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B-type Natriuretic Peptide as Predictor of Heart Failure in Patients with Acute ST Elevation Myocardial Infarction, Single-vessel Disease, and Complete Revascularization: Follow-up Study

Šime Manola[1], Nikola Pavlović[1], Vjekoslav Radeljić[1], Diana Delić Brkljačić[1], Hrvoje Pintarić[1], Krešimir Štambuk[1], Nikola Bulj[1], Matias Trbušić[1], Tomislav Krčmar[1], Ljerka Lukinac[2]

[1]Departmet of Cardiology, Sisters of Mercy University Hospital, Zagreb, Croatia

[2]Department of Oncology and Nuclear medicine, Sisters of Mercy University Hospital, Zagreb, Croatia

Aim To assess the concentration of B-type natriuretic peptide (BNP) as a predictor of heart failure in patients with acute ST elevation myocardial infarction (STEMI) who underwent primary percutaneous coronary intervention (PCI) with successful and complete revascularization.

Methods Out of a total of 220 patients with acute STEMI admitted to the Sisters of Mercy University Hospital in the period January 1 to December 31, 2007, only patients with acute STEMI undergoing primary PCI who had single vessel disease and were successfully revascularized were included in the study. Selected patients had no history of myocardial infarction or heart failure and a normal or near-normal left ventricular ejection fraction (≥50%) assessed by left ventriculography at admission. Only 58 patients met the inclusion criteria for the study. Out of those, 6 patients refused to participate in the study, and another 5 could not be followed up, so a total of 47 patients were evaluated. Blood samples were taken for measurement of BNP levels at admission, 24 hours later, and 7 days later. Patients were followed up for 1 year. The primary outcome was reduction in left ventricular ejection fraction (LVEF) to <50% after 1 year.

Results Patients who developed echocardiographic signs of reduced systolic function defined as LVEF<50% had significantly higher values of BNP (≥80 pg/mL) at 24 hours ($P=0.001$) and 7 days ($P=0.020$) after STEMI and successful reperfusion. Patients who had BNP levels ≥80 pg/mL after 7 days were 21 times more likely to develop LVEF<50 (odds ratio, 20.8; 95% confidence interval, 2.2-195.2; $P=0.008$).

Conclusion BNP can be used as a predictor of reduced systolic function in patients with STEMI who underwent successful reperfusion and had normal ejection fraction at admission.

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Correspondence to:
Nikola Pavlović
Department of Cardiology
Sisters of Mercy University Hospital
Vinogradska cesta 29
10000 Zagreb, Croatia
nikolap12@yahoo.com

Natriuretic peptides are peptides that are released from the heart in situations of pressure and volume overload of the ventricles. There are 3 types of natriuretic peptides: atrial natriuretic peptide, B-type natriuretic peptide (BNP), and C-type natriuretic peptide. Atrial natriuretic peptide is released predominantly from the atria, BNP from the ventricles, and C-type natriuretic peptide from the endothelium (1-4). BNP is a 32-amino acid neurohormone synthesized in the form of pre-proBNP, which is first cleaved to proBNP and then to active BNP and inactive fragment NT-proBNP. Its serum levels are increased in left ventricular dysfunction, atrial fibrillation, acute myocardial ischemia (acute coronary syndromes, acute myocardial infarction), pulmonary embolism, advanced age, renal dysfunction, etc (4). The actions of BNP include natriuresis, vasodilatation, inhibition of renin-angiotensin-aldosterone axis, and inhibition of sympathetic nerve activity.

In the first hours of acute myocardial infarction, BNP is released as a result of ischemia and necrosis of myocardial cells. BNP then rises as a result of systolic and diastolic dysfunction and increased wall stress of the left ventricle (5).

Patients with acute ST elevation myocardial infarction (STEMI) who had higher levels of BNP have been shown to have worse prognosis (death, congestive heart failure, myocardial infarction, and no-reflow phenomenon) (5). Also, patients who died after the STEMI had significantly higher values of BNP (5).

