longstanding hypertension and in patients with signs of hypertensive cardiomyopathy.

NT-proBNP showed good sensitivity in detecting heart failure in the group of patients with hypertension and cardiomyopathy. A single measurement of NT-proBNP at the time of hospital admission provides important information about left ventricular EF in patients with hypertension [1]. Comparison with the group of patients with hypertension showed that levels of this natriuretic peptide correlated equally ($p < 0.001$) with systolic blood pressure, EF, CRP and creatinine. Piechota et al. [24] reported that NT-proBNP correlated equally well with the clinical and echocardiographic parameters of chronic heart failure, which makes them equally adequate in the biochemical staging of chronic heart failure severity.

Several clinical trials have shown that NT-proBNP is a sensitive marker of cardiac function whose rise indicates the presence of heart failure, and on the other hand, when the level of NT-proBNP is within the normal limits, it excludes cardiac dysfunction. The level of NT-proBNP is directly correlated with the severity of disease (I–IV NYHA classification) [9, 19]. In our study patients in the group with NYHA class II and III had significantly higher plasma concentrations of NT-pro-BNP, hsCRP and lower EF ($p < 0.001$). Seino et al. [10] also evaluated NT-proBNP in 105 patients with chronic heart failure, and a progressive increase in NT-proBNP in proportion to the NYHA classification was confirmed in this study.

It was shown that CRP is elevated in patients with chronic heart failure and its prognostic value was established in these patients [16–18]. Our study confirms these findings. The mean CRP of patients in the group 2 (patients with hypertension and cardiomyopathy) was 4.17 ± 1.03 mg/L, and 2.73 ± 1.07 in the group 1 (patients with hypertension) ($p < 0.0001$). Because we had excluded patients with infections or inflammatory diseases, our data suggest that inflammation was related to heart failure and not to external factors.

Conclusion

This study supports the importance of NT-proBNP measurement in patients with longstanding hypertension with signs of hypertensive cardiomyopathy. It shows that NTproBNP correlates significantly with EF. NT-proBNP showed a progressive increase in proportion to the NYHA classification. These data suggest that NT-proBNP is a useful biomarker in the treatment of patients with longstanding hypertension who are at risk for heart failure.

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