ORIGINAL SCIENTIFIC ARTICLE

NT-PROBNP IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION WITHOUT HEART FAILURE

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ABSTRACT

NT-proBNP is marker of acute heart failure. Recent investigation implicate its role in different cardiac and non-cardiac diseases and different mechanism of release in patients with STEMI and NSTEMI. Our study included 66 patients with diagnosis of acute myocardial infarction, hospitalized in Clinical Centre Kragujevac. We evaluated standard biochemical analysis including NT-proBNP, electrocardiography, transthoracic echocardiography and coronary angiography. The most common cardiovascular risk factors were emotional stress (93,94%), and physical inactivity(81,82%). NT-proBNP values were higher in patients with AMI vs health volunteers (943 vs. 162,5 pg/ml, p = 0,0001), NSTEMI vs STEMI patients (1427 pg/ml vs. 592 pg/m, p = 0,005), patients with culprit lesion on left vs right coronary artery (1421 vs. 548, p =0.02), and anterior vs inferior location AMI (1714vs. 625, p =0.022). We found positive correlation NT-proBNP values with CRP, urea, creatinine, and negative correlation with triglicerides, hemoglobin, left ventricular ejection fraction. Higher values of NT-proBNP values are recorded in patients with AMI, NSTEMI, anterior location AMI and with culprit lesion on left coronary artery.

Keywords: *Acute myocardial infarction, NT-proBNP.*

INTRODUCTION

Discovering natriuretic peptides caused progress in cardiology emphasizing endocrine heart function.NT-proBNP is marker mostly used for diagnosis of acute heart failure. Recent studies showed high level of this marker in acute myocardial infarction (AMI), and in other different cardiac and non-cardiac diseases (1). Mechanism of its synthesis and release in AMI is still controversial. Some experimental studies identified myocardial stretch and increase in intraventricular pressure as causes of higher values of this marker (2). Releasing this marker in patients with acute cardiac disease can be protective according to its mechanism of action and final outcome.

MATERIAL AND METHODS

Our study included 66 patients with diagnosis of AMI (33 STEMI (ST Elevation Myocardial Infarction) and 33 NSTEMI (Non ST Elevation Myocardial Infarction)).

Inclusion criteria:

- diagnosis of AMI (STEMI: chest pain more than 30 min., ST segment elevation at least in two consecutive leads(with the cut-off point being > 0.2 mV in leads V1, V2, or V3, and > 0.1 mV in the other leads),positive troponin; NSTEMI: chest pain more than 30 min., ST segment abnormalities (except ST elevation), positive troponin),
- age ≥ 18 years,
- hospitalization at Clinic of cardiology, Clinical Centre Kragujevac, Serbia,
- voluntary written informed consent prior to enrollment in the study.

Exclusion criteria: acute heart failure, (≥ Killip 2), renal and respiratory failure.

Anamnesis(criteria for physical inactivity: < 30 min./day), electrocardiography (ECG)and blood samples from the antecubital vein (in order to evaluate standard biochemical analysis including NT-proBNP) were eveluated first day of hospitalization. During hospitalization we performed transthoracic echocardiography to evaluate left ventricular ejection fraction (LVEF) and coronary angiography to evaluate culprit lesion.

The study protocol was approved by the Ethical Committee of Clinical Center Kragujevac, Serbia.

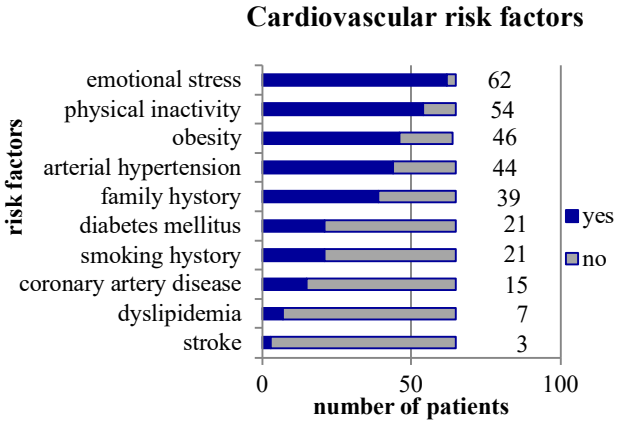
Statistical analysis

Categorical variables are expressed as count with percentages. Continuous variables with non-normal distribution are expressed as median with first and third quartiles (Q1, Q3). Differences between continuous variables were analyzed using Mann-Whitney test. Correlation between variables was performed using Spearman correlation test. The statistical significance level was set at $p<0.05$. The data was analyzed using commercially available software IBM SPSS Statistics for Windows, version 26.0 (IBM Corporation, Armonk, New York).

