Relationship between Serial Measurement of Plasma Brain Natriuretic Peptide and Left Ventricular Remodeling or Long-term Prognosis after Acute Myocardial Infarction

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Relationship between Serial Measurement of Plasma Brain Natriuretic Peptide and Left Ventricular Remodeling or Long-term Prognosis after Acute Myocardial Infarction

A Master's thesis

Submitted to the Department of Medicine

And the Graduate School of Yonsei University

in partial fulfillment of the

requirements for the degree of

Master of Medical Science

Min-Soo Ahn

July 2008 of submission

This certifies that the Master's thesis

of Min-Soo Ahn is approved.

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July 2008

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2008년 7월

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Abstracts

Relationship between Serial Measurement of Plasma Brain Natriuretic Peptide and Left Ventricular Remodeling or Long-term Prognosis after Acute Myocardial Infarction

Background and Objective: B-type natriuretic peptide (BNP) is a significant prognostic marker after acute myocardial infarction (AMI). But, it's obscure of a suitable sampling time for BNP because the plasma levels of BNP dramatically changes depending on the period after the onset of AMI. We investigated the relationships between serial measurement of BNP and left ventricular (LV) remodeling or long-term prognosis in patients with AMI.

Method: We prospectively analyzed 129 patients of ST elevation myocardial infarction (STEMI) with reperfusion therapy from April 2003 to June 2006. Levels of BNP (Triage®) were serially checked at acute (on admission), early (2-6 days after admission), and late phase (at least 6 months after discharge). All subjects were performed echocardiography within 3 days after admission and at least 6 months after discharge. LV remodeling was defined as an increase in LV end-diastolic volume (LVEDV) ≥15% between initial and follow-up period. We also evaluated long-term major adverse cardiac events (MACE) such as, cardiac death, myocardial infarction and readmission due to heart failure during follow-up.

Results; Mean age was 59.7±11.7 years and male was 71.3%. Mean duration of follow-

up was 35.9±11.8 month. Levels of BNP at acute, early and late phase were 168.1±300.0, 451.1±700.7 and 205.5±293.2 pg/mL in remodeling group and 44.9±68.6, 78.1±104.6, 43.2±57.1 pg/mL in non-remodeling group (p=0.000 in both groups). Independent predictors of remodeling were BNP at early phase (odds ratio; 1.006, 95% CI 1.001-1.010) and wall motion scores (odds ratio; 1.020, 95% CI 1.022-1.413).

According to the presence or absence of MACE, levels of BNP at acute, early and late phase were 208.0±382.3, 594.0±903.9 and 281.2±369.8 pg/mL in MACE group and 57.2±86.7, 110.4±141.0, 54.4±67.6 pg/mL in non-MACE group. Independent predictors of MACE were BNP at 2-6 days after admission (odd ratio; 1.001, 95% CI 1.000-1.002) and LV ejection fraction (odds ratio; 0.944, 95% CI 0.899-0.991) in Cox proportional hazards regression analysis. The optimal prognostic thresholds of BNP at early phase were 109 pg/mL (sensitivity 69.5%, specificity 68.9%). MACE free survival was significant higher in patients with level of BNP<109 pg/mL (p=0001).

Conclusion: Early phase BNP (2-6 days after AMI) is an independent predictor of LV remodeling and long-term prognosis in patients with AMI and reperfusion treatments.

Key words: B-type natriuretic peptide; Acute myocardial infarction; Remodeling; Prognosis.

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1. Introduction

Plasma hormones, particularly the cardiac natriuretic peptides, reflect ventricular impairment and the severity of homodynamic decompensation in heart disease.[1] B-type natriuretic peptide (BNP) is released from cardiac myocytes in response to increased wall stress, and is elevated in settings in which myocardial ischemia occurs.[2] The synthesis and

secretion of BNP was augmented before progressive ventricular dilatation after myocardial infarction and that plasma BNP concentration predicted magnitude of subsequent left ventricular (LV) dilatation and maladaptive LV remodeling.[3] High level of BNP is a strong, independent marker of death or re-admission after decompensated heart failure, more relevant than common clinical or echocardiographic parameters.[4] De Lemos et al demonstrated the single measurement of plasma B-type natriuretic peptide (BNP) within a few days of acute coronary syndromes, predict the risk of mortality, clinical heart failure, and new myocardial infarction.[5] But, the profile of BNP is biphasic pattern that plasma levels of BNP are elevated in the early stages following acute myocardial infarction (AMI), peaking within 48 h before declining over the next 48 h and followed by a secondary rise in plasma N-BNP at around day 5, maintained 6 weeks later.[3] Like this, the changing pattern of the plasma BNP level after AMI is dynamic release, therefore, identification of a suitable time frame for blood sampling for BNP measurement is an important issue. However, few studies have evaluated serial measurements of BNP during the follow-up period in patients with AMI. We investigated the relationships between serial measurements of BNP at admission, 2-6 days after admission and after 6 months and LV remodeling or long-term prognosis in patients with AMI.

