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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

The impact of NT-proBNP on admission for early risk stratification of patients undergoing primary percutaneous coronary intervention

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Abstract

Background: Incompleted ST segment resolution (STR) after primary percutaneous coronary intervention (PCI) is associated with worse clinical outcomes.

Aim: To investigate the association between plasma N-terminal pro B-type natriuretic peptide (NT-proBNP) levels on admission and STR after reperfusion, in a patient with ST-segment elevation myocardial infarction (STEMI) undergoing primary PCI.

Methods: After exclusion, 81 consecutive patients with STEMI (mean age: 61.3 ± 13.4 years) undergoing primary PCI were prospectively enrolled in this study. Patients were divided into two groups according to ST-segment resolution: ∑STR < 50%, the no-reflow phenomenon positive (+) group (n = 20), and ∑STR ≥ 50%, the no-reflow phenomenon negative (–) group (n = 61). Patients were followed up for six months.

Results: The no-reflow phenomenon (+) group had similar baseline cardiovascular risk factors (e.g. age, sex, hypertension, diabetes mellitus) but higher mid-term mortality (25% vs. 6.5%, p = 0.02) than the no-reflow phenomenon (–) group. The frequency of anterior MI in the no-reflow phenomenon (+) group was higher (75%, p = 0.02). NT-proBNP levels on admission were higher in the no-reflow phenomenon (+) group (p = 0.001). A NT-proBNP level ≥ 563.4 pg/mL measured on admission had a 72.7% sensitivity and 72.9% specificity in predicting no-reflow phenomenon at ROC curve analysis. At multivariate analysis, anterior MI, high NT-proBNP levels, prolonged chest pain-to-reperfusion time (> 6 h) and post-TIMI-3 flow were independent predictors of no-reflow phenomenon after primary PCI.

Conclusions: Plasma NT-proBNP level on admission is a strong and independent predictor of no-reflow phenomenon following primary PCI and mid-term cardiovascular mortality in patients with STEMI.

Key words: NT-proBNP, ST-segment resolution

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INTRODUCTION

The beneficial effect of the successful restoration of epicardial coronary flow on myocardial salvage may be offset by inadequate tissue perfusion, a condition referred to as the no-reflow phenomenon [1]. So, the focus of reperfusion therapy in patients with acute ST-segment elevation myocardial infarction (STEMI) has shifted from restoring early epicardial patency to improving microvascular perfusion [2].

ST-segment changes reflect myocardial rather than epicardial flow and, hence, yield prognostic information beyond that

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provided by coronary angiogram alone [3]. Numerous studies have shown a remarkably consistent relationship between the degree of ST segment resolution (STR) and subsequent mortality [4].

B-type natriuretic peptide (BNP) and the N-terminal part of its prohormone — NT-proBNP, are released from the cardiac ventricles in response to increased wall stress and to ischaemia per se. Vila et al. [5] demonstrated that plasma NT-proBNP is increased in a model of systemic infection/inflammation in healthy men with normal heart function. Therefore, NT-proBNP is accepted as an acute phase reactant [6]. NT-proBNP level was found to be significantly higher in patients with coronary slow flow compared to a normal flow group [6]. NT-proBNP levels on admission in STEMI patients is a known predictor of cardiovascular (CV) mortality [7, 8]. In the literature, studies investigating the prognostic interaction between initial elevated plasma NT-proBNP levels in patients with STEMI and incomplete STR are available, however often these studies have included patients treated with fibrinolytic agents [7, 8]. When compared to fibrinolytic therapy, there have been only limited studies with primary percutaneous coronary intervention (PCI), which has a higher probability of achieving normalised epicardial coronary perfusion (Thrombolysis in Myocardial Infarction [TIMI] flow grade 2 or 3).

This study investigated whether the initial plasma NT-proBNP levels could predict the status of myocardial tissue perfusion and mid-term mortality in STEMI patients who were treated with primary PCI.

METHODS

Patient population

A total of 81 consecutive patients with STEMI admitted to the emergency department of Erzurum Education and Research Hospital (between September and December 2010) who were treated with urgent cardiac catheterisation procedures were prospectively evaluated. Patients fulfilling the following criteria were included in the study: (i) presentation within 12 hours of the onset of symptoms (typical chest pain lasting for > 30 min); (ii) the amplitude of the ST segments measured 60 ms after J point being ≥ 2 mm in at least two contiguous electrocardiography (ECG) leads; (iii) undergoing primary PCI. The exclusion criteria were as follows: no indication for angioplasty, treatment with coronary bypass surgery, presence of advanced valve disease, left or right bundle branch block, pacemaker rhythm, a history of congestive heart failure, chronic renal disease, TIMI-1 flow after primary PCI, left ventricular (LV) hypertrophy, and infarct history. 12-lead ECGs (having the rate of 25 mm/s and the calibration at amplitude of 1.0 mV/10 mm) were recorded in all patients soon after admission to the hospital. A repeat 12-lead ECG was obtained 60 minutes after restoration of TIMI-2 or 3 flow. ST-segment elevation in mm was measured 20 ms after the J point. The sum of ST-segment elevations were measured in leads I, aVL, and V_1 through V_6 for anterior infarctions, and in leads II, III, aVF, V_5, and V_6 for inferior infarctions. The difference between two measurements was accepted as resolution of the sum of ST-segment elevation and expressed as ∑STR. Patients were separated into two groups thereafter. According to the classification of Schroder et al. [9], patients with ∑STR ≥ 50% were accepted as a no-reflow phenomenon negative (–) group, and patients with ∑STR < 50% were accepted as a no-reflow phenomenon positive (+) group. ST depression was defined as 1 mm ST-segment depression 80 ms from the J point in any lead remote from the infarction site. ST-segment depression normalisation (STDN) was estimated in the lead with the maximum baseline ST depression (the differences between two measurements) [10]. ECGs were analysed by two independent readers blinded to the outcome data. There was 99% concordance for ECG interpretation for the presence of ∑STR and STDN. The study protocol was approved by the local Ethics Committee.

