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N-TERMINAL PRO-B-TYPE NATRIURETIC PEPTIDE IN PATIENTS WITH HYPERTENSIVE HEART DISEASE

N-TERMINALNI PRO-B-TIP NATRIURETSKOG PEPTIDA KOD PACIJENATA SA HIPERTENZIVNIM SRČANIM OBOLJENJIMA

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Summary: Patients with hypertensive heart disease have elevated concentrations of N-terminal pro-B-type natriuretic peptide (NT-proBNP). The aim of our study was to evaluate NT-proBNP in patients with long-standing hypertension and in patients with signs of hypertensive cardiomyopathy. The study included three groups of 50 subjects: healthy persons (Control Group), patients with hypertension and normal left ventricular systolic function (Group 1) and patients with long-standing hypertension and signs of hypertensive cardiomyopathy with impaired left ventricular systolic function (Group 2). Our results show a very good correlation (Pearson's test) between NT-proBNP in Group 1 and Group 2 and C-reactive protein (Group 1: r = 0.8424; Group 2: r = 0.6650), systolic blood pressure (Group 1: r = 0.7213; Group 2: r = 0.4856), diastolic blood pressure (Group 1: r = 0.4282; Group 2: r = 0.3989) and ejection fraction (Group 1: r = –0.7390; Group 2: r = 0.9111). ROC analysis revealed that the AUC between the Control Group and Group 1 for NT-proBNP (0.912) was not significantly different (p>0.05) from the AUC for systolic (0.924) and diastolic pressure (0.937). A cut-off value for NT-proBNP of 5.89 pmol/L can be used to reliably distinguish patients of Group 1 from the Control Group, and a cut-off value of 21.67 pmol/L reliably separates patients from Group 1 and Group 2 (in both cases, the AUC is 1.000). Patients in Group 2 who belonged to the II and III New York Heart Association (NYHA) class had significantly higher levels of NT-proBNP than those in NYHA class I (ANOVA test, p=0.001).

Kratak sadržaj: Pacijenti sa hipertenzivnim srčanim oboljenjima imaju povišene koncentracije N-terminalnog pro-B-tipa natriuretskog peptida (NT-proBNP). Cilj rada bio je da se izvrši evaluacija razlika u NT-proBNP kod pacijenata sa dugogodišnjom arterijskom hipertenzijom i znacima hipertenzivne kardiomiopatije. Ispitivanje je obuhvatilo tri grupe sa po 50 ispitanika: zdrave osobe (kontrolna grupa), pacijente sa arterijskom hipertenzijom i normalnom sistolnom funkcijom leve komore (grupa 1) i pacijente sa dugogodišnjom arterijskom hipertenzijom i znacima hipertenzivne kardiomiopatije sa oslabljenom sistolnom funkcijom leve komore (grupa 2). Dobijeni podaci pokazali su da NT-proBNP u grupi 1 kao i u grupi 2 veoma dobro koreliše (Pearsonov test) sa CRP (grupa 1: r = 0,8424; grupa 2: r = 0,6650), sistolnim pritiskom (grupa 1: r = 0,7213; grupa 2: r = 0,4856), dijastolnim pritiskom (grupa 1: r = 0,4282; grupa 2: r = 0,3989) i ejekcionom frakcijom (grupa 1: r = –0,7390; grupa 2: r = 0,9111). ROC analiza je pokazala da se AUC izme u kontrolne grupe i grupe 1 za NT-proBNP (0,912) značajno ne razlikuje (p > 0,05) od AUC za sistolni (0,924) i dijastolni pritisak (0,937). Na osnovu *cutoff* vrednosti za NT-proBNP od 5,89 pmol/L mogu se pouzdano razlikovati pacijenti u grupi 1 od kontrolne grupe, dok se pomoću *cutoff* vrednosti od 21,67 pmol/L pouzdano razdvajaju pacijente iz grupe 1 i grupe 2 (u oba slučaja AUC su 1,000). Pacijenti u grupi 2 koji su pripadali II i III New York Heart Association (NYHA) klasi su imali značajno više vrednosti NT-proBNP od onih u I

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Introduction

Identification of patients with arterial hypertension and onset heart failure through the determination of the concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP) allows timely inten-

These data suggest that NT-proBNP is a useful biomarker for distinguishing patients with long-standing hypertension who are at risk of heart failure, allowing optimization and proper treatment of these patients.