2. Methods and Materials

2.1 Study population

We included 129 ST segment elevation myocardial infarction (STEMI) patients into this study who fulfilled the following criteria: 1) admitted within 12 hours from the onset and treated with successful reperfusion therapy (primary coronary angioplasty or thrombolysis), 2) completed serial BNP check and echocardiographic evaluation at initial and 6 month follow up, 3) absence of cardiomyopathy, severe valvular disease, ventricular septal defect, 4) absence of cardiogenic shock (systolic pressure <90 mm Hg), prior history of cardiopulmonary resuscitation, and 5) absence of renal dysfunction at admission (Cr>1.5mg/dL), nephrotic syndrome, and liver cirrhosis.

STEMI was defined by electrocardiogram (ECG) showing ST segment elevation in at least two contiguous precordial leads and subsequent increase of creatine kinase-MB (CK-MB) activities more than twice normal range or increase of troponin activities above upper normal limit.

2.2 Method

2.2.1 Serial BNP measurements

Serial blood samples were taken from all subjects in each of the following periods: at admission (acute phase, <24hous), 2-6 days after admission (early phase) and after at least 6 months (late phase) following AMI. All blood samples were collected in a chilled plastic syringe and transferred to chilled siliconised disposable tubes containing EDTA. Plasma natriuretic peptide concentrations were measured by a radioimmunoassay kit specific for BNP kit (Triage®, Biosite, San Diego, USA). The upper and lower limit of sensitivity for BNP in this assay was 5,000 pg/mL and 5.0 pg/ml.

2.2.2 Echocardiography

Echocardiography was performed within 3 days after admission and at least 6 months after discharge. LV end systolic (LVESV), diastolic volume (LVEDV) and ejection fraction (EF) at baseline and follow-up were measured using the modified biplane Simpson's method from the 2- and 4-chamber views. Regional wall motional abnormality was analyzed individually and scored on the basis of its motion and systolic thickening. Segment scores are as follows: normal or hyperkinesis=1, hypokinesis =2, akinesis (negligible thickening)=3,

dyskinesis (paradoxical systolic motion)=4, and aneurysmal (diastolic deformation)=5. Wall-motion score index can be derived as a sum of all scores divided by the number of segments visualized.[6] Diastolic filling is classified on the basis of the peak mitral flow velocity, the mitral annulus velocity and pulmonary vein flow velocities: early rapid filling wave (E), peak velocity of the late filling wave due to atrial contraction (A), the E/A ratio, deceleration time (DT), and the mitral anulus velocity of early diastolic velocity (E'). E/E', pulmonary systolic and diastolic velocity (PVs1, PVs2 and PVd). Normal diastolic filling pattern was defined as following: E/A≥1.5, DT 160 to 230msec, E' 10cm/sec or more, E/E' less than 8, and Vp≥5010cm/sec, grade 1 diastolic dysfunction (impared myocardial relaxation): E/A<1, E.<7cm/sec and E/E'<8cm/sec, grade 2 diastolic dysfunction (Pseudonormalized pattern): E/A ration 1 to 1.5, DT 160 to 230msec, E'<7cm/sec, and E/E'>15, grade 3-4 dysfunction (Restrictive filling): E/A>2.0, DT<160msec, E<7cm/sec and E/E'>15.[7] LV remodeling was defined as an increase in LV end-diastolic volume (LVEDV) ≥15% between initial and follow-up period.[8]

2.2.3 Clinical follow up

We collected long-term follow-up data at the time of this analysis by telephone interview, or by direct visit. If the patient was rehospitalized, hospital records were reviewed to assess the occurrence of clinical events. The major adverse cardiovascular events (MACE) were defined as cardiac death, any myocardial infarction, and rehospitalization due to aggravated heart failure. Death was considered as cardiac unless otherwise demonstrated. Myocardial infarction was documented by the presence of new pathologic Q waves on the electrocardiogram or a rise in CK-MB of more than twice the upper normal limit. When more than one clinical event occurred in a patient, the event occurring first was considered for survival analysis.

