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Full Length Research Paper

Prognostic value of N-terminal pro-B-type natriuretic peptide in patients with non-ST-segment elevation acute coronary syndromes

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The aim of this study was to compare the predictive value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and other frequently used biomarkers, such as creatine kinase (CK), creatine kinase-mB (CK-MB), cardiac troponin T (cTnT) and C-reactive protein (CRP) for systolic and diastolic left ventricular function (SLVF and DLVF), and adverse coronary events in patients with non-ST-segment elevation acute coronary syndrome. The research was carried out within a group of 75 patients. Patients with referent NT-proBNP levels (<14.75 pmol/l) had significantly less compromised SLVF as compared to patients with elevated NT-proBNP levels. Initially determined levels of NT-proBNP showed statistically significant correlations with all parameters of left ventricular function measured on the control examination, while other biomarkers, except creatine kinase, did not. High sensitivity and negative predictive value of NT-proBNP for SLVF (up to 95.1 and 88.9%, respectively) and adverse coronary events (up to 100.0%) was found. These results make us assume that NT-proBNP may be the single best predictor of left ventricular function in patients with non-ST-segment elevation acute coronary syndromes.

Key words: Cardiovascular disease, serum biomarkers, left ventricular function, myocardial infarction, unstable angina.

INTRODUCTION

Acute coronary syndromes are a major cause of morbidity and mortality (Goodman et al., 2009). The term "acute coronary syndrome" (ACS) refers to a range of thrombotic coronary artery diseases, including unstable angina (UA) and both ST-segment elevation (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) (Achar et al., 2005; Thygesen and Alpert, 2001). Advances in our understanding of the pathophysiology of ACS have led to the marked increase in development of biomarkers for diagnosis, risk stratification, therapeutic decision-making and assessment of clinical outcomes (Anderson et al., 2007; Bonaca and Morrow, 2008; Moe and Wong, 2010). There are several biomarkers that are widely used for the previously mentioned purposes (Loria et al., 2008; Tousoulis et al.,

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2008; Eggers et al., 2009; Park et al., 2011), which reflect different pathophysiological aspects of non-ST-segment elevation acute coronary syndrome (NSTE-ACS), such as minor myocardial cell injury, inflammation, platelet activation or neurohormonal activation.

Neurohumoral activation of the heart can be monitored by measurements of systemic levels of natriuretic peptides (NPs) secreted from the heart (Miller et al., 2007; Piechota et al., 2008; Di Angelantonio et al., 2009). Ischemia and myocardial damage cause transient and permanent increase in wall tension and myocardial stretch (Lindahl et al., 2005). Brain (B-type) natriuretic peptide (BNP) and its more stable counterpart N-terminal pro-BNP (NT-proBNP) (Mueller et al., 2004) are synthesized in ventricular myocardium and released into the circulation in response to ventricular dilatation and pressure overload (de Lemos and Morrow, 2002; Hall, 2004). BNP and NT-proBNP are elevated in patients with ACS and can identify ACS patients who are at higher risk for adverse cardiovascular events (Jernberg et al., 2002; Godkar et al., 2008). It is estimated that elevated levels of NPs in patients with ACS are associated with 3 to 5-fold higher risk of death or heart failure compared to patients with low concentrations (Scirica et al., 2010).

The primary aim of this study was to assess the correlation between levels of NT-proBNP and echocardiographic parameters of systolic and diastolic ventricular function in patients with NSTE-ACS, as well as to assess the prognostic value NT-proBNP for adverse coronary events. The secondary aim of our study was to compare the prognostic value of NT-proBNP for both echocardiographic results and adverse coronary events with prognostic values of other frequently used biomarkers of ACS, such as creatine kinase (CK), creatine kinase-MB (CK-MB), cardiac troponin T (cTnT) and C-reactive protein (CRP). To our knowledge, no study investigated the correlations between all these ACS biomarkers and echocardiographic parameters of left ventricular function.

MATERIALS AND METHODS

Subjects

The research was carried out within a group of 75 patients who were consecutively admitted to the Clinic for Urgent Internal Medicine, Military Medicine Academy (MMA), Belgrade. All patients met the criteria for ACS diagnosis (the presence of two out of these three criteria is enough to diagnose ACS): (1) Chest pain, (2) Electrocardiographic changes (ST elevation or depression ≥ 1 mm, or T wave inversion), and (3) Serum cardiac markers changes (CK, CK-MB and TnT) (Kumar and Cannon, 2009).