Keywords: N-terminal pro-B-type natriuretic peptide, hypertensive heart disease, hypertensive cardiomyopathy

NYHA klasi (ANOVA test, p = 0,001). Ovi podaci ukazuju na to da je NT-proBNP koristan biomarker za razlikovanje pacijenata sa dugogodišnjom arterijskom hipertenzijom kojima preti zastojna srčana slabost, što omogućava optimizaciju i adekvatan tretman ovih pacijenata.

Ključne reči: N-terminalni pro-B-tip natriuretskog peptida, hipertenzivna srčana oboljenja, hipertenzivna kardiomiopatija

sification of therapy and enables clinical physicians to prescribe and implement optimal and appropriate treatment. This significantly improves the quality of life for these patients, by delaying progression of the disease, reducing hospitalizations, lowering the economic burden of health care and the costs of hospital treatment. Detection of heart failure in its initial or early stage and stopping the disease progression are the key concerns for these patients (1–3).

Elevated blood pressure exerts »surplus« mechanical force, damaging the endothelium of the blood vessels and disrupting its function, which contributes to the development of atherosclerosis and its clinical manifestations. At the same time, hypertension causes left ventricular hypertrophy, as an independent factor for the development of arrhythmias, heart failure and sudden death (4–7).

Heart failure is difficult to diagnose, especially in its early stages. Typical clinical symptoms such as rapid breathing, joint swelling and rapid fatigue are often absent in mild cases. Even when these symptoms are present, it is often very difficult to clearly identify this condition, especially in obese and elderly patients with hypertension. Diagnosis of heart failure in its primary stage using only clinical criteria in 50% of cases gives false positive results (8, 9). The most important methods for the diagnosis of heart failure include: echocardiography, radionuclide angiography and magnetic resonance imaging of the heart. But none of these methods is completely reliable or reproducible, and using them in daily practice is expensive and requires considerable time. For clinicians there is a legitimate medical requirement for a biomarker that would be a reliable and objective test to identify hypertensive patients with onset heart failure (10–14).

The aim of our study was to evaluate NT-proBNP in patients with long-standing hypertension and in patients with signs of hypertensive cardiomyopathy. The objectives of the present study were twofold: (*a*) to determine the relationship between the parameters of clinical examination and biomarkers (systolic blood pressure, diastolic blood pressure, ejection fraction, C-reactive protein and creatinine) and NT-proBNP concentrations in patients with hypertensive heart disease, and (*b*) to compare the diagnostic performance of NT-proBNP with that of parameters of clinical examination and biomarkers with respect to heart failure.

Materials and Methods

Subjects and samples

The study included three groups, each consisting of 50 subjects: healthy persons (Control Group), patients with hypertension and normal left ventricular systolic function (Group 1) and patients with long-standing hypertension and signs of hypertensive cardiomyopathy with impaired left ventricular systolic function (Group 2). Control Group comprised healthy adults of both sexes who had been subjected to a routine systematic health examination at the Institute of Occupational Medicine, Military Medical Academy, and voluntary blood donors at the Institute of Transfusion, Military Medical Academy. Patients in Group 1 and Group 2 were treated at the Clinic of Cardiology, Military Medical Academy, and had a diagnosis of heart disease. These patients underwent a clinical examination which included physical examination of the heart with blood pressure, pulse rate, electrocardiogram (ECG) and ECHO cardiogram. Left ventricular ejection fraction (EF) was derived from 2-dimensional echocardiography. Blood samples were taken from all subjects and serum was separated from cells within 60 minutes of collection and centrifuged at 2028 g (4000 rpm) for 10 min. We measured all the biomarkers in a single batch at the Institute of Medical Biochemistry, Military Medical Academy. All study participants gave written informed consent.

Measurements

All the biomarkers were measured according to the manufacturer's instructions. Levels of NT-proBNP were measured by a one-step enzyme immunoassay based on electrochemiluminescence technology on the Elecsys® 2010 platform (Roche Diagnostics). The total imprecision (as CV) was <7% at concentrations of 5 to 488 pmol/L. The reference range, as reported by the manufacturer, was <14.75 pmol/L. Levels of C-reactive protein (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/ Sie-

mens Medical Solutions Diagnostics). The reference range, as reported by the manufacturer, was 53–115 mmol/L (71–115 mmol/L for men and 53–88 mmol/L for women). Inter- and intraassay CVs for CRP and creatinine were <5%.