Assessment of biomarkers

Blood sampling for the measurement of serum biomarkers was done in the emergency room before PCI. Measured biomarkers included NT-proBNP and high-sensitivity C-reactive protein (hsCRP). NT-proBNP was quantified using a one-step enzyme immunoassay based on electrochemiluminescence technology (Elecsys 2010, Roche Diagnostics, Mannheim, Germany). The inter- and intra-assay coefficients of variation were both < 3.1%. The sensitivity of the assay was 5 pg/mL. The hsCRP was measured by an immunonephelometric assay (Hitachi High Technologies Co., Tokyo, Japan) with a decision limit of 0.3 mg/dL.

Data sources

Demographic data and clinical history concerning risk factors such as age, sex, diabetes mellitus, hypertension, hyperlipidaemia, smoking, family history of coronary artery disease (CAD), MI and previous drug use were obtained from patients and medical records. Chest pain-to-reperfusion time, door-to-balloon time and the presence of prodromal angina were recorded. In addition, heart rate, blood pressure, waist circumference and body mass index were measured at initial presentation. A physical examination was also performed. Blood values were measured at initial presentation (before catheterisation procedures) and on a daily basis during the hospital stay. Transthoracic echocardiography (TTE) was performed within the first 24 hours after admission to the intensive cardiologic care unit. TTE was performed by using a system V (Vingmed, GE, Horten, Norway) with a 2.5-MHz phased-array transducer. The LV ejection fraction (LVEF) was measured using a modified Simpson's rule.

Coronary angiography, primary angioplasty, and stent implantation

All patients received chewable aspirin (300 mg, unless contraindicated) and clopidogrel (300 mg, loading dose) before

the primary PCI. Angiographic data was obtained from the records of the cardiac catheterisation laboratory. Emergency coronary angiography was performed by the percutaneous femoral approach. In all cases, nonionic low-osmolality contrast media was used. The first injection was performed in the contralateral artery. Flow in the infarct-related artery (IRA) (left anterior descending artery [LAD], circumflex artery [CX], right coronary artery [RCA], and others [intermediate, diagonal, marginal, septal, postero-lateral arteries]) was graded according to the TIMI classification [11]. Heparin (100 U/kg, 60 U/kg if tirofiban used) was administered following the evaluation of coronary anatomy. A coronary artery stenosis of more than 50% was considered clinically significant. Occlusion of the IRA was crossed by using a 0.014-inch guidewire. Primary PCI, including balloon angioplasty, and/or stent implantation were performed only on the IRA as determined by the lesion anatomy.

After angioplasty, all patients were admitted to the coronary care unit, where 1.0 mg/kg subcutaneous low molecular weight heparin was given every 12 hours until hospital discharge (in the absence of bleeding complications). Aspirin (100 mg/day) and clopidogrel (75 mg/day) were continued in all patients. The use of tirofiban was left to the discretion of the interventional cardiologist. All the patients were prescribed acetylsalicylic acid, clopidogrel, beta-blockers, an angiotensin converting enzyme inhibitor, and a statin on discharge. During the follow-up period, these five groups of drugs were administered to all patients.

Definitions

Diabetes mellitus was considered to be present in patients on oral hypoglycaemic agents, insulin, or patients with a known previous diagnosis being controlled only by diet, as well as in patients being discharged from the hospital with a diagnosis of diabetes mellitus and/or a prescription of hypoglycaemic agents. Hyperlipidaemia was defined as the use of lipid-lowering agents, a total serum cholesterol level > 240 mg/dL, or a serum triglyceride level > 200 mg/dL. Chest pain-to-reperfusion time was defined as the interval from the onset of chest pain symptoms to the first balloon inflation. Door-to-balloon time was defined as the time between the hospital admission and balloon inflation. On the basis of the definition of the World Health Organisation, anaemia was described as the presence of a haemoglobin level of less than 13 g/dL in men and 12 g/dL in women. Cardiogenic shock was defined as marked and persistent (> 30 min) hypotension with a systolic arterial pressure lower than 80 mm Hg, in combination with signs of hypoperfusion due to LV dysfunction and mechanical complications. Patients were also evaluated according to the Killip classification**.** Multivessel disease was defined as presence of a stenosis greater than 50% in three major epicardial coronary arteries.