RESULTS

Gender distribution was not similar, we included 49 (74.2%) men and 17 (25.8%) women. Mean age of patients was 64,45 ±10,36years. The most common symptoms were chest pain (63 patients - 95,45%)and weakness(56 patients - 84,85%). Graphic 1 summarizes cardiovascular (CV) risk factors in patients with AMI: the most common were emotional stress (62 patients - 93,94%), physical inactivity (54 patients - 81,82%) and obesity (46 patients - 69,69%) (graphic 1.)

Graphic 1. Cardiovascular risk factors in patients with acute myocardial infarction



ECG showed that more than half of patients (34 patients - 53,04%) had AMI anterior left ventricle location. Ventricular extrasystoles (39 patients - 59.09%) were the most common heart rhythm disorder. Ventricular fibrillation was recorded in 3 patients (4.45%) and atrioventricular blocks in 2 patients (3,03%)(table 1).

Coronary angiography was performed in 61 (92,42%) patients. Distribution of culprit lesions were equal on left anterior descending artery (LAD) (34,85%) and right coronary artery (RCA) (34,85%) (Table 2). One-vessel disease was recorded in 26 (39,39%) patients and multi-vessel disease in 35 (53,03%) patients.

NT-proBNP values were higher in patients with AMI vs. reference range in health volunteers (943vs. 162,5 pg/ml, p = 0,0001), NSTEMIvs. STEMI (1427 pg/ml vs. 592 pg/m, p = 0,005), culprit lesion on left vs.right coronary artery (1421 vs. 548, p =0.020), and anterior vs inferior location AMI (1714 vs 625, p=0.022). We didn't found statistically significant difference depending of gender and number of coronary artery vessel disease (Table 3).

Table 1. Heart rhythm disorders in patients with AMI

ECG	AF	VF	RBBB	LBBB	Nodal rhythm	AV block	VES
N (%)	2(3,03)	3(4,54)	3 (4,54)	3 (4,54)	1(1,51)	2(3,03)	39(59,09)

ECG - electrocardiography, AF - Atrial fibrillation, VF - ventricular fibrillation,
LBBB- left bundle branch block, RBBB- right bundle branch block,
AV- atrio-ventricular, VES - ventricular extrasystoles

Table 2. Culprit lesion in patients with acute myocardial infarction

culprit artery %	LCA 65,15%					RCA 34,85%	all
	LM	LAD	LCx	DG	OM	RCA	
N (%)	3 (4,54%)	23 (34,85%)	6 (9,09%)	2 (3,03%)	4 (6,06%)	23 (34,85%)	61 (92,42%)

LCA - left coronary artery, RCA- right coronary artery, LMCA- left main coronary artery,
LAD-left anterior descending artery; LCx -left circumflex artery,
DG- diagonal branch, OM- obtuse marginal

Table 3. pro-BNP values in patients with acute myocardial infraction

Variable		median (25-75 percentile) NT-proBNP (pg/ml)	p (Mann Whitney U)
	AMI	943 (437,5- 2034)	0,0001
	health volunteers	162,5 (125-350)	
AMI	STEMI	592 (315-714)	0,005
	NSTEMI	1427 (658-2438)	
culprit artery	left	1421 (586-2290)	0.020
	right	548 (393-1017)	
location	anterior	1714 (604-2424)	0.022
	inferior	625 (393-1354)	
number of coronary vessel disease	multi-vessel	1354,5 (493,5-2034)	0.124
	one-vessel	660 (254,5-1070,5)	
gender	male	821 (469-1943)	0.528
	female	1439 (367-1987)	

NT-proBNP- pro brain natriuretic peptide; AMI - acute myocardial infarction;
STEMI - ST Elevation Myocardial Infarction; NSTEMI- Non ST Elevation Myocardial Infarction

We found positive correlation pro-BNP values with CRP, urea, creatinine, and negative correlation with triglicerides, hemoglobin, LVEF (Table 4).