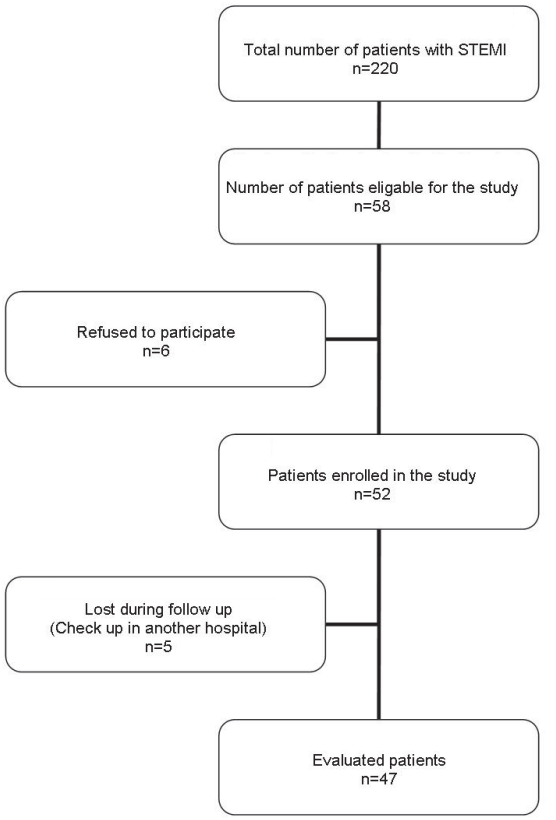
We assessed the predictive value of BNP for heart failure in patients who underwent primary percutaneous coronary intervention (PCI) for acute STEMI with single-vessel disease and the optimal timing for the measurement of BNP. We included only patients with no previous known heart failure and normal or near-normal global left ventricular systolic function at admission (LV≥50%). To our knowledge, none of the previous studies evaluated BNP as predictor of heart failure in STEMI patients with previously normal LVEF who underwent successful reperfusion.

PATIENTS AND METHODS

Patients

From January 1 until December 31, 2007, we prospectively studied 220 patients with acute STEMI admitted to the Sisters of Mercy University Hospital. Only the patients within 12 hours from the onset of symptoms who underwent primary PCI, had only single-vessel disease, underwent complete and successful revascularization (TIMI III flow and MBG III), and had normal or slightly reduced LVEF (≥50%) were included. Patients with cardiogenic shock, symptoms lasting more than 12 hours, significant double-vessel, triple-vessel or left main disease, unsuccessful reperfusion, history of MI, and significant mitral regurgitation were excluded from the study. Among a total of 220 patients with STEMI admitted to our hospital during that period, only 58 met the inclusion criteria. Six patients refused to participate in the study, so 52 patients were included while another 5 patients were lost during the follow-up (had a check up at another hospital). This left the final group of 47 patients (Figure 1). Signed informed con-

Figure 1.



Flowchart of the study. Among 220 patients with acute myocardial infarction, those with cardiogenic shock, symptoms lasting more than 12 hours, significant double-vessel, triple-vessel, or left main disease, unsuccessful reperfusion, history of myocardial infarction, and significant mitral regurgitation were excluded from the study (n = 162). Fifty eighth patients were eligible for the study. STEMI – ST elevation myocardial infarction.

sent for PCI and for participation in the study was obtained before angiography from all patients.

Clinical evaluation

Patients were admitted through the emergency department, where standard history and physical status were taken. They were evaluated for onset and duration of pain, comorbidities, and risk factors. Vital signs and complete physical status were also obtained. In 12 patients, lead electrocardiogram (ECG) was obtained and patients with STEMI were presented to the interventional cardiologist and taken to the catheterization laboratory for primary PCI. All patients were managed and treated according to European Society of Cardiology Guidelines for PCIs (6) and Croatian primary PCI network. Ethical approval of the study was obtained from the hospital Ethics Committee.

Blood sampling

Blood samples were taken for routine laboratory tests (complete blood count, creatinine, electrolytes, glucose, creatine kinase, lactate dehydrogenase, troponin T levels, prothrombin time and activated partial thromboplastin time, C reactive protein, and lipid profile), as well for the measurement of BNP levels. The hospital laboratory sets the normal value of BNP at <18.4 pg/mL. Blood samples were collected into a plastic tube (EDTA 1.5 mg/mL), and concentration of BNP was determined by an immunoradiometric assay (SHIONORIA BNP in vitro test, CIS Bio International, Gif-Sur-Yvette Cedex, France). BNP levels were measured at admission, 24 hours after the PCI, and 7 days after the PCI. Creatine kinase and lactate dehydrogenase levels were monitored until normalization.