Prodromal angina was defined as typical chest pain episode(s) persisting < 30 minutes either at rest or during effort 24 hours before the onset of STEMI. A positive family history of CAD was defined as documented evidence of CAD in a parent or sibling under the age of 60. CV mortality was defined as sudden death or mortality associated with acute MI, heart failure, or arrhythmia. Reinfarction was described as the elevation of serum creatine kinase-MB enzyme (CK-MB) levels by twice the upper limit of normal values along with ST segment re-elevation. Target vessel revascularisation (TVR) was defined as an angioplasty or a coronary artery bypass surgery due to restenosis or reocclusion in the IRA. Major adverse cardiac events (MACE) were defined as CV mortality, reinfarction, and repeat TVR (percutaneous or surgical). Myocardial blush grade (MBG) was assessed according to the dye density score proposed by Van't Hof et al. [12] in patients with primary PCI, from 0 (no contrast density or abnormal persistence of contrast medium) to 3 (normal contrast density relative to the dye density in uninvolved areas). The coronary flow rates of all patients were measured by the TIMI frame count (TFC) method with cineangiography at 25 frames per second. TFC for each coronary artery was determined from a distal marking point specific for the coronary artery of interest. Since the LAD artery is usually longer than other coronary arteries, the corrected-TFC of the LAD artery was calculated by dividing TFC by 1.7. The TFC of the LAD was assessed either in right anterior oblique projection with caudal angulation or left anterior oblique projection with cranial angulation, while the assessments of the CX artery and RCA were usually performed in straight left anterior oblique projection.

In-hospital and post-discharge follow-up

In hospital mortality, reinfarction, TVR and and MACE were evaluated during the hospital stay, while data regarding the six-month follow-up period was obtained from hospital records or by interviewing patients (directly or by telephone), their families, or their primary physicians.

Statistical analysis

Quantitative variables were expressed as mean value ± SD, and qualitative variables were expressed as per cent (%). Comparison of parametric values between two groups were performed by means of two-tailed Student's *t* test. Categorical variables were compared by the likelihood-ratio χ^2 test or Fisher's exact test. Pearson correlation coefficients examined the degree of association between examined variables. P value < 0.05 was considered as significant. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of NT-proBNP, optimal cut-off value for predicting no-reflow phenomenon after primary PCI in patients with STEMI. The effects of different variables on no-reflow and mid-term CV mortality were calculated in univariate analysis for each. The variables for which the unadjusted p value was < 0.10 in logistic regression analysis were identified as potential risk markers and included in the

full model. The model was reduced by using backward elimination multivariate logistic regression analyses and potential risk markers were eliminated by using likelihood ratio tests. P value < 0.05 was considered as significant and confidence interval (CI) was 95%. The cumulative survival curves for mid-term all cause mortality were constructed with the use of the Kaplan-Meier method with differences assessed with the log-rank test. All statistical studies were carried out with the SPSS program (version 15.0, SPSS, Chicago, IL, USA).

RESULTS

Patient characteristics

Baseline characteristics are shown in Table 1. There were 61 patients in the no-reflow phenomenon (–) group and 20 patients in the no-reflow phenomenon (+) group. There was no significant difference between the groups in age and gender. The patients were predominantly male. With respect to coronary risk factors, there was no significant difference in the presence of diabetes mellitus, hypertension, age or active smoking.

With respect to baseline laboratory status, there was no significant difference in serum lipid profile, glucose level, haemoglobin, platelet and white blood cell count, peak CK-MB, or creatinine, between groups. Also, LVEF, door-to-balloon time and multi-vessel disease were not significantly different between groups. However, chest pain-to-reperfusion time was significantly longer in the no-reflow phenomenon (+) group ($p < 0.001$).

There was no significant difference in involvement of CX, RCA, LAD artery and saphenous graft between groups. In the PCI procedure, stent implantation percentage was similar between groups ($p = 0.38$). Also, there was no significant difference in the stent length or stent diameter between groups.

Overall, in-hospital CV mortality and reinfarction rate was similar in both groups, although CV mortality and reinfarction rate during the six month follow up period was significantly