When choosing patients for subjects of this study, we had in mind that NT-proBNP levels can be elevated in individuals older than 75 even if they do not have any cardiovascular disease, as well as that some diseases can be accompanied by elevated levels of NT-proBNP (patients with arterial hypertension (systolic blood pressure > 160 mmHg, diastolic > 90 mmHg), signs of heart failure, congenital or acquired heart defects, ventricular fibrillation, pulmonary hypertension, chronic respiratory diseases, acute and chronic renal insufficiency, hyperthyroidism, hypothyroidism, Cushing's syndrome, diabetes, etc.) (Balion et al., 2008). All patients admitted to the hospital were asked about existence of any excluding criteria earlier in their life. If they did not meet the excluding criteria, they were included to the study. Also, all patients that were initially included, but met any of the excluding criteria after some time, were excluded from the study; results from the initial examination were removed from the study data, and they did not participate in the control examination. Twenty percent of the admitted patients were excluded before or during the study duration. The study was approved by ethical committee of Military Medical Academy, Belgrade.

Protocol

The research was designed as a prospective clinical study. It consisted of two parts: The first, initial examination and the second, control examination, 6 months later. The examination included blood sampling and echocardiographic examination. Three independent physicians who made echocardiographic exams were not involved in biochemical analysis. The values of echocardiographic parameters of left ventricular function presented in the results are calculated means of the data obtained from the three physicians.

Levels of NT-proBNP, creatine kinase (CK), creatine kinase-MB (CK-MB), cardiac troponin T (cTnT) and C-reactive protein (CRP) were determined in the blood. Echocardiographic examination (transthoracic echocardiography) included determination of parameters of systolic and diastolic left ventricular function. Systolic left ventricular function (SLVF) was assessed by determining ejection fraction (EF) and fraction shortening (FS), while diastolic left ventricular function (DLVF) was assessed by determining the ratio of early to late peak filling velocity (PE/PA: peak early/peak atrial (late) filling velocity ratio), deceleration time of early diastolic flow (DT) and left isovolumetric ventricle relaxation time (IVRT).

Since it was suggested that natriuretic peptide levels reach their peak around 24 h after hospitalization (Gill et al., 2004), NT-proBNP levels in serum were determined 24 h after hospitalization of the patient. NT-proBNP levels were determined by Roche NT-proBNP electrochemiluminescence immunoassay on a Roche Elecsys 2010 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) according to the manufacturer's protocol. This method was described previously (Karl et al., 1999). Other biochemical analyses (CK, CK-MB, cTnT and CRP) were routinely determined in Central Biochemical Laboratory, MMA. Because cTnT is generally not detected in the blood of healthy persons, the cut off value for elevated cTnT level may be set to slightly above the upper limit of the performance characteristics of the assay for a normal healthy population. For the assay we used, the cut off value was 0.03 µg/L.

Based on the level of NT-proBNP, subjects were divided into two groups: (1) Group 1 (G1): values lower than 14.75 pmol/L, and (2) Group 2 (G2): values higher than 14.75 pmol/L. Some patients changed the group after the control examination, due to elevated or increased levels of NT-proBNP.

Echocardiography was done with ultrasound device, Agilent Sonos 5500 (Philips Medizin Systeme, Boeblingen, Germany). Systolic function was considered normal if EF > 50.0% and FS = 28.0 to 42.0%, while criteria for normal dyastolic functions included: PE/PA = 1.9 ± 0.6 (for patients under 50) and 1.1 ± 0.3 (for patients over 50), DT = 179 ± 20 (for patients under 50) and 210 ± 36 (for patients over 50), and IVRT 76 ± 11 (for patients under 50) and 90 ± 17 (for patients over 50).

Statistics

Statistical analysis was done using SPSS 10.0 for Windows. To

Table 1. Characteristics of the investigated groups.

Parameter	Initial examination		Control examination	
	Group 1	Group 2	Group 1	Group 2
Number of patients (n)	18 (29.0%)	44 (71.0%)	13 (21.0%)	49 (79.0%)
Sex (male/female)	14 / 4	35 / 9	11 / 2	37 / 12
Age (X ± SD years)	60.0 ± 6.6	70.0 ± 5.0	65.0 ± 3.0	67.0 ± 8.0
NT-proBNP				
(X ± SD pmol/l)	5.9±3.2	157.0 ± 178.0	4.3 ± 7.0	58.8 ± 231.0
Number of patients (n)	18	44	13	49

NT-proBNP: N-terminal pro-B-type natriuretic peptide.

Table 2. Levels of serum biomarkers in the initial and control examination.

