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International Journal of Cardiology 141 (2010) 175–181

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Serum B-type natriuretic peptide on admission can predict the 'no-reflow' phenomenon after primary drug-eluting stent implantation for ST-segment elevation myocardial infarction

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Received 27 January 2008; received in revised form 23 July 2008; accepted 28 November 2008
Available online 13 January 2009

Abstract

Background: The angiographic 'no-reflow' phenomenon after primary percutaneous coronary intervention (PPCI) is associated with a poor short-term and long-term clinical prognosis of ST-elevation myocardial infarction (STEMI). Although the increasing use of primary drug-eluting stent (DES) deployment for STEMI resulted in reduced adverse clinical outcomes, the prevalence of no-reflow has been unchanged. The purpose of our study was to evaluate the predictors for no-reflow for STEMI and identify such high-risk patients in the DES era.
Methods: The study prospectively enrolled 300 consecutive STEMI patients (80% men; 57±11 years) who underwent PPCI within 12 h of symptom onset. The no-reflow phenomenon was defined as an angiographic outcome of Thrombolysis In Myocardial Infarction (TIMI) grade <3 without accompanying mechanical factors.
Results: Compared to normal reflow patients, no-reflow patients ($n=15$, 5% of the total study population) were older (64±13 vs. 57±11 years; $P=0.019$), transferred to hospital later (7.1±3.2 vs. 4.5±3.8 h; $P=0.011$), and had a higher TIMI risk score (5.5±2.0 vs. 3.8±2.2; $P=0.004$). B-type natriuretic peptide (BNP), high sensitivity C-reactive protein, and serum creatinine levels were higher in the no-reflow than the normal reflow group. Multivariate analysis (including clinical, angiographic and procedural variables with a $P<0.2$ in univariate analysis) showed that high BNP level on admission was the only independent predictor of no-reflow. The area under the receiver-operating characteristics curve analysis value for BNP was 0.786. BNP ≥90 pg/ml showed a sensitivity of 80% and a specificity of 70% for predicting no-reflow after primary DES implantation (OR 14.953, 95% CI 3.131–71.419, $P=0.001$).
Conclusions: Angiographic 'no-reflow' phenomenon after primary DES implantation for STEMI can be predicted by BNP levels on admission. BNP-guided approach may be useful in identifying patients at high risk of the no-reflow phenomenon after primary stenting.

Keywords: ST-elevation myocardial infarction; No-reflow phenomenon; B-type natriuretic peptide; Drug-eluting stent

1. Introduction

Optimal reperfusion therapy is the current treatment of choice for ST-segment elevation myocardial infarction (STEMI) [1]. Primary percutaneous coronary intervention (PPCI) is more effective than fibrinolytic therapy for STEMI when rapidly performed by an experienced team [2,3].

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doi:10.1016/j.ijcard.2008.11.189

Compared with balloon angioplasty, primary stenting of the infarct-related artery results in less abrupt closures, restenosis and recurrent angina [4]. Furthermore, drug-eluting stent (DES) appears further to reduce the rate of target-vessel revascularization within 12 months compared to using an uncoated stent [5,6]. PPCI restores normal angiographic flow in occluded arteries in more than 90% of cases, but no-reflow phenomenon cannot be evitable in some cases [7,8]. Because angiographic 'no-reflow' phenomenon is associated with a poor short-term and long-term prognosis, the risk of a major adverse event could be as high as 10 times that of a historical control [7,9].

Although the increasing use of primary DES deployment for STEMI resulted in reduced adverse clinical outcomes, mainly related with restenosis, the prevalence of no-reflow has been unchanged. The purpose of our study was to evaluate the predictors for no-reflow for STEMI and identify such high-risk patients in the DES era.