Angiography and PCI

Coronary angiography was performed by transfemoral approach. Patients received 300 mg of aspirin and 600 mg of clopidogrel before the procedure. They also received 3000-5000 IU heparin bolus after arterial sheath placement and additional 3000-5000 IU heparin before the PCI (total of 100 IU/kg). Before coronary angiography, left ventriculogram was performed in all patients with 2 standard projections (right anterior oblique 30 and left anterior oblique 60) and LVEF was calculated. At this point, patients with significantly reduced systolic function (LVEF<50%) or significant mitral regurgitation were excluded from the study. After visualizing of left and right coronary artery, provisional stenting of culprit lesion on infarct related artery was done by standard techniques. Use of eptifibatide was decided by the operator. TIMI angiographic scale was used to determine the reperfusion of infarct related artery. During coronary angiography, patients with reduced ejection fraction, more than single-vessel disease, and with unsuccessful reperfusion were excluded from the study (n = 162).

After the procedure, all patients were admitted to coronary care unit, received aspirin 100 mg and clopidogrel 75 mg daily and other standard concomitant therapy (beta blockers, ACE inhibitors, and statins) depending on clinical indications. Patients received low molecular weight heparin during 3-5 days, starting 6 hours from the femoral artery sheath removal. Echocardiography was done in all patients by a standard protocol, 2-4 days after admission; ejection fraction was calculated using the methods by Simpson (7) and Teicholz (8). Diastolic dysfunction, segmental hypo- or akynesis, pulmonary hypertension, and the presence of mitral regurgitation were also recorded. Patients were discharged from hospital 7-10 days after the admission and continued to receive aspirin 100 mg, clopidogrel 75 mg, beta blocker, statin, and ACE inhibitor.

Follow up

All patients were followed at 3, 6, and 12 months. Three months after the myocardial infarction clinical examination, laboratory tests and ECG stress test were done, and 6 and 12 months after the discharge echocardiography and ECG stress tests were done.

End points

Primary end point at 12 months after the myocardial infarction was the reduction in ejection fraction to less than 50%, with or without clinical signs and symptoms of heart failure.

Statistical analysis

Smirnov Kolmogorov test was used to analyze data distribution. According to these findings, appropriate tests were used in further analysis. Chi square test was used to analyze differences in frequencies of qualitative variables. To determine predictive values of BNP levels, binary logistic regression was performed. Ejection fraction after 12 months was used as the dependent variable (0 – ejection fraction ≥50% and 1 – ejection fraction <50%). BNP levels ≥80 pg/mL (0 hours, 24 hours, 7 days), age, sex, positive history of illness, and body mass index (BMI) were used

as predictor variables. *P* value lower than 0.05 was considered significant. SPSS for Windows, version 17.01 (SPSS Inc., Chicago, IL, USA) was used in all statistical procedures except for receiver operating (ROC) analysis which was calculated using MedCalc for Windows, version 11.0 (MedCalc Software, Mariakerke, Belgium).

RESULTS

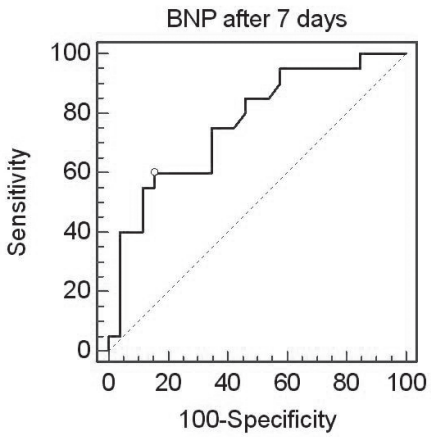
At admission, all 47 patients had normal LVEF (≥55%), and all 47 patients underwent primary PCI with stent implantation (Table 1). Patients were divided in 2 groups depending on whether their BNP values were lower than 80 pg/mL at admission, 24 hours, and 7 days. The cut-off point of BNP levels was set to 80 pg/mL, as described in previous studies (10,11). ROC curve analysis showed that values of BNP≥80 pg/mL had 60.0% sensitivity and 82.2% specificity for predicting reduced ejection fraction after 12 months (Figure 2).