Parameter	Initial examination			Control examination		
	Group 1	Group 2	Test	Group 1	Group 2	Test
NT-proBNP (pmol/L)	5.9 ± 3.2	157.0 ± 178.0	p < 0.01	4.3 ± 7.0	58.8 ± 231.0	p < 0.01
CK (u/L)	85 ± 69	253 ± 62	p < 0.01	55 ± 36	178 ± 42	p< 0.01
CK-MB (u/L)	11 ± 5	39 ± 23	p < 0.05	9 ± 3	17 ± 4	p > 0.05
CRP (mg/L)	2.1 ± 1.8	6.9 ± 2.3	p < 0.05	2.1 ± 1.8	4.8 ± 1.5	p < 0.05
TnT (+/-)	0/18	18/26	p < 0.01	0/13	0/49	p > 0.05

NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase-Mb; cTnT, cardiac troponin T; CRP, C-reactive protein.

represent the results, methods of descriptive statistics were used (measures of central tendency and variability; means, mean ± SD, percentages, minimum and maximum), as well as graphical and tabular representation. For the analysis of the data, the following test were used: Student T test, Chi square test, linear correlation, sensitivity, and specificity and positive and negative predictive value were calculated.

RESULTS

Out of the 75 patients who participated in the first examination, 7 patients did not show up on the second control examination, while there was a lethal event in 6 patients. Thus, their results were excluded from analysis, except for the part of the study that researched the correlation between lethal event end biochemical parameters (Tables 6 and 7). Primary data about patients are shown in Table 1.

Levels of serum biomarkers

Levels of ACS biomarkers are shown in Table 2. In the first examination, elevated levels of CK (> 190 u/L) were found in 8 (45.0%) patients of Group 1 and 40 (90.0%) patients of Group 2. Three (17.0%) G1 patients and 26 (59.0%) G2 patients had elevated levels of CK-MB (> 24 u/L). Two (11.0%) G1 patients and 24 (55.0%) G2 patients had elevated levels of CRP (> 5 mg/l). Positive TnT was not found in G1 patients, while it was found in 18 (41.0%) G2 patients.

In the control examination, elevated levels of CK and CK-MB were not found in G1 patients. In G2 patients, 13 (22.5%) patients had elevated CK levels, while CK-MB levels were between reference limits. G1 patients did not have elevated CRP values, while 8 (16.3%) G2 patients did. Positive TnT was not found in either group.

Seven patients who were initially classified to the G1 group had elevated levels of NT-proBNP on the second examination, so they moved to the G2 group. Two patients from the G2 group moved to the G1 group due to lowered levels of NT-proBNP.

Systolic and diastolic left ventricular function

Results of echocardiographic examination of systolic and diastolic left ventricular function are shown in Table 3. Group 2 had significantly lower values of EF than group 1, both in initial and control examination. All parameters

Table 3. Echocardiographic parameters of SLVF and DLVF in the initial and control examination.

Parameter			Group 1		Group 2		Test
			Min-Max	X ± SD	Min-Max	X ± SD	
Initial examination	SLVF	EF (%)	55 - 65	56 ± 4	25 - 65	49 ± 9	P<0.01
		FS (%)	22 - 37	31 ± 8	12 - 41	30 ± 7	P>0.05
	DLVF	PE/PA	0.9 - 1.2	1.1 ± 0.1	0.8 - 1.1	0.9 ± 0.0	P<0.05
		DT (ms)	203 - 221	213 ± 7	212 - 239	229 ± 8	P<0.05
		IVRT (ms)	89 - 117	97 ± 7	88 - 121	112 ± 7	P<0.05
Control examination	SLVF	EF (%)	45 - 65	57 ± 7	35 - 60	52 ± 8	P<0.05
		FS (%)	26 - 38	30 ± 6	19 - 37	27 ± 9	P>0.05
	DLVF	PE/PA	0.9 - 1.4	1.2 ± 0.2	0.8 - 1.2	0.9 ± 0.2	P<0.01
		DT (ms)	201 - 222	209 ± 9	205 - 231	225 ± 7	P<0.01
		IVRT (ms)	87 - 106	94 ± 9	88 - 111	105 ± 8	P<0.05

SLVF,Systolic left ventricular function; DLVF, diastolic left ventricular function; EF, ejection fraction; FS, fraction shortening; PE/PA, ratio of early to late peak filling velocity; DT,deceleration time of early diastolic; IVRT, left isovolumetric ventricle relaxation time.

of DLVF were also statistically different between groups in both examinations.

Correlation between serum biomarkers and echocardiographic parameters of LVF

In G1, the only significant correlation was found between NT-proBNP and DT ($p < 0.01$ and 0.676) and NT-proBNP and IVRT ($p < 0.05$ and 0.586), in the initial examination. In G2, NT-proBNP significantly correlated with all SLVF and DLVF parameters in both examinations (Figure 1).