Table 1. Baseline characteristics of study patients

	No-reflow phenomenon (–) N = 61 (%)	No-reflow phenomenon (+) N = 20 (%)	P
Age [years]	60 ± 13.8	63.5 ± 11.7	0.31
Sex (male)	48 (78.6)	17 (85)	0.54
Hypertension	27 (44.2)	6 (30)	0.26
Diabetes mellitus	11 (18)	4 (20)	0.84
Hyperlipidaemia	13 (21.3)	1 (5)	0.09
Family history of CAD	16 (26.2)	4 (20)	0.53
Current smoker	32 (52.4)	10 (50)	0.85
Prodromal angina	28 (45.9)	9 (45)	0.82
Anterior MI	27 (44.2)	15 (75)	0.02
Prior aspirin use	9 (14.7)	1 (5)	0.25
Prior beta-blocker use	6 (9.8)	2 (10)	0.98
Prior ACE/ARB use	9 (14.7)	1 (5)	0.25
Loop diuretics	2 (3.2)	0 (0)	0.41
Oral antidiabetic drug	5 (8.1)	1 (5)	0.64
Insulin	0 (0)	1 (5)	0.08
Statin	3 (4.9)	1 (5)	0.98
Pre procedural SBP [mm Hg]	133.7 ± 25.9	140.6 ± 26.7	0.34
Pre procedural DBP [mm Hg]	84.6 ± 15.5	93.6 ± 16.1	0.04
Pre procedural heart rate [bpm]	80 ± 22.2	85.2 ± 16.6	0.38
Post procedural SBP [mm Hg]	116.9 ± 26.7	126.5 ± 22.2	0.18
Post procedural DBP [mm Hg]	76.7 ± 17.9	83.2 ± 15.7	0.18
Post procedural heart rate [bpm]	79.8 ± 18.9	78.3 ± 15.2	0.75
∑STR [mm]	7.5 ± 2.3	0.9 ± 0.23	< 0.001
Door-to-balloon time [min]	31.8 ± 7.8	34.8 ± 8.1	0.87
Chest pain-to-reperfusion time [min]	366.4 ± 300.6	810 ± 547.7	< 0.001
Killip class > 1	7 (11.4)	1 (5)	0.5
Admission glucose [mg/dL]	156.2 ± 70.8	156.4 ± 76.1	0.99

→

Table 1. Baseline characteristics of study patients (cont.)

	No-reflow phenomenon (–) N = 61 (%)	No-reflow phenomenon (+) N = 20 (%)	P
Peak CK-MB [U/L]	282.1 ± 221.3	240.5 ± 204.1	0.45
Total cholesterol [mg/dL]	244.9 ± 47.1	195.9 ± 41.2	0.11
LDL-cholesterol [mg/dL]	141.2 ± 38.6	123.2 ± 36.5	0.06
HDL-cholesterol [mg/dL]	40.9 ± 12.4	43.6 ± 10.7	0.39
Triglycerides [mg/dL]	182.3 ± 129.9	155.8 ± 123.7	0.43
Admisson creatinine [mg/dL]	0.89 ± 0.24	0.82 ± 0.26	0.3
Haemoglobin [g/dL]	15.7 ± 1.5	15.1 ± 2.4	0.17
HsCRP [mg/dL]	8.6 ± 1.33	21.8 ± 5.6	< 0.001
NT-proBNP [pg/mL]	693.8 ± 111.1	2251.5 ± 640.4	0.001
LVEF [%]	44 ± 8.8	40.7 ± 9.6	0.58
Stent	56 (91.8)	17 (85)	0.38
Stent length [mm]	19.6 ± 6.2	18.5 ± 5.8	0.53
Stent diameter [mm]	3.14 ± 0.29	3.1 ± 0.29	0.57
Pre TIMI grade 0/1	53 (86.8)	15 (75)	0.21
Post TIMI grade3	57 (93.4)	16 (80)	0.08
Multivessel disease	9 (14.7)	3 (15)	0.98
Tirofiban	44 (72.1)	10 (50)	0.02
Procedure:			0.45
Balloon angioplasty	5 (8.1)	3 (15)	
Stent	8 (13.1)	4 (20)	
Balloon angioplasty + stent	48 (78.6)	13 (65)	
Culprit lesion:			0.4
LAD	29 (47.5)	13 (65)	
CX	11 (18)	4 (20)	
RCA	20 (32.7)	3 (15)	
Others	1 (1.6)	0 (0)	
Duration of hospital stay [days]	4.9 (3.2)	5.5 (3.3)	0.58
In-hospital mortality	3 (4.9)	0 (0)	0.31
Reinfarction	2 (3.2)	0 (0)	0.42
Target-vessel revascularisation	1 (1.6)	0 (0)	0.57
MACE	8 (13.1)	1 (5)	0.34
Cardiogenic shock	3 (4.9)	0 (0)	0.31
6-month follow-up outcomes:			
All-cause mortality			
Cardiac death	4 (6.5)	5 (25)	0.02
Non-cardiac death	0 (0)	0 (0)	–
Reinfarction	4 (6.5)	8 (40)	< 0.001
Target-vessel revascularisation	3 (4.9)	5 (25)	0.009
MACE	6 (9.8)	10 (50)	< 0.001
HF requiring hospitalisation	2 (3.2)	4 (20)	0.01

Mean values (SD) and % (n) are reported for continuous and categorical variables, respectively; CAD — coronary artery disease; MI — myocardial infarction; ACE/ARB — angiotensin converting enzyme/angiotensin receptor blocker; SBP — systolic blood pressure; DBP — diastolic blood pressure; STR — ST segment resolution; CK-MB— creatinine kinase-MB; LDL — low-density lipoprotein; HDL — high-density lipoprotein; HsCRP — high-sensitivity C-reactive protein; NT-proBNP — N-terminal pro-B-type natriuretic peptide; LVEF — left ventricular ejection fraction; TIMI — Thrombolysis In Myocardial Infarction; LAD — left anterior descending artery; CX — circumflex artery; RCA — right coronary artery; MACE — major adverse cardiac events; HF — heart failure