TABLE 1. Clinical and demographic features of studied patients*

Characteristics	No (%) of patients
Age (mean±SD)	58.9 ± 10.3
Sex:	
male	35 (74.5)
female	12 (25.5)
Body mass index (mean±SD)	28.865 ± 4.318
Duration of pain at presentation (minutes)	137.76 ± 94.55
Infarct location:	
anterior	36.17
inferior	59.57
other	2.12
Infarction-related artery:	
LAD	38.29
ACx	12.77
RCA	48.94
Killip class:†	
I	74.47
II	25.53
Previous history:	
hypertension	59.57
diabetes	44.68
smoking	53.19
family history	57.44
hyperlipidemia	42.55
BNP levels (pg/mL):	
at a admission	41.04 ± 50.23
24 h	164.93 ± 94.82
7 d	107.03 ± 137.14
TIMI flow:	
at baseline	0.234 ± 0.427
after reperfusion	3
STENT	100

*Abbreviations: LAD – left anterior descedening artery; ACx – circumflex artery; RCA – right coronary artery ; BNP – brain natriuretic peptide; TIMI – thrombolysis in myocardial infarction; SD – standard deviation.
†Killip class I-IV used for risk stratification of patients with myocardial infarction (9).

Figure 2.



Receiver operating characteristic (ROC) curve analysis for B-type natriuretic peptide (BNP) after 7 days as predictor of reduced ejection fraction after 12 months. Criterion BNP ≥80 pg/mL after 7 days; sensitivity, 60.0% (95% confidence interval, 36.1-80.9); specificity, 82.2% (95% confidence interval, 60.6%-93.4%); area under the ROC curve=0.765; P (area=0.5) <0.001.

At admission, BNP was ≥80 pg/mL in only 8 patients, while in 39 patients it was lower than 80 pg/mL. After follow-up of 12 months, 4 patients out of 8 with BNP over 80 pg/mL had LVEF<50%, and other 4 had LVEF≥50%. Among patients with BNP lower than 80 pg/mL (n=39), 17 (43.5%) had reduced LVEF after 12 months. There was no significant difference between the 2 groups (*P*=0.740) (Table 2).

After 24 hours, there was the greatest number of patients with BNP levels higher than 80 pg/mL (n=37), while there were 10 patients with BNP lower than 80 pg/mL. After 12 months of follow-up, 2 patients with BNP levels lower than 80 pg/mL had LVEF<50% (20.0%), while 19 patients of 37 had LVEF<50% (51.4%). The differences in the number of patients at different time intervals were not significant (*P*=0.770).

After 7 days, there was statistical difference between 2 groups. Eighteen patients had BNP levels higher than 80

TABLE 2. Difference in left ventricular ejection fraction (LVEF) after 12 months of follow-up in patients with brain natriuretic peptide (BNP) levels higher or lower than 80 pg/mL at admission, 24 h, and 7 days

LVEF at time point	No. of patients with BNP (pg/mL)			
	≤80	≥80	Total	*P*
Admission:	39	8	47	
<50	17	4	21	0.740
≥50	22	4	26	
24 h:	10	37	47	
<50	2	19	21	0.770
≥50	8	18	26	
7 d:	29	18	47	
<50	8	13	21	0.003
≥50	21	5	26	

TABLE 3. Median values of BNP at admission, 24 h, and 7 days between 2 groups (normal and reduced ejection fraction after 12 months)*

BNP at	LVEF		
	<50% (21 patients)	≥50% (26 patients)	*P*
0 h	47.19 ± 58.37	36.07 ± 43.14	0.457
24 h	212.93 ± 107.24	126.16 ± 62.01	0.001
7 d	164.60 ± 177.26	69.28 ± 81.56	0.020

*BNP – B-type natriuretic peptide: LVEF – left ventricular ejection fraction.