Specificity, sensitivity and predictive value of NT-proBNP for LVF

Based on the data about frequency of normal and compromised systolic and diastolic left ventricular function in groups (Table 4), we acquired the results about NT-proBNP specificity, sensitivity and predictive value for SLVF and DLVF (Figure 2).

Coefficients of correlation between levels of biomarkers (CK, CK-MB, CRP, TnT and NT-proBNP) assessed in the initial examination and echocardiographic parameters of LVF assessed in the control examination are shown in Table 5. NT-proBNP showed statistically significant correlation with all LVF parameters (except PE/PA of group 1), CK showed some correlations but less significant than NT-proBNP, while other biomarkers (CK-MB, CRP and TnT) showed no correlation with any of the LVF parameters.

Adverse coronary events

Frequency of adverse coronary events (heart failure (HF), unstable angina (UA) and acute myocardial infarction (AMI), as well as lethal event (LE)) between the initial and control examination was similar between groups (22.2% in G1 and 25.0% in G2), but patients from G1 had only UA (22.2%), while patients from G2 experienced more serious adverse coronary events (UA (11.3%), AMI (6.8%) and HF (6.8%), and almost 12.0% of them died.

Average values of ACS biomarkers assessed in the initial examination in patients who suffered coronary events are shown in Table 6.

Patients who suffered UA (n = 9) had values of NT-proBNP from 2.52 to 411.8 pmol/L, patients who suffered heart failure (n = 3) had 42.4 to 672.0 pmol/l, patients who suffered AMI (n = 3) had NT-proBNP values from 61.8 to 832.0 pmol/L, while patients who suffered lethal event (n = 6) had NT-proBNP values from 204.4 to 6147.0 pmol/L.

The diagnosis of the rest 41 patients during the time between the initial and control examination was stable angina or some minor signs of ACS, which can be viewed as a success of therapy applied. NT-proBNP showed high sensitivity (100.0%) for AMI, HF and LE, while its specifity for adverse coronary events and lethal event was low (maximum, 30.5%) (Table 7).

DISCUSSION

Advances in our understanding of the pathophysiology of

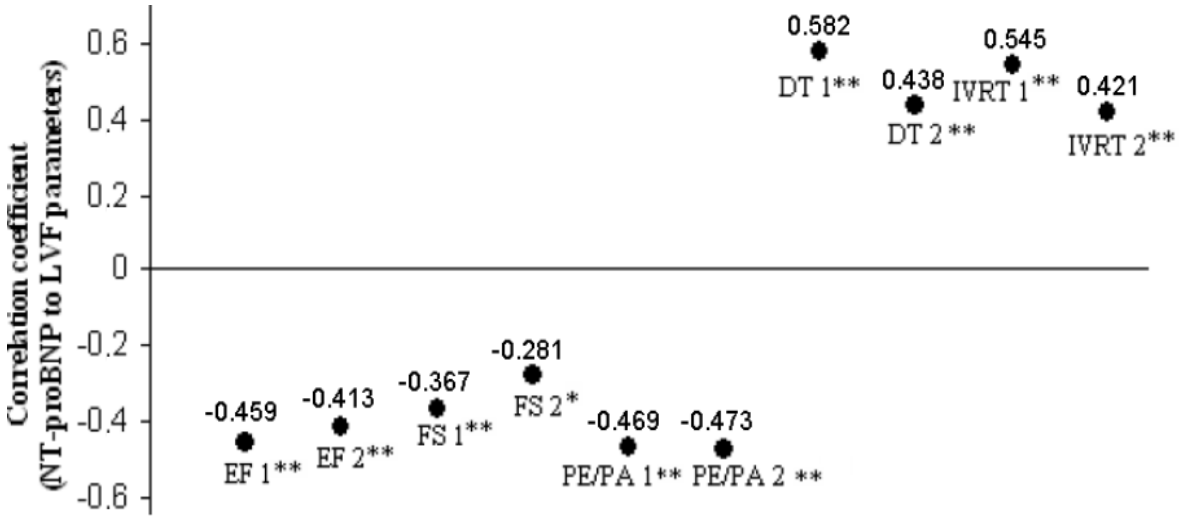

Figure 1. Correlation between NT-proBNP and echocardiographic parameters of LVF of patients from Group 2. *, p < 0.05; **, p<0.01; NT-proBNP, N-terminal pro-B-type natriuretic peptide; EF 1, ejection fraction on the examination 1; EF 2, ejection fraction on the examination 2; FS 1, fraction shortening on the examination 1; FS 2, fraction shortening on the examination 2; PE/PA 1, ratio of early to late peak filling velocity on the examination 1; PE/PA 2, ratio of early to late peak filling velocity on the examination 2; DT 1, deceleration time of early diastolic flow on the examination 1; DT 2, deceleration time of early diastolic flow on the examination 2; IVRT 1, left isovolumetric ventricle relaxation time on the examination 1; IVRT 2, left isovolumetric ventricle relaxation time on the examination 2.