2. Methods

2.1. Study population

The study prospectively enrolled 300 consecutive STEMI patients (240 men; 57 ± 11 years) who underwent primary DES implantation within 12 h of symptom onset, admitted to Asan Medical Center between September 2003 and September 2006: 261 patients (87%) treated with sirolimus-eluting stent (Cypher stent, Cordis/Johnson and Johnson, Warren, NJ) and 39 patients (13%) treated with paclitaxel-eluting stent (TAXUS stent, Boston Scientific Corp., Natick, MA) at doctor's discretion during procedure. According to physicians' preference, only 5 patients were treated with uncoated stent during the study period. The inclusion criteria were chest pain lasting for ≥30 min which was refractory to nitrates, ST-segment elevation ≥1 mm in at least 2 contiguous leads according to the admission electrocardiogram with a subsequently documented increase in cardiac markers, and PPCI less than 12 h after the onset of pain. Exclusion criteria were uncoated stent implantation, severe valvular heart disease or late arrival (>12 h). Preinfarct angina was defined as cardiac symptoms for >30 min that occurred within 2 days before infarct onset [10]. Patients were transported immediately to a catheterization room. Detailed demographic, clinical, angiographic and procedural data were collected and entered into a uniform registry. Informed consent was obtained from all enrolled patients. The study protocol was approved by the regional ethics committee.

2.2. Laboratory and echocardiographic tests

Peripheral blood samples were obtained immediately on admission to the emergency department via direct venipuncture of an antecubital vein. Complete blood count, cardiac enzymes, glucose and creatinine profile, inflammation markers, and cardiac biomarkers measurements were obtained prior to PPCI. B-type natriuretic peptide (BNP) levels were measured using a direct chemiluminescence assay in whole-blood specimens (Triage BNP Test; Biosite Incorporated, San Diego, CA: range 2.0 to 5000.0 pg/ml). Cardiac troponin I (cTnI) levels on admission were assessed (ADVIA Centaur, Bayer, Tarrytown, NY). High sensitivity C-reactive protein (hs-CRP) levels were measured using an immunoturbidimetric assay (Integra 800, Roche, Lewes, Sussex, UK). Hemoglobin A1c and lipid profile were assessed within 24 h after admission to the emergency department. A standard two-dimensional echocardiogram was performed within 24 h after PPCI. Left ventricular ejection fraction (LV EF) was assessed using the modified Simpson method [11].

2.3. Procedures and medical treatment

All PPCI procedures were performed by experienced interventional cardiologists using a femoral approach. All patients received loadings of 300 mg aspirin and 600 mg clopidogrel immediately after arrival in the emergency room. After administration of 5000 IU heparin and conventional wire crossing, balloon predilation was undertaken, and direct stenting was performed where possible. Glycoprotein IIb/IIIa inhibitors (GPI) and thrombus aspiration device were used at the clinician's discretion. Additional medical therapies including beta-blockers, nitrates, calcium antagonists, angiotensin-converting enzyme inhibitors/angiotensin receptor blockades, and statins, were administered at the decision of the first attending physicians.

2.4. Angiographic results

Coronary angiographies were reviewed by 2 experienced interventional cardiologists blinded to the purpose of study. Reviews performed at the angiographic core laboratory using a guiding catheter for magnification calibration and an on-line quantitative coronary angiographic system (ANCOR V2.0, Siemens, Germany). Minimal luminal diameter, percent diameter stenosis and reference vessel diameter were measured before and after the intervention from a single matched view showing the smallest luminal diameter. Coronary blood flow patterns before and after primary PCI were assessed according to the Thrombolysis In Myocardial Infarction (TIMI) flow scale, using grades 0, 1, 2, and 3 [12]. The no-reflow phenomenon was defined as an angiographic outcome of TIMI grade <3 without mechanical factors including flow-limiting dissection, persistent thrombus in epicardial artery or side-branch occlusion that might decrease coronary flow, according to classic definitions [13]. Myocardial blush grades (MBG) were also assessed as previously described by Van't Hof et al. [14].