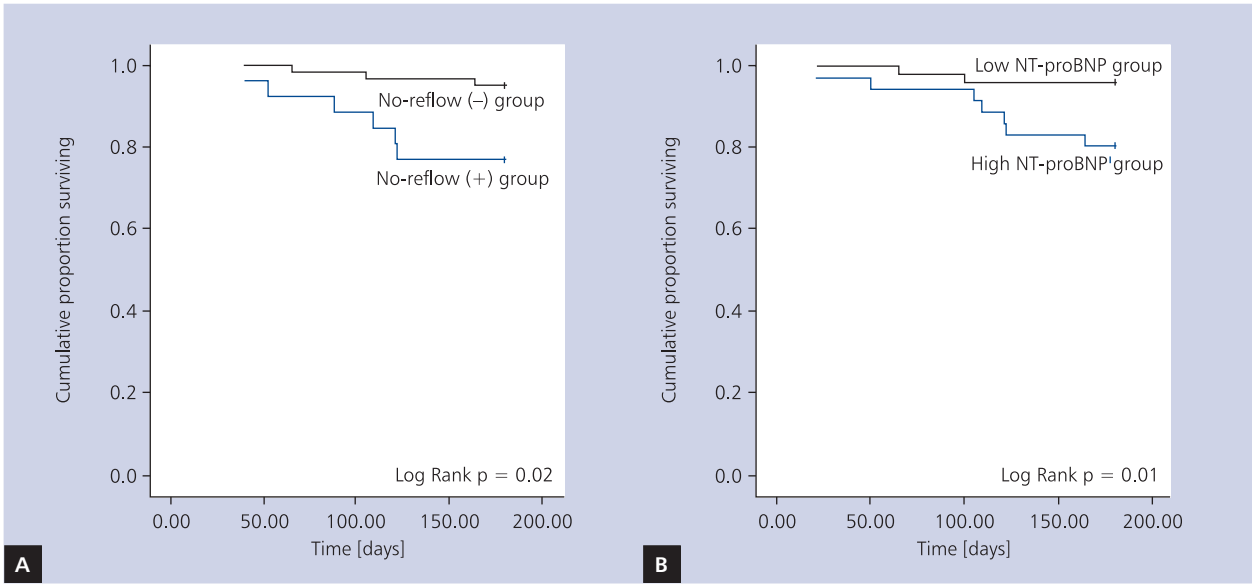

Figure 1. Kaplan-Meier curve for all-cause cardiovascular mortality of patients with no-reflow phenomenon (**A**) and high NT--proB-type natriuretic peptide (NT-proBNP) (**B**) at mid-term

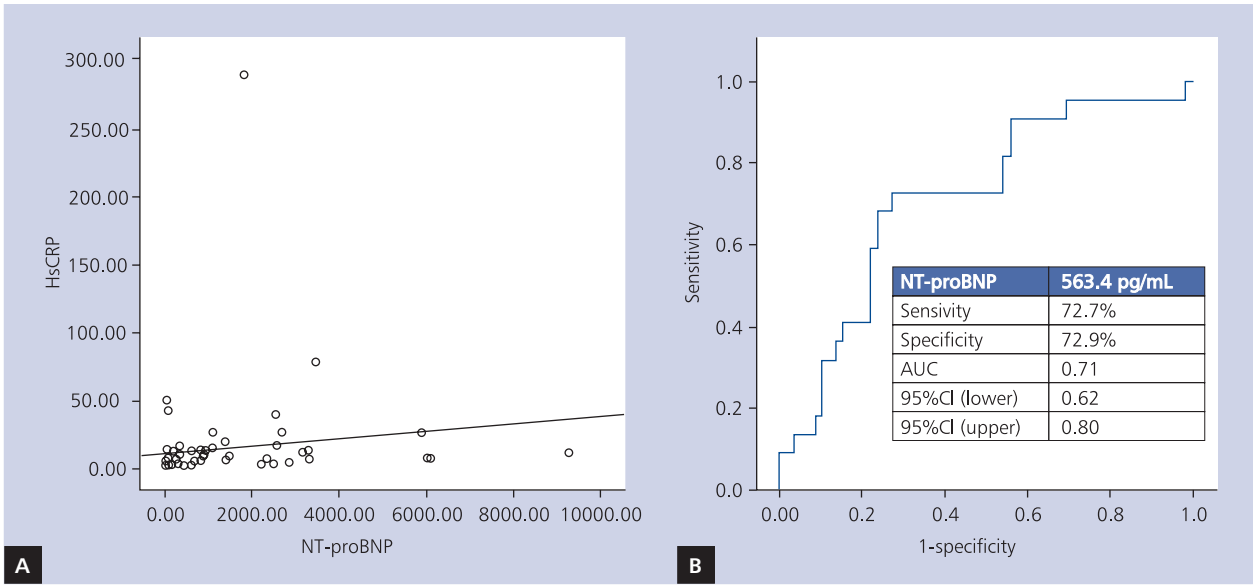

Figure 2. **A**. Correlation between high-sensitivity C-reactive protein (hsCRP) and NT-pro B-type natriuretic peptide levels (NT-proBNP); **B**. Receiver operating characteristics curve analysis of NT-proBNP for predicting no-reflow phenomenon

higher in the no-reflow phenomenon (+) group ($p = 0.02$ and $p < 0.001$, respectively). Mid-term survival curves for both groups are shown in Figure 1A. NT-proBNP and hs-CRP levels on admission were higher in the no-reflow phenomenon (+) group when compared to the no-reflow phenomenon (–) group. There was a significant correlation between each of these two parameters ($r = 0.465$, $p < 0.001$) (Fig. 2A).