Table 4. Frequency of normal and compromised LVF in patients in the initial and control examination.

Parameter	Initial examination		Control examination	
	Group 1	Group 2	Group 1	Group 2
Normal SLVF	16 (89.0%)	5 (11,4%)	10 (77.0%)	7 (14,3%)
Compromised SLVF	2 (11.0%)	39 (88,6%)	3 (23.0%)	42 (85,7%)
Normal DLVF	3 (16,7%)	0 (0.0%)	4 (30,8%)	11 (23.0%)
Compromised DLVF	15 (83,3%)	44 (100.0%)	9 (69,2%)	38 (77.0%)

SLVF, Systolic left ventricular function; DLVF, diastolic left ventricular function.

ACS have led to the marked increase in development of biomarkers for diagnosis, risk stratification, therapeutic decision-making, and assessment of clinical outcomes. To be useful in clinical practice, a predictor should also improve the selection of the most effective treatment strategy. When evaluating NT-proBNP, we wanted to challenge it against the best predictors of outcome and treatment efficacy of ACS (CK, CK-MB, CRP and TnT).

Levels of ACS biomarkers

Hess et al. (2005b) suggested that in the elderly population, a cut-off level of 125 pg/ml (14.75 pmol/L; 1 pg/ml = 0.118 pmol/L) is useful either to exclude cardiac dysfunction in symptomatic individuals or to risk stratify elderly individuals in terms of the necessity for intervention. Thus, our subjects were classified into these groups according to their NT-proBNP levels, and there was higher number of patients (> 70.0% of all examinees) in group 2 (levels of NT-proBNP higher than 14.75 pmol/L) as expected, since it was shown in earlier studies that patients with NSTE-ACS have elevated levels of NT-proBNP (Sabatine et al., 2002; Lindahl et al., 2005; Jernberg et al., 2004; Heeschen and Hamm, 2004). It was also suggested that the NT-proBNP level increases with the level of symptoms as assessed by New York Heart Association (NYHA) classification and the level of impaired left ventricular dysfunction as assessed by echocardiography (Bay et al., 2003; Pfister et al., 2004; Hess et al., 2005a; Drewniak et al., 2008; Kaski et al., 2010). Numerous studies indicate that levels of NT-proBNP in ACS patient can vary between very low and very high (James et al., 2003; Heeschen and Hamm, 2004; Hess et al., 2005a), for example in a study by Khan et al. (2009) median NT-proBNP was 1106.6 pmol/L, and