Statistical analysis

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

The diagnostic value of serum NT-proBNP, creatinine, CRP, ejection fraction (EF), systolic and diastolic blood pressure for identifying heart failure was evaluated using receiver operating characteristic (ROC) curve analysis, and the data are expressed as area under the curve (AUC; 95% confidence interval, 95% CI; standard error, SE), positive and negative predictive value (PV). AUC for these variables were compared, with $p<0.05$ taken as a significant result.

Results

The control group included 25 women and 25 men aged 50–65 years ($\bar{x} \pm$ SD, 56.3 ± 4.20). Group 1 included 19 women and 31 men aged 50–65 years ($\bar{x} \pm$ SD, 57.7 ± 4.57), and Group 2 – 17 women and 33 men aged 50–65 years ($\bar{x} \pm$ SD, 58.1 ± 4.82). The number of patients from Group 2 in a NYHA class was: I (N = 29), II (N = 16) and III (N = 5). Patients from Group 2 who belonged to the II and III New York Heart Association (NYHA) class had significantly higher levels of NT-proBNP than those with NYHA class I (ANOVA test, $p = 0.001$).

In the control group, the mean (SD) values of NT-proBNP, creatinine, CRP, systolic blood pressure, diastolic blood pressure and ejection fraction were: 2.794 (1.515) pmol/L, 85.5 (12.4) μmol/L, 2.64 (1.02) mg/L, 126.9 (9.5) mm/Hg, 81.2 (4.9) mm/Hg, and 67.2 (4.5) %, respectively.

In patients with hypertension (Group 1), the mean (SD) values of NT-proBNP, creatinine, CRP, systolic blood pressure, diastolic blood pressure and ejection fraction were: 9.575 (5.449) pmol/L, 90.9 (13.7) μmol/L, 2.73 (1.07) mg/L, 146.3 (9.4) mm/Hg, 92.2 (5.0) mm/Hg, and 60.8 (5.3) %, respectively. The values of NT-proBNP, creatinine, systolic and diastolic blood pressure were significantly higher, while ejection fraction values were significantly lower in Group 1 than in controls.

In patients with hypertension and cardiomyopathy (Group 2), the mean (SD) values of NT-proBNP, creatinine, CRP, systolic blood pressure, diastolic blood pressure and ejection fraction were: 204.60 (84.93) pmol/L, 90.9 (14.3) μmol/L, 4.17 (1.03) mg/L, 150.5 (6.3) mm/Hg, 95.5 (11.0) mm/Hg, and 48.0 (6.0) %, respectively. The values of NT-proBNP, CRP and systolic blood pressure were significantly higher, while ejection fraction values were significantly lower in Group 2 than in controls and in Group 1. Creatinine and diastolic blood pressure were higher in Group 2 only as compared to controls.

In Group 1, NT-proBNP correlated significantly with all the determined parameters (creatinine, r = 0.3379, 95% CI 0.0657–0.5633; CRP, r = 0.8424, 95% CI 0.7369–0.9079; systolic blood pressure, r = 0.7213, 95% CI 0.5542–0.8325; diastolic blood pressure, r = 0.4282, 95% CI 0.1701–0.6313; ejection fraction, r = –0.7390, 95% CI –0.8438 – –0.5800). In Group 2, NT-proBNP correlated significantly with CRP (r = 0.6650, 95% CI 0.4745–0.7960), systolic blood pressure (r = 0.4856, 95% CI 0.2396–0.6730), diastolic blood pressure (r = 0.3989, 95% CI 0.1355–0.6095) and ejection fraction (r = –0.9111, 95% CI –0.9489 – –0.8478).

Table I Data from ROC analyses for NT-proBNP, creatinine, systolic blood pressure (sBP), diastolic blood pressure (dBP) and ejection fraction (EF) for comparing patients with hypertension (Group 1) versus Control Group. AUC for NT-proBNP was not significantly different from AUC for sBP and dBP ($p > 0.05$).

	NT-proBNP (pmol/L)	Creatinine (μmol/L)	sBP (mm/Hg)	dBP (mm/Hg)	EF (%)
AUC	0.912	0.603	0.924	0.937	0.811
SE	0.0302	0.0565	0.0281	0.0256	0.0434
95% CI	0.838–0.959	0.501–0.700	0.853–0.967	0.869–0.975	0.720–0.882
Sensitivity	94.0	80.0	98.0	100.0	94.0
Specificity	80.0	40.0	68.0	78.0	60.0
Cutoff	4.74	96	140	85	60
(+) PV	82.5	57.1	75.4	82.0	70.1
(–) PV	93.0	66.7	97.1	100.0	90.9

Table II Data from ROC analyses for NT-proBNP, creatinine, CRP, systolic blood pressure (sBP), diastolic blood pressure (dBP) and ejection fraction (EF) for comparing patients with hypertension and cardiomyopathy (Group 2) versus Control Group. AUC for NT-proBNP was not significantly different from AUC for sBP and EF ($p > 0.05$).