The ROC curves of NT-proBNP for predicting no-reflow are shown in Figure 2B. NT-proBNP ≥ 563.4 pg/mL measured on admission had a 72.7% sensitivity and 72.9% specificity in predicting no-reflow. When we divided the study population into two groups according to the ≥ 563.4 pg/mL NT-proBNP level cut-off value used in the ROC analysis, no-reflow phenomenon was significantly higher in the high NT-proBNP group ($p = 0.001$). Age and sex were significantly different between groups ($p < 0.001$ and $p = 0.04$ for male sex, respectively). High-NT-proBNP group is more likely to have higher TFC and lower MBG compared to low-NT-proBNP group. There was

Table 2. Baseline risk factors and 6-month follow-up outcomes stratified by NT-proBNP levels

	Low NT-proBNP group (n = 49)	High NT-proBNP group (n = 32)	P
Age [years]	55.8 ± 12.8	68.5 ± 10.2	< 0.001
Sex (male)	43 (87.7)	22 (68.7)	0.04
Diabetes mellitus	11 (22.4)	4 (12.5)	0.26
Hypertension	22 (44.8)	11 (34.3)	0.35
Current smoker	29 (59.1)	13 (40.6)	0.11
Family history of CAD	15 (30.6)	5 (15.6)	0.1
Multivessel disease	7 (14.2)	5 (15.6)	0.87
Anterior MI	23 (46.9)	19 (59.3)	0.27
No-reflow phenomenon	6 (12.2)	14 (43.7)	0.001
Chest pain-to-reperfusion time [min]	388.3 ± 326.9	648.7 ± 524.7	0.02
Killip class > 1	5 (10.2)	3 (9.3)	0.99
TIMI frame count			0.03
LAD (corrected)	39 ± 6.4	45 ± 7.4	
CX	28 ± 3.3	34 ± 3.1	
RCA	27 ± 4.1	31 ± 4.9	
Myocardial blush grade			0.02
0	0 (0)	4 (12.5)	
1	6 (12.3)	5 (15.6)	
2	9 (18.4)	9 (28.1)	
3	34 (69.3)	14 (43.8)	
ST-segment depression normalisation			0.13
< 30%	3 (6.1)	6 (18.8)	
30–70%	16 (32.7)	12 (37.5)	
> 70%	30 (61.2)	14 (43.7)	
In hospital mortality	1 (2)	2 (6.2)	0.33
Reinfarction	1 (2)	1 (3.1)	0.74
Target-vessel revascularisation	1 (2)	0 (0)	0.42
MACE	5 (10.2)	4 (12.5)	0.71
6-month follow-up outcomes:			
Cardiac death	2 (4)	7 (21.8)	0.01
Reinfarction	4 (8.1)	9 (28.1)	0.01
Target-vessel revascularisation	3 (6.1)	5 (15.6)	0.16
MACE	6 (12.2)	10 (31.2)	0.03
HF requiring hospitalisation	4 (8.1)	2 (6.2)	0.84

Mean values (SD) and % (n) are reported for continuous and categorical variables, respectively; NT-proBNP — N-terminal pro-B-type natriuretic peptide; CAD — coronary artery disease; MI — myocardial infarction; LAD — left anterior descending artery; CX — circumflex artery; RCA — right coronary artery; MACE — major adverse cardiac events; HF — heart failure

no significant difference between the two groups with regards to the STDN (p = 0.13). Overall, in-hospital CV mortality and reinfarction rate was similar in both groups, however CV mortality and reinfarction rates during the six month follow up period were significantly higher in NT-proBNP (+) (p = 0.01 and p = 0.01, respectively) (Table 2). Mid-term survival curves for both groups are shown in Figure 1B.

Determinants of the no-reflow phenomenon and six month cardiovascular mortality

Some of the variables that can affect impaired flow after primary PCI and mid term CV mortality were significantly different between the groups. So, the effects of multiple variables were analysed with univariate and multivariate logistic regression analyses (Table 3). The variables for which

Table 3. Effects of multiple variables on the no-reflow in univariate and multivariate logistic regression analyses

	Odds ratio	95% confidence interval	P
Univariate predictors			
Anterior MI	3.8	1.22–11.8	0.02
Pre procedural DBP	1.04	1.001–1.08	0.04
Chest pain-to-reperfusion time (> 6 h)	4.8	1.34–17.2	0.02
LDL-cholesterol	0.99	0.97–1.001	0.07
HsCRP	1.07	1.016–1.12	0.01
High NT-proBNP	5.57	1.85–16.8	0.002
Post TIMI grade 3	0.28	0.06–1.25	0.09
Tirofiban	0.26	0.08–0.83	0.02
Independent predictors			
Anterior MI	19.4	1.25–300.1	0.03
High NT-proBNP	10.7	1.37–82.8	0.02
Chest pain-to-reperfusion time (> 6 h)	14.4	1.12–184.1	0.04
Post TIMI grade 3	0.01	0.001–0.55	0.02