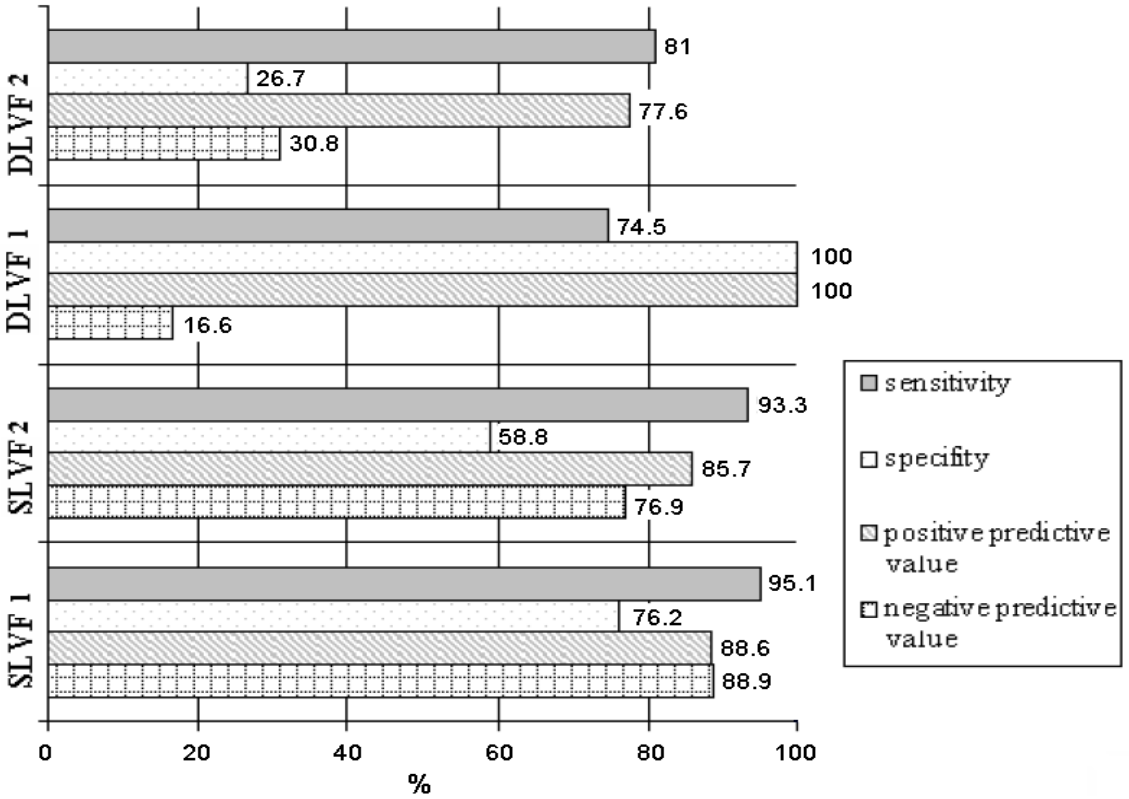

Figure 2. NT-proBNP specificity, sensitivity and predictive value for SLVF and DLVF. NT-proBNP, N-terminal pro-B-type natriuretic peptide; SLVF1, SVLF on the initial examination; SLVF2, SLVF on the control examination; DLVF1, DVLF on the initial examination and DLVF2: DLVF on the control examination.

Table 5. Correlation between initial levels of ACS biomarkers and echocardiographic parameters of LVF on the control examination.

Parameter		SLVF		DLVF		
		EF	FS	PE/PA	DT	IVRT
CK	Group 1	-0.245	-0.176	-0.315	0.573*	0.548
	Group 2	-0.254	-0.215*	-0.255	0.328*	0.331*
CK-MB	Group 1	-0.325	-0.097	-0.211	0.167	0.365
	Group 2	-0.283	-0.228	-0.254	0.178	0.169
CRP	Group 1	0.023	-0.026	-0.418	0.347	0.399
	Group 2	0.195	-0.143	-0.216	0.231	0.159
TnT	Group 1	-0.038	0.054	-0.305	0.247	0.312
	Group 2	-0.098	0.076	-0.227	0.185	0.152
NT-proBNP	Group 1	-0.832**	0.614*	-0.278	0.676*	0.586*
	Group 2	-0.427**	0.536**	-0.281*	0.573**	0.323*

*, $p<0.05$; **, $p<0.01$; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase-Mb; cTnT, cardiac troponin T; CRP, C-reactive protein; SLVF, systolic left ventricular function; DLVF, diastolic left ventricular function; EF, ejection fraction; FS, fraction shortening; PE/PA, ratio of early to late peak filling velocity; DT, deceleration time of early diastolic; IVRT, left isovolumetric ventricle relaxation time.

Table 6. Levels of ACS biomarkers in patients who suffered adverse coronary events.

Biomarker	Group	Adverse coronary event			
		HF	UA	AMI	LE
CK (u/L)	G1	/	125	/	/
	G2	194	159	133	242
CK-MB (u/L)	G 1	/	6	/	/
	G2	9	8	26	34
CRP (mg/L)	G1	/	2.7	/	/
	G 2	7.1	5.2	6.5	11.4
TnT (+/-)	G 1	-	-	-	/
	G 2	-	+	+	-
NT-proBNP (pmol/L)	G 1	/	4.6	/	/
	G 2	396.0	243.0	476.0	1232.0

G1, Group 1; G2, Group 2; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CK, creatine kinase; CK-MB,creatine kinase-Mb; cTnT, cardiac troponin T; CRP, C-reactive protein; HF, heart failure; UA, unstable angina; AMI, acute myocardial infarction; LE, lethal event.

Table 7. NT-proBNP specificity, sensitivity and predictive value for adverse coronary events.

Biomarker	Sensitivity (%)	Specifity (%)	Positive predictive value (%)	Negative predictive value (%)	Adverse coronary event
NT-proBNP	100.0	30.5	6.8	100.0	HF
	55.6	26.4	11.4	77.8	UA
	100.0	30.5	6.8	100.0	AMI
	100.0	29.0	12.0	100.0	LE
CK	33.3	20.3	20.8	85.7	HF
	66.6	20.7	12.5	78.6	UA
	100.0	23.7	6.2	100.0	AMI
	100.0	53.2	17.1	100.0	LE
CK-MB	0.0	45.3	0.0	72.7	HF
	0.0	45.3	0.0	72.7	UA
	100.0	55.9	10.34	100.0	AMI
	50.0	22.6	5.9	82.4	LE
CRP	66.7	59.3	7.7	97.2	HF
	33.3	56.6	11.5	83.3	UA
	100.0	61.0	11.5	100.0	AMI
	100.0	58.1	18.7	100.0	LE
TnT	0.0	69.5	0.0	93.2	HF
	12.5	68.0	5.6	81.8	UA
	100.0	74.6	16.7	100.0	AMI
	33.3	71.0	10.0	91.7	LE