2.2.4 Statistical Methods

All data were analyzed by SPSS version 11.0 (SPSS Inc, Chicago, Illinois, USA). Data are expressed as mean ± standard deviation. For continuous variables, differences between groups were assessed by Student's t test; for categorical variables, chi-square test was used. Comparisons of BNP levels at different time points were by analysis of variance (ANOVA) with correction for multiple measures. Event rates for clinical outcomes were determined using the Kaplan-Meier method. Multivariate logistic regression analysis was used to identify

the independent factors determining the remodeling of LV. Multivariable analyses of the association between BNP levels and MACE were performed using the Cox proportional hazards regression model to adjust for the effects of other major clinical predictors of mortality. Receiver-operating characteristic curves were constructed to assess the best BNP level for the prediction of remodeling or MACE. The area under receiver-operating characteristic curve and 95% confidence limits were used to assess predictive power for remodeling and MACE. Comparisons with p <0·05 were considered significant.

3. Results

3.1. Baseline characteristics of study groups

All subjects were treated revascularization therapy; 95 (73.6%) patients with primary percutaneous coronary intervention and 34 (26.4%) patients with thrmobolytics. Mean duration of follow-up was 35.9 ± 11.8 month. Forty-one patients (remodeling group, 31.8%) had significant LV dilatation, defined as an increase in end diastolic volume of at least 15% during follow up periods, and 88 patients (68.2%) were non-remodeling group. Initial LVEDV was not different between two groups (71.1±20.3 vs. 73.8±15.9 mL, p=0.46), but increased

significantly in remodeling group (70.1±19.4 vs. 93.4±20.0 mL, p=0.000). There were no significant differences of baseline demographic and angiographic findings between these two groups in terms of sex, presence of established risk factors (diabetes mellitus, smoking, and hypertension), creatinine levels, the extents of coronary vessel involvements, medical treatment during follow-up and revascularization procedures. However, age was higher (58.2±11.2 vs. 63.1±12.1, p=0.03), pain to reperfusion time after AMI was delayed (4.7 ± 2.3 vs. 6.6 ± 3.0 hours, p=0.001), anterior infraction was more frequent and cardiac biomarkers (CK-MB and troponin-I) were significantly higher in remodeling group (Table 1, 2.). In remodeling group, LVEF was significantly lower, wall motion scores and E/E' were higher at initial and follow up ($p<0.005$) (Table 2.).

Table 1. Demographic, therapeutic, and laboratory characteristics between non-remodeling and remodeling group

	Non-remodeling group (n=88)	Remodeling group (n=41)	p value
Age (years)	58.2±11.2	63.1±12.1	0.03
Male (%)	67 (76.1)	25 (61.0)	0.08
Smoking (%)	44 (50.0)	18 (43.9)	0.49
Diabetes mellitus (%)	26 (29.5)	10 (24.4)	0.54
Hypertension (%)	45 (51.1)	17 (41.5)	0.31
Total cholesterol (mg/dL)	190.5±35.7	193.8±42.9	0.67
Triglyceride (mg/dL)	164.1±87.8	137.2±83.2	0.10
LDL-cholesterol (mg/dL)	38.3±8.1	40.9±8.3	0.52
Creatinine (mg/dL)	0.97±0.2	1.02±0.3	0.22
Peak troponin-I (ng/mL)	33.8±25.2	48.7±28.5	0.003
Peak CK-MB (ng/mL)	171.7±110.3	247.6±89.1	0.000
Pain to reperfusion time (hour)	4.7±2.3	6.6±3.0	0.001
Revascularization therapy (%)			0.41
Primary PCI	79 (74.5)	16 (69.6)	
Thrombolysis	27 (25.5)	7 (30.4)	
Medication (%)			
HMG-CoA reductase inhibitors	49 (55.7)	21 (51.2)	0.64
ACEI	25 (28.4)	9 (22.0)	0.44
ARB	40 (45.5)	18 (43.9)	0.87
Beta-blocker	62 (70.5)	23 (56.1)	0.11
Diuretics	59 (55.7)	16 (69.6)	0.22