Table 4. Correlation between NT-proBNP and other variables

Variables	Correlation coefficient (r)	p (Spearman correlation)
Pro-BNP	1,000	
Glucosae	0,099	0,449
CRP	0,287	0,033
TnI	0,241	0,066
Cholesterol	-0,081	0,520
HDL cholesterol	0,111	0,386

Variables	Correlation coefficient (r)	p (Spearman correlation)
LDL cholesterol	-0,024	0,856
Triglicerides	-0,311	0,012
CKMB	0,157	0,217
Hemoglobin	-0,481	0,000
Urea	0,369	0,003
Creatinine	0,316	0,011
Weight	-0,028	0,828
Height	0,158	0,212
BMI	-0,154	0,225
Heart rate	0,211	0,092
Left ventricular ejection fraction	-0,352	0,004

CRP- C reactive protein; HDL- high density lipoprotein; LDL -low density lipoprotein; CKMB –isoenzyme creatine kinase MB; TnI- Troponin I; BMI - body mass index

DISCUSSION

Our study showed statistically higher values of NT-proBNP in patients with AMI, NSTEMI, anterior location of AMI and culprit lesion on left coronary artery. Also, we found positive correlation NT-proBNP values with CRP, urea, creatinine and negative correlation with triglicerides, hemoglobin, LVEF.

The most common CV risk factors in AMI are emotional stress, physical inactivity and obesity, according to our results. We can explain high participation rate of emotional stress because of its influence on sympathetic as possible trigger of atherosclerotic plaque rupture. Previously reported study described emotional stress as risk factor for one-month re-hospitalization and mortality in patients with acute coronary syndrome (ACS) (3). Pimple et collegues didn't found clear correlation between psychological distress and CVD events, but they found a sex based interaction. In women, higher psychological distress was associated with a higher incidence of CVD events (4). The most common symptom in our study was chest pain. Wouters and collegues showed influence of time onset of chest pain on risk of ACS. Patients with chest pain between 0 and 9 AM have twice higher risk of ACS than those with chest pain in other hours (5).

Initially, NT-proBNP was used for differentiation cardiac and non-cardiac dyspnea. This marker has high prognostic value in combination with National Early Warning Score 2 in patients with acute dyspnea (6). In our study, NT-proBNP was higher in patients with AMI without heart failure vs health volunteers. This marker is higher in patients with coronary artery disease (CAD) without ventricular dysfunction as well as in patients with heart failure without CAD, without significant difference between this two groups. In patients with CAD exist positive association between the ventricular BNP mRNA expression and the plasma BNP concentration, but there is no correlation between atrial BNP mRNA and plasma BNP despite higher expression atrial BNP mRNA. This indicate different stimulus for synthesis in this two localizations (1). Similarly, other studies showed higher values of this marker in patients with higher oxidative stress: patients with multiple CV risk factors (7) and percutaneous coronary interventions (PCI) in spite of stable intraventricular pressure (8).NT-proBNP can serve as a sensitive marker for diagnosis NSTE-ACS patients (9).It is associated with all AMI, but is a more powerful risk factor for microsize than typical MI (10).NT-proBNP level in patients with AMI is independently associated with extent, severity, and complexity of coronary artery disease assessed by SYNTAX score (12).

There are a few explanations for this.

Myocardial hypoxia increase the local BNP gene expression (11), but hypoxia, volume overload and mechanical stress induce HIF-1α (hypoxia inducibile factor)which alsoincrease local BNP gene expression. It means that acute myocardial ischemia activate the HIF system, which in turn could amplify the BNP response. Therefore, an increased BNP level may be an indicator of regional myocardial hypoxia or activation of the HIF system, even before the onset of clinical symptoms or reduced coronary blood flow(13).

Exposure of cultured rat cardiomyocytes to specific proinflammatory cytokines (IL-1 β (interleukine -1 beta) and TNF- α (tumor necrosis factor alpha)) results in up regulation of cardiac BNP at transcriptional and translational levels without a corresponding increase in ANP gene expression. Treatment of human adult cardiac fibroblasts with TNF-alpha, IL-1 alpha or TGF- β (transforming growth factor beta) significantly increase NT-proBNP levels compared with untreated cells which suggest that cardiac fibroblasts are a potential source of BNP in the human heart. Therefore, elevated plasma BNP levels might not only reflect increased myocardial stretch but also inflammatory and remodeling processes during AMI(14).

Role of natriuretic peptides is not to counterbalance overloaded pressure, but to regulate oxygen transport through leading to an increased oxygen-carrying capacity per unit volume of blood (15). All conditions that increase the oxygen consumption or change the oxygen diffusion of cardiomyocytes, such as stretch, pressure or metabolic challenges, will ultimately initiate the synthesis and enhance the release of natriuretic peptides from intracellular locations indicating protective effect of natriuretic peptides which could be therapeutic usable.