TABLE 4. Binary logistic regression for prediction of reduced ejection fraction after 12 months*

Variables	OR (95% CI)	*P*
BNP≥80 pg/mL at 0 h	0.10 (0.01-1.58)	0.101
BNP≥80 pg/mL at 24 h	10.40 (0.73-147.13)	0.083
BNP≥80 pg/mL at 7 d	20.76 (2.21-195.16)	0.008
Age (years)	0.98 (0.90-1.06)	0.605
Male sex	0.29 (0.04-2.18)	0.227
BMI	0.76 (0.58-0.99)	0.042
Positive history	0.39 (0.07-2.25)	0.289

*Abbreviations: OR – odds ratio, CI – confidence interval; BNP – B-type natriuretic peptide; BMI – body mass index.

pg/mL and 29 had levels lower than 80 pg/mL. In patients with elevated levels of BNP after 7 days, 13 (72.2%) had LVEF<50% after 12 months of follow-up and among 29 patients with BNP levels lower than 80 pg/mL after 7 days, 8 had LVEF<50% (27.6%) ($P=0.003$).

Also, at 12 months there were 21 patients with LVEF<50% and 26 patients with LVEF≥50%. The group with reduced ejection fraction had higher mean values of BNP at 0 ($P=0.470$), 24 hours, and 7 days with significant difference at 24 hours (P = 0.001) and 7 days ($P=0.020$) (Table 3).

Using binary logistic regression, we found that patients with BNP levels ≥80 pg/mL after 7 days were 21 times more likely to develop EFLV<50 (odds ratio, 20.8; 95% confidence interval, 2.2-195.2, $P=0.008$). Also, patients with lower values of BMI were more likely to develop LVEF<50% (Table 4).

DISCUSSION

We studied the value of BNP in predicting left ventricular systolic dysfunction in patients with STEMI and normal left ventricular systolic function at admission and successful reperfusion. BNP levels were measured at 3 different time points (admission, 24 hours, and 7 days). Our study showed that that BNP in patients who underwent primary PCI due to STEMI with successful reperfusion could serve as a predictor of systolic dysfunction with LVEF<50% after 12 months of follow-up. The risk of developing heart failure with reduced systolic function was higher in patients with elevated BNP levels after 24 hours and 7 days, with a significant increase at 7 days with a cut-off point of 80 pg/mL. BNP levels ≥80 pg/mL after 7 days were found to be an independent risk factor for development of reduced ejection fraction after 12 months, when patients with BNP levels ≥80 pg/mL were 21 times more likely to have a reduced ejection fraction. Also, patients who developed reduced ejection fraction after 12 months had significantly higher mean values of BNP at 24 hours and 7 days. A limitation of the study is a relatively small number of patients, so data should be interpreted with caution. Although we had a total of 220 patients with STEMI, only 58 met the inclusion criteria and in the end only 47 were evaluated. In the first 24 hours, natriuretic peptides are released from the myocardium in response to acute ischemia. Later, BNP is secreted due to myocardial stunning, left ventricular systolic, or diastolic dysfunction as was described in previous studies (4,5). Previous studies have also found that BNP levels at admission could serve as predictor of short and long term mortality after STEMI, worse outcome as well as "no reflow" phenomenon and impaired reperfusion (10,12-14). Also the relation between the level of BNP is associated with the infarct size and infarct mass assessed with cardiac MR and echocardiography (15-17). Although all our patients had single vessel disease and angiographycally successful reperfusion, it is possible that patients who had elevated BNP levels after 7 days had impaired or delayed reperfusion and, therefore, higher risk of

left ventricular remodeling and developing left ventricular systolic dysfunction. This study showed that BNP could serve as a predictor of reduced systolic function in patients who had normal systolic function at admission, single-vessel disease, and were successfully revascularized during the primary PCI. Therefore, in this population BNP could be used to recognize patients who are at high risk for developing heart failure and should be clinically followed more often than others. Due to a relatively small number of patients, more studies are needed to confirm the prognostic value of the BNP for reduced systolic function after percutaneous coronary intervention.

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