	NT-proBNP (pmol/L)	Creatinine (μmol/L)	CRP (mg/L)	sBP (mm/Hg)	dBP (mm/Hg)	EF (%)
AUC	1.00	0.596	0.867	0.984	0.947	0.999
SE	0.00	0.0567	0.0369	0.0128	0.0235	0.0025
95% CI	0.963–1.000	0.493–0.693	0.785–0.927	0.936–0.998	0.883–0.981	0.962–1.000
Sensitivity	100.0	66.0	94.0	98.0	100.0	100.0
Specificity	100.0	54.0	64.0	90.0	82.0	98.0
Cutoff	5.89	92	3.8	140	85	58
(+) PV	100.0	58.9	72.3	90.7	84.7	98.0
(–) PV	100.0	61.4	0.867	0.984	0.947	0.999

Table III Data from ROC analyses for NT-proBNP, CRP, systolic blood pressure (sBP) and ejection fraction (EF) for comparing patients with hypertension (Group 1) versus patients with hypertension and cardiomyopathy (Group 2). AUC for NT-proBNP was significantly different from the other AUC ($p < 0.05$).

	NT-proBNP (pmol/L)	CRP (mg/L)	sBP (mm/Hg)	EF (%)
AUC	1.000	0.838	0.631	0.951
SE	0.000	0.0405	0.0556	0.0225
95% CI	0.963–1.000	0.750–0.904	0.528–0.725	0.889–0.984
Sensitivity	100.0	90.0	58.0	100.0
Specificity	100.0	64.0	70.0	76.0
Cutoff	21.67	3.8	145	52
(+) PV	100.0	71.4	65.9	80.6
(–) PV	100.0	86.5	62.5	100.0

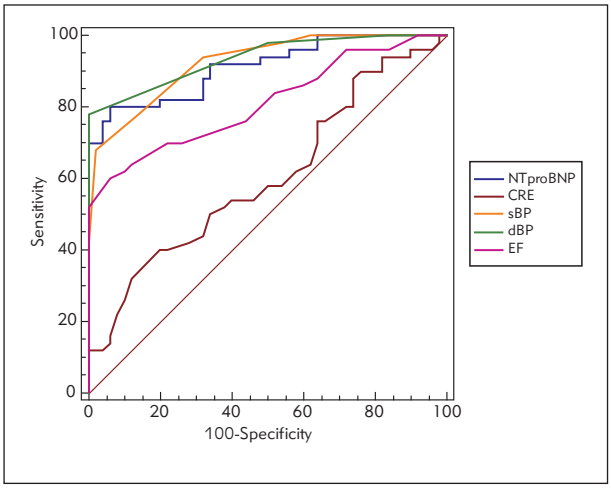

Figure 1 ROC curves for NT-proBNP, creatinine (CRE), systolic (sBP) and diastolic blood pressure (dBP) and ejection fraction (EF) for distinguishing between controls and Group 1.

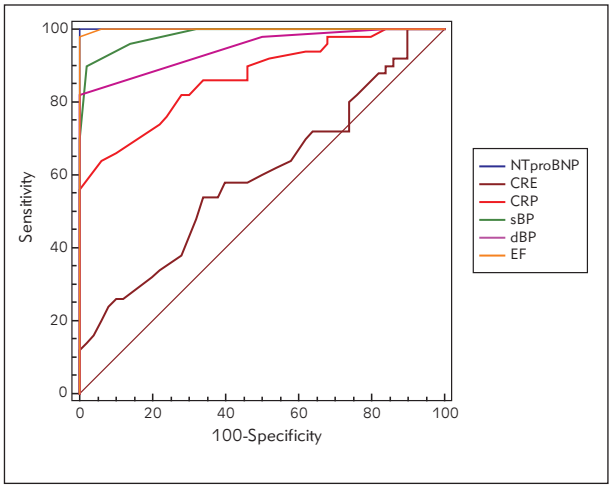

Figure 2 ROC curves for NT-proBNP, creatinine (CRE), CRP, systolic (sBP) and diastolic blood pressure (dBP) and ejection fraction (EF) for distinguishing between controls and Group 2.