Possible protective effect of pro-BNP on heart muscle in AMI is limiting the expansion of the infarct zone during reperfusion and ischemia. Cell-protective mechanism is based on cGMP accumulation and opening ATP depending potassium channels (16). Early activation pro-BNPP/cGMP signaling system could be important autocrine/paracrine answer on ischemia. That include inotropic effects, acute regulation of vascular pressure and weakening of sensitivity heart muscle on ischemia, growth suppression and proliferative answer in different myocardial and vascular cells. In ischemic heart, acute treatment with pro-BNP before and during artery occlusion act protective depending of dose. It could be alternative endogenous protective road which could be potentially therapeutically useful (17).

We found higher NT-proBNP values in NSTEMI vs STEMI patients. Recent studies showed higher levels of this marker in STEMI(18), NSTEMI (10,19) or there were no difference in groups (20). Our results suggest larger ischemic insult despite the smaller extent of myocardial necrosis in STEMI patients. Considering the same pathophysiological mechanism of atherosclerotic plaque rupture, and different final result, we can assume that in necrotic tissue released NT-proBNP depends of pre-synthesized NT-proBNP. Synthesis can be present in non-necrotic ischemic tissue and this can explain higher value in NSTEMI patients with higher ischemic insult vs STEMI patients.

Time of evaluating of NT-proBNP could be also key of higher NT-proBNP levels. In our study, in almost all STEMI patients, reperfusion happened after admission (thrombolysis was performed in 25 patients), and NT-proBNP was analized at admission. In patients with NSTEMI ischemic cardiomyocytes which belong to the irrigation area of culprit artery synthesis NT-proBNP. In STEMI patients, in acute phase, borderline cardiomyocytes around infarcted area synthesis NT-proBNP, and in infarcted area released NT-proBNP is probably presynthesized. After reperfusion, survived cardiomyocytes in infarcted area participate in synthesis too, and additionally increase levels of NT-proBNP. In this group of patients, mechanism of overloaded cardiomyocytes in acute heart failure (not clinically significant) can explain additional stimulus for its synthesis. Infarct area suffer higher pressure, resulting in increased NT-proBNP synthesis. Buchner et coauthors could confirm this explanation. They found higher levels in NSTEMI vs STEMI patients but there was a different time to presentation from onset of pain (>48h in NSTEMI, and < 6h in STEMI). They also found increased levels of this marker 24 hours after reperfusion in STEMI patients and no changes in NSTEMI patients (21).

Our results indicate that NT-proBNP level depend of amount of ischemic tissue in AMI. Mathbut et colleagues showed that NT-proBNP value directly correlate with size of myocardial injury on CMR imaging (22). In post-hoc analysis of the On-TIME II trial (STEMI patients to pre-hospital tirofiban administration vs placebo), higher baseline NT-proBNP level and anterior infarct location were independently associated with higher risk of poor myocardial reperfusion (23).This can explain our results of higher NT-proBNP levels in left coronary culprit artery, anterior location AMI and negative correlation with LVEF, as it was found in other papers (24, 25). Sarak et colleagues found the highest NT-proBNP values in patients with left anterior descending artery (LAD) lesions, following by values in circumflex artery (CX) lesionsand inright coronary artery (RCA) lesions. They found statistically significant difference in NT-proBNP values between LAD and RCA lesions but not between LAD-CX and CX-RCA lesions (12). Also, patients with multivessel disease have higher levels of NT-proBNP (26). In our study there was no statistical difference between groups and number of involved patients could be a limit of our study.

We also found positive correlation between pro-BNP values with CRP, urea, creatinine and negative correlation with triglicerides, hemoglobin. Similarly, in recent study with STEMI patients treated by primary percutaneous intervention, Marjanovic and collegues found positive correlation with high-sensitive troponin I, lactate dehydrogenase, urea, creatinine, C-reactive peptides (24).

Higher levels of NT-proBNP is higher in health females and can be explained by positive correlation of NT-proBNP with sex hormone binding protein and inverse correlation with total testosterone, free testosterone and free androgen index (27).We didn't found difference in NT-proBNP levels between females and males, indicating impact of other stimulus (ischemia) than hormonalfor NT-proBNP levels in patients with AMI.

CONCLUSION

NT-proBNP values are higher in patients with AMI, NSTEMI, anterior AMI, and left artery culprit lesion anddepends of amount of ischemic cardio-myocites and type of AMI.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national) and the Helsinki Declaration of 1975, as revised in 2013. Voluntary written informed consent was obtained from each participant prior to enrollment in the study. Study was approved by Ethical

committee of University clinical center Kragujevac, decision number 01/9440.

CONFLICT OF INTEREST

There are no conflicts of interest.

FUNDING

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