NT-proBNP, N-Terminal pro-B-type natriuretic peptide; CK, creatine kinase; CK-MB, creatine kinase-mB; cTnT, cardiac troponin T; CRP, C-reactive protein; HF, heart failure; UA, unstable angina; AMI, acute myocardial infarction; LE, lethal event.

range 0.3 to 34 135 pmol/L. Based on the cardiovascular mortality, in a study by Alehagen et al. (2007), the critical plasma NT-proBNP concentration was set to ~200 pmol/L (~1692 ng/L). Concentrations above these threshold were associated to a 5 to 24-fold increased risk of cardiovascular mortality.

Observed lower levels of NT-proBNP in the control examination compared to its levels in the initial examination, which was a consequence of applied therapy, were associated with better clinical findings in the control examination. Levels of NT-proBNP showed downward trend over time (months) in some other studies (Gill et al., 2004; Eggers et al., 2009). Lindahl et al. (2005) took patients' blood samples at baseline, day 2, 6 weeks, 3 months, and 6 months, and NT-proBNP levels were found to decrease throughout the whole sampling period, rapidly in the early phase followed by a more gradual decline.

Regarding values of other biomarkers measured in the examinations (CK, CK-MB, CRP and TnT), they showed behavior similar to NT-proBNP (they were higher in patients from group 2, and they showed improvement six months later).

Systolic and diastolic left ventricular function

Results of echocardiography conducted in the initial examination showed that patients from Group 2 (patients with higher levels of NT-proBNP) had significantly lower EF than patients from group 1 ($p < 0.01$), while FS was similar among groups. Since it is thought that ischemia is a basic cause of increased NT-proBNP levels, it was expected that patients with normal peptide levels would have larger EF values. Although many studies found that NT-proBNP level increases with the level of left ventricular dysfunction, some studies did not find that kind of correlation (Fernández-Bergés et al., 2010). Coppola et al. (2009) showed that NT-proBNP levels in patients with ACS were higher even though cardiac function was maintained (LVEF 54.7 ± 7.6%). In another study, NT-proBNP was sensitive enough to detect patients with increased risk even in the subgroup without impaired ejection fraction and expected lower risk of adverse events (Schnabel et al., 2005). NT-proBNP represents a valuable indicator for left ventricular dysfunction, and the fact that elevated NT-proBNP levels can be recorded in asymptomatic individuals and in individuals with unimpaired ejection fraction indicates that NT-proBNP may recognize cardiac dysfunction earlier than standard methodology used by cardiologists (Hess et al., 2005a).

Regarding diastolic left ventricular function in the initial examination, G2 patients had significantly lower values of PE/PA ($p < 0.05$) and significantly higher DT and IVRT ($p < 0.05$). Impaired diastolic function was characteristic of both groups, but in Group 2 this function was more severely compromised. High percentage of patients with average NT-proBNP but still with impaired DLVF suggests that diastolic function disorder is not necessarily followed by NT-proBNP level increase. Changes in NT-pro-BNP concentration are directly related to systolic function disorder, but no relation with diastolic function of the left ventricle was found. Jernberg et al. (2004) compared the results of a few clinical trials regarding NT-pro-BNP and discovered that increased NT-proBNP was followed by a decrease in systolic and diastolic heart functions, but the correlation between NT-proBNP values and SFLV parameters was higher than the correlation of T-pro-BNP and DLVF.

Comparing parameters of SLVF assessed in the initial and in the control examination, EF increased in both groups, so the significance of difference between groups was slightly lower than the initial examination ($p < 0.05$). EF increase was followed by the fall of NT-proBNP values in all patients. DLVF also improved, but significance of difference between groups was still high (for PE/PA and DT: $p < 0.01$ and for IVRT: $p < 0.05$).

Correlation between serum biomarkers and echocardiographic parameters of LVF

Since correlation between SLVF parameters and NT-proBNP among patients from Group 1 was not found in either examination, we assumed that changes in SLVF cannot be assessed by monitoring NT-proBNP levels, if NT-proBNP is within normal range. Regarding group of patients that had high NT-proBNP levels (G2), correlation was found between all NT-proBNP and all parameters of SLVF and DLVF. This shows that increased NT-pro-BNP levels are directly related to parameters of left ventricle systolic and diastolic function, which is not the case for normal peptide levels.

Regarding other biomarkers, only CK correlated with FS, DT and IRVT. This proves that NT-proBNP is a potent diagnostic aid as a means of identifying patients with systolic or diastolic dysfunction (Seino et al., 2004).