In order to determine the diagnostic accuracy of NT-proBNP and the other parameters for detection of heart failure in the investigated groups of patients, ROC plots were calculated. The data from ROC analyses are presented in *Table I–III*. ROC plots are shown in *Figures 1–3*.

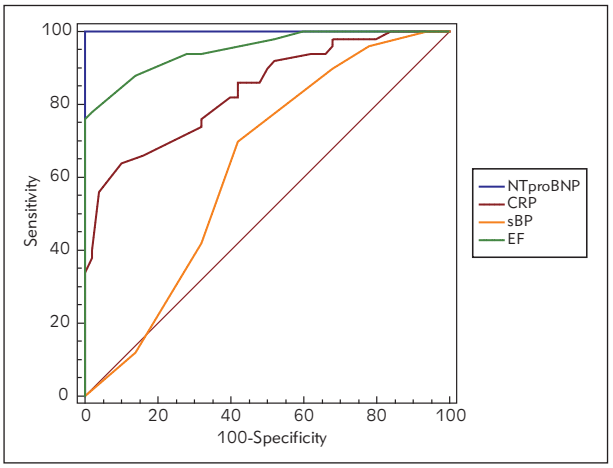

Figure 3 ROC curves for NT-proBNP, CRP, systolic blood pressure (sBP) and ejection fraction (EF) for distinguishing between Group 1 and Group 2.

Discussion

N-terminal proBNP (NT-proBNP) is becoming more heavily integrated into clinical practice as a diagnostic and prognostic biomarker. Clinical biomarker testing in the settings of heart failure has three important goals: 1) to identify possible underlying (and potentially reversible) causes of heart failure; 2) to confirm the presence or absence of the heart failure syndrome; and 3) to estimate the severity of heart failure and risk of disease progression (13–14).

We demonstrated that NT-proBNP is an accurate biomarker for distinguishing between patients with hypertension and patients with hypertension and cardiomyopathy. The AUC for NT-proBNP was significantly different from the AUC for creatinine, CRP, systolic and diastolic blood pressure and ejection fraction ($p < 0.05$) (*Table III* and *Figure 3*). The area under the curve for NT-proBNP was 1.000 (SE = 0.000; 95% confidence interval, 0.963–1.000), and the cutoff concentration with the highest diagnostic accuracy was 21.67 pmol/L (sensitivity 100%; specificity 100%;). Nakamura et al. (6) reported that NT-proBNP displayed satisfactory accuracy associated with a high AUC (0.97) with a threshold value of 50 pg/ml (5.9 pmol/L) for the diagnosis of heart failure in patients with hypertensive heart disease.

We demonstrated, however, that NT-proBNP can distinguish between healthy subjects and a group of patients with hypertension in the same way as systolic blood pressure and diastolic blood pressure. Natriuretic peptides are moderately increased (20–100%) in some but not all patients with systemic hypertension as compared to controls where blood pressure is normal. The increase of these peptides is related to left ventricular mass index, left ventricular hypertrophy and diastolic left ventricular dysfunction. The concentrations of natriuretic peptide in plasma were not significantly increased in hypertensive patients with normal left ventricular geometry as compared to normotensive individuals (17, 18).

Several clinical trials have shown that NT-proBNP is increased in patients with ventricular dysfunction and that its level is directly correlated with the severity of disease (I–IV in the New York Heart Association – NYHA classification). Some of these tests show that NT-proBNP is a sensitive marker of cardiac function, which, when on the rise, indicates the presence of heart failure; on the other hand, when the level of NT-proBNP is within the normal limits, it excludes cardiac dysfunction (9, 19). Patients with hypertension and cardiomyopathy who belonged to the II and III New York Heart Association (NYHA) class had significantly higher levels of NT-proBNP than patients in the NYHA class I. Seino et al. (7) 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 validated in this study.

Recent data have also confirmed the association between increased serum concentrations of CRP and functional limitation and prognosis (but not with the severity of left ventricular ejection fraction) (20). Values of CRP and systolic blood pressure were significantly higher, and the ejection fraction values were significantly lower in the group of patients with hypertension and cardiomyopathy than in the healthy individuals and patients with hypertension.