LDL: low density lipoprotein, CK-MB: creatinine kinase-MB, PCI: percutaneous coronary intervention, HMG-CoA: beta-hydroxy-beta-methylglutaryl coenzyme A, ACEI: angiotensin

converting enzyme inhibitor, ARB; angiotensin II receptor blocker,

Table 2. Angiographic and echocardiographic characteristics between non-remodeling and remodeling group

	Non-remodeling group (n=88)	Remodeling group (n=41)	p value
Infarction territory (%)			0.47
Anterior	50 (47.2)	14 (60.9)	
Lateral	10 (9.4)	2 (8.7)	
Inferior	46 (43.4)	7 (30.4)	
Angiographic disease extent			0.579
1/2/3/Left main disease (%)	54.5/28.4/13.6/3.4	53.7/26.8/17.1/2.4	
LVEDV (mL)			
Initial	71.1±20.3	73.8±15.9	0.46
Follow-up	70.1±19.4	93.4±20.0	0.000
LVEF (mL)			
Initial	56.8±9.3	50.4±9.4	0.000
Follow-up	60.1±10.5	49.2±10.7	0.000
Wall motion scores			
Initial	22.0±4.6	26.4±5.2	0.000
Follow-up	20.5±4.8	26.4±6.5	0.000
E/E’			
Initial	11.1±4.2	13.3±4.8	0.009
Follow-up	7.9±3.8	11.2±6.2	0.003

LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, Initial: within 3 days after admission, Follow-up: at least 6 months after discharge

3.2 Serial BNP and LV remodeling

Levels of BNP at acute, early and late phase after AMI were 84.1±186.1, 196.7±437.3 and 94.8±186.7 pg/mL, respectively.. Levels of BNP at acute, early and late phase were 168.1±300.0, 451.1±700.7 and 205.5±293.2 pg/mL in remodeling group and 44.9±68.6, 78.1±104.6, 43.2±57.1 pg/mL in non-remodeling group. The difference of BNP levels was statistically significant within and between groups (p=0.000) and the difference between groups was greatest at early phase (Fig. 1).

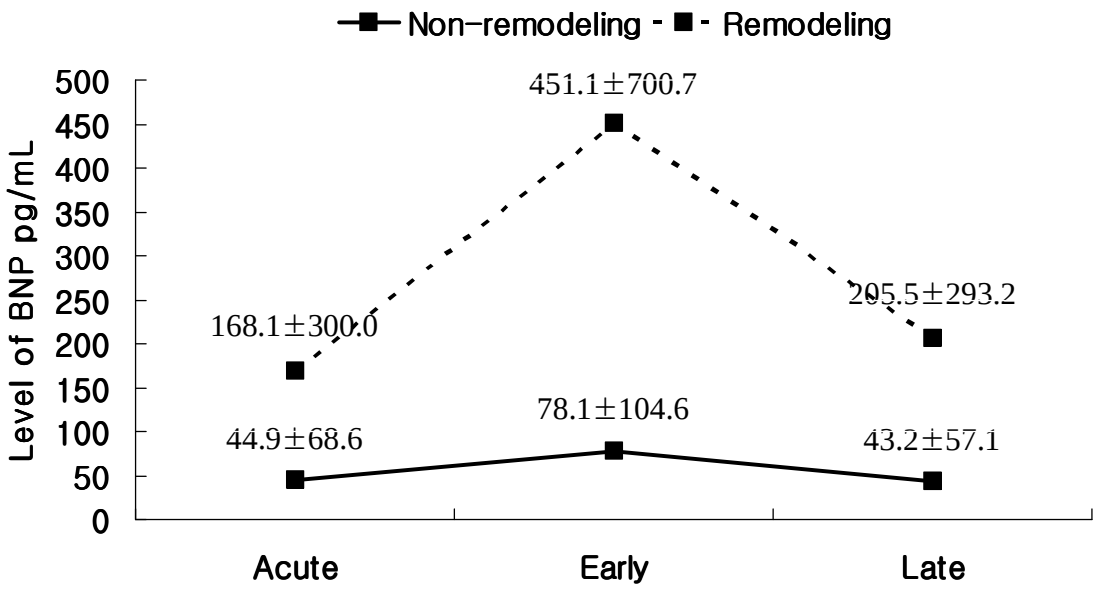

Fig.1. Serial change of BNP according left ventricular remodeling. Repeated measures ANOVA analysis p=0.000

3.3 Predictors of LV remodeling

We included the BNP levels at acute phase, early and late phase together with age, peak creatine kinase-MB, peak troponin-I, anterior site of infarct, pain to reperfusion time after AMI, initial LVEDV, LV ejection fraction, E/E'ratio, and wall motion score index as independent variables in multivariate logistic regression models for determining the predictors of remodeling. The independent predictors of remodeling were BNP at early phase (Odd ratio 1.006, 95% CI 1.001-1.010) and wall motion score index (Odd ratio 1.020, 95% CI 1.022-1.413) (Table 3).