MI — myocardial infarction; DBP — diastolic blood pressure; LDL — low-density lipoprotein; HsCRP — high-sensitivity C-reactive protein; NT-proBNP — N-terminal pro-B-type natriuretic peptide; TIMI — Thrombolysis In Myocardial Infarction

Table 4. Effects of variables on mid-term mortality in univariate and multivariate logistic regression analyses

	Odds ratio	95% confidence interval	P
Univariate predictors			
Sex (male)	9.8	2.44–39.1	0.001
No-reflow phenomenon	3.96	1.06–14.7	0.04
High NT-proBNP	5.57	1.2–27.5	0.03
Independent predictors			
High NT-proBNP	5.7	1.2–27	0.03
No-reflow phenomenon	2.1	0.9–10.5	0.02

NT-proBNP — N-terminal pro-B-type natriuretic peptide

the unadjusted p value was < 0.10 in univariate analysis were identified as potential risk markers for no-reflow phenomenon and included in the full model. Anterior MI, chest pain-to-reperfusion time (> 6 h), LDL cholesterol, hs-CRP, NT-proBNP, post TIMI-3 flow and tirofiban usage were analysed with multivariate logistic regression model. At multivariate analyses, anterior MI ($p = 0.03$), high NT-proBNP ($p = 0.02$), chest pain-to-reperfusion time (> 6 h) ($p = 0.04$) and post-TIMI-3 flow ($p = 0.02$) levels were still independent predictors of no-reflow phenomenon after primary PCI (Table 3). Post-TIMI-3 flow had a protective role for no-reflow phenomenon. In the multivariate analyses for mid-term CV mortality, no-reflow phenomenon, high NT-proBNP (> 563.4 pg/mL), and gender (male) were analysed with multivariate logistic regression model. High NT-proBNP levels (> 563.4 pg/mL) ($p = 0.03$), and no-reflow phenomenon ($p = 0.02$) were independent predictors of mid-term CV mortality (Table 4).

DISCUSSION

This study includes two major findings in patients with STEMI. There was a significant relationship between serum NT-proBNP levels and no-reflow phenomenon after primary PCI. Baseline serum NT-proBNP level is a specific and sensitive predictor of poor coronary blood flow after primary PCI in STEMI. Additionally, there was a significant correlation between each of NT-proBNP and hsCRP parameters.

Although the pathophysiology of no-reflow has not been fully elucidated, its aetiology appears to be multi-factorial. These factors include ischaemic endothelial damage, microvascular leukocytes and platelet plugging, reactive oxygen species, and complex interactions between leukocytes and platelets induced by the inflammatory process [13]. It is known that no-reflow is strongly correlated with short and long-term morbidity and mortality in acute MI [14]. Although Dobrzycki et al. [15] proposed that hypercholesterolaemia was associated with a no-reflow phenomenon, the present study does not support this hypothesis. Kozuch et al. [10] reported a relationship between STDN and no-reflow phenomenon after primary PCI and our study revealed a relationship between long term mortality and poor STDN. As is known, the definition of no-reflow phenomenon is based on angiographic findings (post TIMI flow grade) or ECG changes (∑STR). ST segment resolution is more objective and less inter observer. Hong et al. [16] demonstrated that patients with STEMI who had higher NT-proBNP level on admission had inadequate myocardial tissue perfusion status after primary PCI, as in our study. However, in this study, the definition of no-reflow was based on the angiographic method.

The prognostic value of ST-segment resolution has been extensively studied in thrombolysis trials showing that patients with STEMI with incomplete ST-segment resolution are more likely to have persistent coronary artery occlusion [17] and are at higher risk of death and congestive heart failure [18]. However, even after restoration of a TIMI-3 flow using combinations of thrombolytics or primary PCI, 30% to 50% of the patients still have incomplete ST-segment resolution.

The relationship we observed between incomplete STR and NT-proBNP level on admission may be explained by several mechanisms. The failure of optimal myocardial tissue perfusion after primary PCI identifies patients with a higher risk of LV dysfunction, presumably because of microvascular

damage in the infarct zone, despite normalised epicardial coronary artery flow [7]. Although there is sufficient epicardial coronary artery flow after the primary PCI with the developing subclinical/clinical LV dysfunction (which can be identified by elevated plasma NT-proBNP levels), LV end-diastolic pressure and myocardial wall stress may increase. In both situations, infarcted coronary beds lose the ability to clear or wash out microthromboemboli (due to the compressive effect), which may be associated with incomplete STR [7].

The effect of natriuretic peptides on survival in STEMI is well known. Similar to the study of Tycińska et al. [19], we found high NT-proBNP is an independent predictor of mortality in the mid term. While in the study of Lorgis et al. [8] independent factors for incomplete STR were high NT-proBNP level, the use of fibrinolytic agent, and heart failure, in the present study the anterior wall STEMI, higher NT-proBNP level and prolonged chest pain-to-reperfusion time (> 6 h) were independent factors for incomplete STR. Also, in this study high NT-proBNP level (≥ 563.4 pg/mL) measured on admission had a 72% sensitivity and 72.9% specificity in predicting myocardial tissue perfusion, which is similar to results of the study done by Seo et al. [7].