2.5. Statistical analysis

Statistical analysis was performed using SPSS 13 software (SPSS Inc, Chicago, Illinois). Baseline characteristics were

compared using the *t*-test or Wilcoxon rank-sum test for continuous variables, and the chi-square or Fisher's exact test (if an expected frequency was <5) for categorical variables.

Table 1
Baseline clinical characteristics.

	No reflow (n=15)	Normal reflow (n=285)	P value
Demographics			
Age (yrs)	64±13	57±11	0.019
Male	9 (60%)	231 (81%)	0.088
Weight, kg	66±8	67±9	0.927
Preinfarct angina	3 (17%)	54 (19%)	0.714
Previous MI	1 (7%)	17 (6%)	0.840
Previous PCI	2 (13%)	23 (8%)	0.268
Previous CABG	0 (0%)	1 (1%)	0.818
Renal failure (creatinine ≥1.5 mg/dl)	2 (13%)	15 (5%)	0.188
LV ejection fraction (%)	53±14	55±13	0.290
Time from chest pain onset (h)	7.1±3.2	4.5±3.8	0.011
Door-to-balloon time (min)	83±52	86±41	0.382
Risk factors			
Hypertension	8 (57%)	93 (34%)	0.092
Diabetes mellitus	4 (29%)	44 (16%)	0.230
Current smoker	4 (27%)	79 (28%)	0.929
Hypercholesterolemia (>200 mg/dl)	8 (53%)	107 (38%)	0.277
TIMI risk score	5.5±2.0	3.8±2.2	0.004
Age			0.007
65–74 yrs	4 (27%)	67 (24%)	
>75 yrs	4 (27%)	13 (5%)	
History of angina, hypertension and DM	9 (60%)	120 (42%)	0.208
Systolic blood pressure <100 mm Hg	1 (7%)	37 (13%)	0.474
Heart rate >100 beats/min	2 (13%)	31 (11%)	0.767
Killip class II–IV	11 (73%)	160 (56%)	0.191
Weight <67 kg	8 (53%)	119 (42%)	0.429
Anterior ST-elevation or LBBB	8 (53%)	173 (61%)	0.596
Time to treatment >4 h	12 (80%)	107 (38%)	0.001
Biochemical tests			
Hemoglobin (g/dL)	13.6±1.7	13.5±1.5	0.659
WBC count ($\times 10^3/mm^3$)	6.9±1.9	6.7±2.0	0.374
Platelet count ($\times 10^3/mm^3$)	229±54	225±52	0.550
BNP (pg/ml)	464±584	111±237	<0.001
Creatine kinase-MB (IU/L)	39.3±40.6	29.6±55.7	0.588
Troponin I (ng/ml)	16.1±17.9	6.9±21.0	0.095
High sensitivity CRP (ng/ml)	24.9±54.9	8.6±25.1	0.024
Serum creatinine (mg/dl)	1.2±0.5	1.0±0.3	0.026
Glucose (mg/dl)	198±84	174±58	0.251
Hemoglobin A1c	6.3±1.2	6.1±1.0	0.847
Total cholesterol (mg/dl)	222±23	190±41	0.043
LDL cholesterol (mg/dl)	151±22	116±40	0.025
HDL cholesterol (mg/dl)	41±13	40±11	0.848
Triglyceride (mg/dl)	153±98	186±159	0.579
Homocysteine (μmol/L)	13±4	12±3	0.267
Lipoprotein (a) (mg/dl)	149±94	137±84	0.802
Treatment before or during procedure			
Aspirin	15 (100%)	285 (100%)	1.000
Clopidogrel	14 (93%)	276 (97%)	0.904
Beta blocker	2 (13%)	51 (18%)	0.465
ACEI/ARB	0 (0%)	20 (7%)	0.387
Statin	4 (26%)	80 (28%)	0.785
IABP	2 (13%)	21 (8%)	0.241
Glycoprotein IIb/IIIa inhibitor	1 (7%)	18 (6%)	0.962

MI: myocardial infarction, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, LV: left ventricle, TIMI: Thrombolysis In Myocardial Infarction. LBBB: left bundle branch block, BNP: B-type natriuretic peptide, CRP: C-reactive protein, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, IABP: intra-aortic balloon pump.