Conclusion

The presence of elevated levels of NT-proBNP was more frequent in patients with hypertensive heart disease than in the group of »healthy« persons (Control Group). The values of NT-proBNP were significantly higher in patients with signs of hypertensive cardiomyopathy than in the group of patients with hypertensive heart disease. These data suggest that NT-proBNP is a useful biomarker for distinguishing patients with long-standing hypertension who are at risk of heart failure, allowing optimization and proper treatment of these patients. Therefore, at this time, NT-proBNP testing should still be considered only as part of the diagnostic evaluation in heart failure, but not the diagnostic definition.

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Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

References

1. Moe GW, Howlett J, Januzzi JL, Zowall H. N-terminal pro-B-type natriuretic peptide testing improves the management of patients with suspected acute heart failure: primary results of the Canadian prospective randomized multicenter IMPROVE-CHF study. Circulation 2007; 115: 3103–10.
2. Tang WH, Francis GS. The year in heart failure. J Am Coll Cardiol 2007; 50: 2344–51.
3. Jonsson A, Edner M, Alehagen U, Dahlström U. Heart failure registry: a valuable tool for improving the management of patients with heart failure. Eur J Heart Fail 2010; 12: 25–31.
4. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347: 161–7.
5. Ogino K, Ogura K, Kinugawa T, Osaki S, Kato M, Furuse Y, et al. Neurohumoral profiles in patients with hypertrophic cardiomyopathy: differences to hypertensive left ventricular hypertrophy. Circ J 2004; 68: 444–50.
6. Nakamura M, Endo H, Nasu M, Arakawa N, Segawa T, Hiramori K. Value of plasma B type natriuretic peptide measurement for heart disease screening in a Japanese population. Heart 2002; 87: 131–5.
7. Seino Y, Ogawa A, Yamashita T, Fukushima M, Ogata K, Fukumoto H, et al. Application of NT-proBNP and BNP measurements in cardiac care: a more discerning marker for the detection and evaluation of heart failure. Eur J Heart Fail 2004; 6: 295–300.
8. Braunwald E. Congestive heart failure: a half century perspective. Eur Heart J 2001; 22: 825–36.
9. Cowie MR, Jourdain P, Maisel A, Dahlstrom U, Follath F, Isnard R, et al. Clinical applications of B-type natriuretic peptide (BNP) testing [Review]. Eur Heart J 2003; 24: 1710–8.
10. Clerico A, Del Ry S, Giannessi D. Measurement of cardiac natriuretic hormones (atrial natriuretic peptide, brain natriuretic peptide, and related peptide) in clinical practice: the need for a new generation of immunoassay methods [Review]. Clin Chem 2000; 46: 1529–34.
11. Mair J. Role of cardiac natriuretic peptide testing in heart failure [Editorial]. Clin Chem 2002; 48: 977–8.
12. Dajak M, Ignjatović S, Majkić-Singh N. Značaj određivanja srčanih natriuretičnih peptida u srčanoj insuficijenciji. Jugoslov Med Biohem 2003; 22: 311–7.
13. Tang WH, Francis GS, Morrow DA, Newby LK, Cannon CP, Jesse RL, et al; NACB Committee. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: clinical utilization of cardiac biomarker testing in heart failure. Clin Biochem 2008; 41: 210–21.
14. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology: developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 2008; 10: 933–89.
15. Muller T, Gegenhuber A, Poelz W, Haltmayer M. Head-to-head comparison of the diagnostic utility of BNP and NT-proBNP in symptomatic and asymptomatic structural heart disease. Clin Chim Acta 2004; 341: 41–8.
16. Richards M, Troughton RW. NT-proBNP in heart failure: therapy decisions and monitoring. Eur J Heart Fail 2004; 6: 351–4.
17. Yamamoto K, Burnett JC Jr, Jougasaki M, Nishimura RA, Bailey KR, Saito Y, et al. Superiority of brain natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy. Hypertension 1996; 28: 988–94.
18. Yasumoto K, Takata M, Ueno H, Tomita S, Tomoda F, Inoue H. Relation of plasma brain and atrial natriuretic peptides to left ventricular geometric patterns in essential hypertension. Am J Hypertens 1999; 12: 921–4.
19. Fruhwald FM, Fahrleitner A, Watzinger N, Fruhwald S, Dobnig H, Schumacher M, et al. Natriuretic peptides in patients with diastolic dysfunction due to idiopathic dilated cardiomyopathy. Eur Heart J 1999; 20: 1415–23.
20. Windram JD, Loh PH, Rigby AS, Hanning I, Clark AL, Cleland JG. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. Am Heart J 2007; 153: 1048–55.

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