ACC/AHA guidelines [20] do not recommend the use of tirofiban in all STEMI patients. However, Kozuch et al. [21] observed links between the pre-hospital administration of tirofiban and better tissue-level perfusion. Tirofiban might have beneficial effects on survival by preventing no-reflow phenomenon in patients with STEMI.

NT-proBNP levels is a more sensitive predictor of outcome than LVEF, as observed in the study of Jernberg et al. [22]. In this study, patient groups did not differ in respect to LVEF, which is in accordance with the study by Seo et al. [7]. Some studies assessing the recovery of LVEF after primary PCI indicate that the improvement of LVEF in the reperfused myocardium is modest after three days and significant recovery occurs over the first month [23]. In this study, TTE was performed immediately after primary PCI in the coronary care unit. It is possible that stunned myocardial regions caused reduced ejection fraction in both groups. However, if we had evaluated the systolic functions at the end of the hospitalisation or several months later, LVEF could have been significantly higher in the reflow group.

Limitations of the study

There are several limitations to the present study. Firstly, only a small number of patients from one centre were enrolled. Secondly, no-reflow phenomenon has low TIMI flow after primary PCI was excluded, which seriously affects myocardial tissue perfusion. Thirdly, myocardial viability was not assessed during follow-up (using stress echocardiography, magnetic resonance, etc.). Holter monitoring was not used to assess for arrhythmic events. Fourthly, the follow up period in our study was restricted to six months. Fifthly, the relationship between post TIMI-2 flow after primary PCI and the no-reflow phenomenon is unclear. In previous studies [7, 24] associated with no-reflow phenomenon after primary PCI were included patients with post TIMI-2 flow. Compared to previous studies [24, 25], in our study the post TIMI-2 flow patient population is lower (9.9% of total population). Sixthly, there is not enough data to explain the high rate of re-infarction in the no reflow (+) group. More data is needed to clarify the cause of the high rate of reinfarction.

CONCLUSIONS

NT-proBNP on admission is a strong independent predictor of mid term mortality in patients with STEMI treated with primary PCI. The combination of NT-proBNP and STR gives complementary early risk stratification in patients with STEMI.

Conflict of interest: *none declared*

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Wpływ stężenia NT-proBNP przy przyjęciu do szpitala na stratyfikację ryzyka u chorych poddanych pierwotnej przezskórnej interwencji wieńcowej

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Streszczenie

Wstęp: Niezupełna normalizacja odcinka ST (STR) po pierwotnej przezskórnej angioplastyce wieńcowej (PCI) wiąże się z gorszymi efektami klinicznym.

Cel: Celem niniejszego badania była ocena związku między osoczowymi stężeniami N-końcowego fragmentu propeptydu natriuretycznego typu B (NT-proBNP) przy przyjęciu do szpitala a stopniem STR po reperfuzji u chorych z zawałem serca z uniesieniem odcinka ST (STEMI) poddanych pierwotnej PCI.

Metody: Po wykluczeniu osób niespełniających kryteriów klasyfikacji do prospektywnego badania włączono 81 kolejnych pacjentów ze STEMI (średnia wieku: 61,3 ± 13,4 roku) poddanych pierwotnej PCI. Chorych podzielono na dwie grupy w zależności od stopnia normalizacji odcinka ST: grupę z zespołem *no-reflow*, w której stopień normalizacji ∑STR wynosił < 50% (n = 20) i grupę bez cech zespołu *no-reflow*, w której ∑STR ≥ 50% (n = 61). Okres obserwacji wynosił do 6 miesięcy.

Wyniki: Wyjściowe czynniki ryzyka sercowo-naczyniowego (wiek, płeć, nadciśnienie tętnicze, cukrzyca) występowały z podobną częstością w obu grupach, jednak w grupie z zespołem *no-reflow* śmiertelność w obserwacji średniookresowej była wyższa (25% *vs*. 6.5%; p = 0,02) niż w grupie bez zespołu *no-reflow*. Zawał przedniościenny występował częściej w grupie z zespołem *no-reflow* (75%; p = 0,02). Stężenia NT-proBNP przy przyjęciu również były wyższe w tej grupie chorych (p = 0,001). Stężenie NT-proBNP przy przyjęciu ≥ 563,4 pg/ml było czynnikiem, którego czułość i swoistość w prognozowaniu zjawiska *no-reflow* w analizie krzywych ROC wynosiły odpowiednio 72,7% i 72,9%. W analizie wielu zmiennych przedniościenny zawał serca, wysokie stężenie NT-proBNP, przedłużony czas od wystąpienia bólu w klatce piersiowej do reperfuzji (> 6 h) i przepływ TIMI 3 po PCI były niezależnymi czynnikami prognostycznymi wystąpienia zespołu *no-reflow* po pierwotnej PCI.

Wnioski: Osoczowe stężenie NT-proBNP przy przyjęciu do szpitala jest silnym niezależnym czynnikiem prognostycznym wystąpienia zjawisko *no-reflow* po PCI i zgonu sercowo-naczyniowego u chorych ze STEMI w obserwacji średniookresowej.

Słowa kluczowe: NT-proBNP, normalizacja odcinka ST

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