Table 2
Angiographic and procedural characteristics.

	No reflow (n=15)	Normal reflow (n=285)	P value
Angiography			
Initial TIMI flow			0.590
TIMI flow 0	8 (52%)	46 (54%)	
TIMI flow 1	2 (13%)	29 (10%)	
Multivessel disease	3 (19%)	66 (23%)	0.720
Multivessel intervention (≥2)	2 (13%)	51 (18%)	0.652
IRA			0.938
LAD	8 (53%)	150 (53%)	
LCX	0 (0%)	23 (8%)	
RCA	7 (47%)	99 (35%)	
LM	0 (0%)	13 (4%)	
Location			0.794
Anterior wall infarction	8 (53%)	163 (57%)	
Non-anterior wall infarction	7 (47%)	122 (43%)	
AHA/ACC lesion type B2/C	13 (87%)	236 (83%)	0.699
Procedure			
Guidance of IVUS	7 (47%)	143 (51%)	0.734
SES implantation	15 (100%)	246 (86%)	0.125
Direct stenting	0 (0%)	23 (8%)	0.250
Aspiration thrombectomy	2 (13%)	28 (10%)	0.641
Reference vessel diameter (mm)	3.1±0.3	3.2±0.6	0.527
Lesion length (mm)	32.4±7.6	25.8±12.0	0.282
Percent stenosis before procedure (%)	99.7±3.7	98.8±7.8	0.258
Minimal lumen diameter (mm)			
Pre-procedure	0.01±0	0.35±0.58	0.027
Post-procedure	2.58±0.24	2.84±0.46	0.035
Stents per patients	1.3±0.5	1.5±0.8	0.414
Stent length per lesion (mm)	32.2±9.7	33.1±15.1	0.844
Stent diameter (mm)	3.23±0.30	3.30±0.30	0.425
Maximal balloon size (mm)	3.29±0.40	3.53±0.37	0.017
Maximal inflation pressure (atm)	13.3±3.3	16.1±4.3	0.015

TIMI: Thrombolysis In Myocardial Infarction, IRA: infarct-related artery, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, LM: left main artery, AHA: American heart association, ACC: American college of cardiology, IVUS: intravascular ultrasound, SES: sirolimus-eluting stent.

Receiver-operating characteristics (ROC) curve analysis of cardiac biomarkers was performed to identify the optimal cutoff value for predicting the no-reflow phenomenon. Correlations between 2 continuous variables were evaluated using linear regression analysis. Variables with a P value <0.2 in univariate analyses were considered significant, and were included in multivariate analysis. Multivariate linear logistic analysis was performed to identify independent predictors of no-reflow. A P value <0.05 was considered to indicate significance.

3. Results

3.1. Baseline characteristics

The angiographic no-reflow phenomenon was identified in 15 patients (5%) of the total 300 patients. Baseline clinical characteristics are shown in Table 1. Compared with normal reflow patients, no-reflow patients were older and transferred to hospital later, and had higher TIMI risk scores. BNP, hs-CRP, serum creatinine, and total and LDL cholesterol levels were higher in the no-reflow than the normal reflow group. Medical treatment before or during the procedure was similar for the two groups. The 2 groups did not differ significantly in terms of angiographic characteristics (Table 2). In terms of procedural characteristics, larger balloon sizes and higher inflation pressures were used more frequently in normal reflow patients. MBG after stenting was significantly associated with TIMI flow ($P<0.001$). Among patients with no reflow, 2 (13%) had MBG 2/3 and 13 (87%) had MBG 0/1 after stenting. Also, among patients with normal reflow, 220 (77%) had MBG 2/3 after stenting.