Specificity, sensitivity and predictive value of NT-proBNP for LVF

Based on the data for prevalence of normal and compromised systolic and diastolic left ventricular function among patients from different groups, sensitivity, specificity, positive and negative predictive values of NT-proBNP for SLVF and DLVF were calculated. Sensitivity of NT-proBNP for SLVF in both examinations was high (95.1 and 93.3%, respectively). These high levels of sensitivity, found also in other studies (Emdin et al., 2005; Foote and Pearlman, 2004; Bay et al., 2003), suggest that NT-proBNP may be valid marker for SLVF estimation. Sensitivity of NT-proBNP for DLVF was lower than for SLVF, while specificity in the initial examination was 100%. Lubien et al. (2002) studied 294 patients with

ACS and found high specificity (83.0%) and sensitivity (85.0%) of NT-proBNP for DFLV. That NT-proBNP can be an independent predictor of diastolic dysfunction was confirmed in a study by Tschöpe et al. (2005), who researched the role of NT-proBNP in the diagnostics of diastolic dysfunction and its correlation to echo-cardiographic and invasive measurements. Regarding predictive value of NT-proBNP, Tschöpe et al. (2005) found out that NT-proBNP had the best negative predictive value of all methods investigated, Bay et al. (2003) suggested that the negative predictive value of having a "normal" value of NT-proBNP is very high (98.0%) and NT-proBNP therefore seems to be a valuable tool for excluding a decreased LVEF at the time of admission to hospital. In this study, negative predictive value of NT-proBNP for SLVF was 88.9% (initial examination) and 76.9% (control examination), while for DLVF it was low (16.6 and 30.8%). Positive predictive values for SLVF and DLVF were higher, 77.6 to 100.0%.

Adverse coronary events

The prevalence of adverse coronary events in groups was similar (G1: 22.2% and G2: 25.0%), but the fact that no patient with normal NT-proBNP level suffered AMI, HF and especially LE, while patients with elevated NT-proBNP levels did, emphasizes the predictive value of elevated NT-proBNP for these adverse events. Numerous studies aimed to determine the predictive value of the elevated NT-proBNP levels for adverse coronary events (Omland et al., 2002; Sabatine et al., 2002; Boersma et al., 2000; Baggish et al., 2010) and convincingly show that NT-proBNP provides strong prognostic information for an unfavourable outcome (death, cardiovascular death, readmission or cardiac events) in patients with heart failure or asymptomatic left ventricular dysfunction. NT-proBNP was also declared as useful additional prognostic information to many scores, such as TIMI (Thrombolysis in Myocardial Infarction) or GRACE (Global Registry of Acute Coronary Events) risk score (Khan et al., 2009; Bazzino et al., 2004).

In this study, levels of NT-proBNP higher than 42.4 pmol/L warn about possible development of heart failure, levels higher than 61.8 pmol/L point out to the acute myocardial infarction as possible adverse coronary event, and levels higher than 204.4 pmol/L warn about possible lethal event in ACS patients. Those results are slightly higher than the ones observed by Kay et al. (2003) who reported that heart failure is unlikely at NT-proBNP values < 300 pg/ml (35.4 pmol/L) and very likely at NT-proBNP values > 450 pg/ml (53.1 pmol/L).

Our results showed that NT-proBNP had high sensitivity (100.0%) for AMI, HF and LE, while negative predictive value ranged from 77.8% for UA to 100.0% for HF. Although these results are similar to results of other studies (Heeschen and Hamm, 2004), they should be taken with reserve, since our number of patients who suffered those adverse coronary events was small.

Conclusions

This study showed that ACS patients with referent NT-proBNP levels have significantly less compromised systolic left ventricular function compared to ACS patients with elevated NT-proBNP levels. Initially determined levels of NT-proBNP showed statistically significant correlations with all parameters of left ventricular function measured on the control examination, while other biomarkers, except creatine kinase, did not. Also, NT-proBNP showed high sensitivity and predictive value for systolic left ventricular function. These results make us assume that NT-proBNP may be the single best predictor of left ventricular function in patients with non-ST-segment elevation acute coronary syndromes.

In this study, levels higher than 42.4 pmol/L pointed out to possible adverse coronary events, while levels higher than 204.4 pmol/l pointed out to the possible lethal event, but those numbers should be taken with reserve, since the range of normal blood NT-proBNP concentration depends on the method of determination and even on the producer of the reagents used.

General limitations of our study are the small number of participants and the fact that they were recruited from a single intensive care unit. But, these data should be indicators for NT-proBNP dynamics in Serbian population, since Military Medical Academy is representative national hospital.

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