3.2. Predictive value of cardiac biomarkers

ROC curve analysis was performed to assess the predictive power of cardiac biomarkers for the no-reflow phenomenon. The area under the ROC curve for BNP and cTnI were 0.786 and 0.718, respectively (Fig. 1). A BNP concentration ≥90 pg/ml showed a sensitivity of 80% and a specificity of 70%, and a cTnI concentration ≥2.1 ng/ml had a sensitivity of 73% and a specificity of 69% for predicting no-reflow. The area under the ROC curve values for hs-CRP and creatine kinase-MB were relatively low, 0.613 and 0.654, respectively.

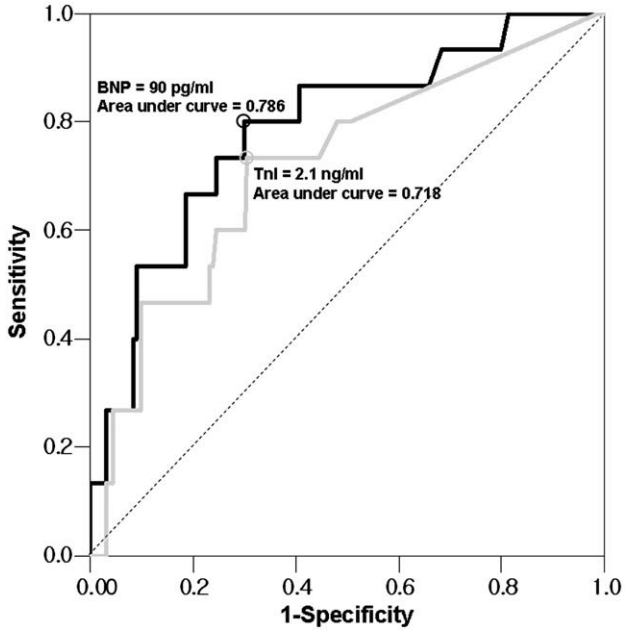

Fig. 1. Receiver-operating characteristics curve analysis of B-type natriuretic peptide and troponin I levels for predicting the angiographic no-reflow phenomenon. The number on the curve indicates the cutoff value of the point. BNP: B-type natriuretic peptide, TnI: troponin I.

Table 3
Independent predictors for the no-reflow phenomenon by multivariate analysis.

Variables	*P* value	OR	95% CI
Age	0.111	0.939	
Male	0.556	0.979	
Renal failure (creatinine ≥1.5 mg/dl)	0.077	6.507	
Time from chest pain onset	0.175	1.074	
Hypertension	0.473	0.547	
TIMI risk score	0.185	1.011	
Killip class II–IV	0.548	1.695	
BNP (≥90 pg/ml)	0.001	14.953	3.131–71.419
Troponin I (≥2.1 ng/ml)	0.736	1.784	
High sensitivity CRP (≥3.1 ng/ml)	0.418	3.465	
Total cholesterol (mg/dl)	0.562	0.981	
LDL cholesterol (mg/dl)	0.457	1.005	
SES implantation	0.131	0.973	
Minimal lumen diameter (mm)			
Pre-procedure	0.986	0.995	
Post-procedure	0.408	0.960	
Maximal balloon size (mm)	0.612	0.369	
Maximal inflation pressure (atm)	0.054	1.233	

TIMI = Thrombolysis In Myocardial Infarction; BNP = B-type natriuretic peptide; CRP = C-reactive protein; SES = sirolimus-eluting stent.

3.3. Predictors of the no-reflow phenomenon

Multivariate logistic regression analysis showed that BNP concentration on admission (≥90 pg/ml; OR 14.953, 95% CI 3.131–71.419, $P=0.001$) was the only independent predictor of no-reflow (Table 3). BNP concentration on admission ≥90 pg/ml had a positive predictive value of 12% and a negative predictive value of 98% for predicting no-reflow, respectively.

3.4. Correlation between BNP level and other variables

An elevated BNP levels (≥90 pg/ml) was present in 97 patients (32.3%) of the total study cohort. When we evaluated the association between BNP level on admission and TIMI risk score parameter, these patients were older (64±9 vs. 54±11 years, $P<0.001$) and had a longer time from symptom onset (7.5±4.7 vs. 3.3±2.5 h, $P<0.001$), lower body weight (63±8 vs. 69±9 kg, $P=0.004$), higher heart rate (heart rate >100 bpm; 23 vs. 5%, $P<0.001$), more risk factors (i.e., history of angina, hypertension and diabetes; 61 vs. 35%, $P<0.001$), and a higher TIMI risk score (5.3±2.1 vs. 3.2±1.9, $P<0.001$) than patients with BNP levels <90 pg/ml. BNP levels on admission positively correlated with age ($r=0.302$, $P<0.001$), time from chest pain onset ($r=0.504$, $P<0.001$), and cTnI ($r=0.252$, $P<0.001$) and hs-CRP ($r=0.543$, $P<0.001$) values. However, BNP concentration did not correlate with creatine kinase-MB ($r=0.099$, $P=0.086$), LV

EF ($r=-0.213$, $P=0.073$), initial TIMI flow ($r=-0.149$, $P=0.259$), or anterior wall infarction ($r=0.051$, $P=0.379$).

3.5. One-month clinical outcomes

During 30 days after procedure, the no-reflow group had a higher prevalence of adverse clinical outcomes compared with the normal reflow group (20.0 vs. 6.3%, $P=0.038$). Mortality rate in the no-reflow group was higher than the normal flow group (13.3 vs. 2.5%, $P=0.021$). All mortality cases (2 patients) in the no-reflow group were related with cardiogenic shock due to poorly controlled heart failure. In the normal reflow group, 5 mortality cases were from cardiac origin and other 2 patients died from non-cardiac origin (sepsis and hypoxia due to progressive pneumonia). There were no significant differences between the two groups in terms of recurrent MI (6.7 vs. 2.5%, $P=0.312$), target vessel revascularization (0 vs. 1.3%, $P=0.542$) and stent thrombosis (0 vs. 0%, $P=1.000$).

4. Discussion

The present study demonstrated that no-reflow after primary DES implantation for STEMI can be predicted by BNP level on admission. This finding implies that BNP level on admission may correspond with angiographic success after PPCI.

After restoration of blood flow to the previously ischemic myocardium, reperfusion of the ischemic tissue depends on microvascular integrity. The no-reflow phenomenon may be defined as incomplete and non-uniform reperfusion at the microvascular level despite adequate re-opening of the occluded artery [13]. This pathological process can be accelerated by coronary reperfusion, which gives rise to tissue edema, endothelial disruption, plugging of capillaries by neutrophils and microthrombi, inflammation due to generation of free radicals and complement activation, and contracture of neighboring myocytes [15]. Many modalities are used for diagnosing no-reflow. TIMI grading according to simple coronary angiography indicates the coronary artery clearance of radiographic dye. A TIMI 2 flow is associated with a no-reflow zone of substantial size, while only a TIMI 3 flow indicates reperfusion success [16]. Clinical outcomes are similar for patients with either a TIMI 2 or TIMI 0/1 flow, and are worse than those for patients with a TIMI 3 flow [17].

Major determinants of no-reflow have been studied in animal models. Duration of coronary occlusion, size of myocardial necrosis and duration of reperfusion were linked to the extent of microvascular damage and the amount of anatomical no-flow [18]. In clinical practice, identification of no-reflow predictors will assist in determining patients at high risk. Although a direct pathophysiological role has not been verified, white cell blood count, and levels of glucose, cholesterol and inflammation markers such as hs-CRP have been suggested to independently predict no-reflow [19–22].

BNP level can be assessed with short time using triage BNP test, and widely used as a biomarker for assessing the prognosis of coronary artery disease. The prognostic value of BNP in patients with acute coronary syndromes in the absence of ST-segment elevation is well documented [23,24]. Grabowski M et al. first showed that high BNP values on admission, along with Killip class II–IV were predictors of no-reflow after PPCI in STEMI patients (uncoated stent implantation: 81.7%, balloon angioplasty:18.3%) [25]. While Hong SN et al. recently reported that the N-terminal pro-BNP on admission was a no-reflow predictor after primary stenting in STEMI patients, that study was relatively small ($n=157$), had many exclusion criteria, and a high no-reflow rate (42.1% of patients) [26].

The present study found that patients with high BNP levels on admission (≥90 pg/ml; 12.4%) had an 8.3-fold higher rate of no-reflow after PPCI than those with lower BNP values (<90 pg/ml; 1.5%). The study excluded only patients with severe valvular disease, included various previously suggested parameters, and had an acceptable no-reflow rate (5% of cohort patients). BNP-guided approach may be useful in identifying patients at high risk of no-reflow after primary DES implantation for STEMI. Although BNP-guided approach can be difficult to do in some circumstances, BNP could be processed before performing PCI if interventional cardiologist wants to know the BNP result and a laboratory support is available. For patients with such high risk, preventive modalities could be applied before PCI. Although preventive effects of embolic protection and some mechanical thrombectomy devices have been disappointing in setting of STEMI [27–29], preventive administration of some drugs before PCI may be helpful. The use of GPI reduced the rate of no-reflow [30,31], and intracoronary thrombolytics or adenosine infusion prior to PCI showed to be beneficial in prevention of no-reflow in small studies [32,33]. Furthermore, the TAPAS study recently suggested that the adjunct of thrombectomy using 6-French Export Aspiration Catheter was associated with improvement of myocardial reperfusion, which translated into substantial improvement of the clinical outcome at 12-month follow-up as compared with conventional primary PCI [34,35]. The appropriate selection of patients who can benefit from some drugs and thrombectomy may be important. High-risk patients for no-reflow based on BNP-guided approach could obtain more benefits from such preventive methods, but large randomized trials are needed to prove the effect of the strategy.

The mechanism underlying the link between BNP level on admission and no-reflow remains to be determined. No reflow can be the cause of the higher BNP or just a consequence. Since time to angioplasty was longer in the patients with no reflow, it is possible that the damaged left ventricle has already been overstretched by which both BNP will be elevated and no reflow is observed. Given the small number of patients, time-to-treatment does not come out as an independent predictor in the multivariate analysis, but this must have a relationship to no reflow. Myocardial stretch

secondary to LV dysfunction is quantitatively the most important stimulus of BNP elevation. Ischemic injury due to coronary artery occlusion first causes LV diastolic dysfunction, followed by elevation of filling pressure. An increase in LV end-diastolic pressure can cause early elevation of serum BNP levels. Thus, BNP level on admission could be influenced more than any other biomarker by the extent of myocardial injury. Moreover, other diverse factors such as increased heart rate, hypoxia and stimulation of vasoconstrictor hormones by ischemia per se may contribute to raising BNP levels in the early phase of myocardial ischemia [36].

The study had several limitations. First, GPI were administered less frequently in the present study, and this may have influenced the outcomes. Second, many biomarkers have been assessed in terms of diagnostic and predictive values for AMI. While the present study involved previously investigated biomarkers, it may transpire that biomarkers not examined in this study are also predictors. Third, the location of the infarct-related artery does not precisely indicate the size of the myocardial necrosis exactly. The present study did not include objective data regarding the size of the infarct-related necrosis.

Acknowledgements

This study was supported by grants from the Cardiovascular Research Foundation, the Asan Institute for Life Science (#2006-217) and the Korea Health 21 R&D Project, Ministry of Health & Welfare, Korea (0412-CR02-0704-0001).

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [37].

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