Table 3. Multivariate analysis of independent risk factors for left ventricular remodeling

Variables	Odd ratio	95% CI		p value
		Lower	Upper	
Age	1.011	0.960	1.065	0.681
CK-MB (ng/mL)	1.006	0.999	1.013	0.085
Troponin (ng/mL)	1.014	0.989	1.040	0.268
Anterior infarction	0.585	0.173	1.979	0.389
Ischemic time (hours)	1.047	0.834	1.315	0.691
LVEDV (mL)	0.978	0.947	1.010	0.174
LVEF (%)	1.004	0.934	1.080	0.906
E/E'	0.961	0.837	1.104	0.573
Wall motion score index	1.020	1.022	1.413	0.026
BNP at acute phase (pg/mL)	1.001	0.994	1.008	0.854
BNP at early phase (pg/mL)	1.006	1.001	1.010	0.017
BNP at late phase (pg/mL)	1.002	0.994	1.010	0.687

CI: confidence interval, CK-MB: creatinine kinase-MB, Ischemic time: time to reperfusion

after onset of infarction, LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, Acute phase: at admission (<24hous), Early phase: 2-6 days after admission, Late phase: after at least 6 months following acute myocardial infarction

3.4 Major adverse events during follow-up

In 129 subjects, there were 23 (17.8%) MACE during follow-up. Four (3.1%) patients died due to cardiovascular cause, 9 (7.0%) patients experienced re-attack of myocardial infarction and 13 (10.1%) patients admitted due to congestive heart failure. Patients with MACE has significantly higher age (64.3±11.5 vs. 58.8±11.5, p=0.04), lower LDL-cholesterol levels (105.5±35.7 vs. 125.1±39.0 mg/dL, p=0.012), higher troponin level (49.1±32.8 vs. 36.3±25.3 ng/mL, p=0.04) and higher incidence of remodeling (56.5% vs. 26.4%, p=0.005) than those with non-MACE . Medications use during follow-up did not differ between both groups (Table 4.). In echocardiographic findings 6 month after AMI, subjects with MACE was significantly higher initial LVEDV (72.9±21.9 vs. 71.8±18.5 ml, p=0.002), lower initial LVEF (49.2±9.7 vs. 55.9±9.4%, p=0.003), higher wall motion scores (25.3±5.0 vs. 23.0±5.2, p=0.048), and higher E/E' (14.4±6.2 vs. 11.2±3.9, p=0.027) (Table 5).

Table 4. Demographic, therapeutic, and laboratory characteristics of patients in Non-MACE and MACE group

	Non-MACE group (n=106)	MACE group (n=23)	p value
Age (years old)	58.8±11.5	64.3±11.5	0.04
Male (%)	78 (73.6)	14 (60.9)	0.222
Smoking (%)	53 (50.0)	9 (39.1)	0.514
Diabetes mellitus (%)	28 (26.4)	8 (34.8)	0.417
Hypertension (%)	50 (47.2)	12 (52.2)	0.663
Total cholesterol (mg/dL)	195.5±38.3	173.6±31.7	0.012
Triglyceride (mg/dL)	158.3±87.8	142.6±83.5	0.433
LDL cholesterol (mg/dL)	125.1±39.0	105.5±35.7	0.029
Creatinine (mg/dL)	0.98±0.24	1.02±0.26	0.494
Troponin (ng/dl)	36.3±25.3	49.1±32.8	0.040
CK-MB (ng/dl)	195.1±108.7	199.0±116.3	0.877
Pain to reperfusion time (hours)	5.1±2.5	6.5±3.2	0.059
Revascularization therapy (%)			0.412
Primary PCI	79 (74.5)	16 (69.6)	
Thrombolysis	27 (25.5)	7 (30.4)	
LV Remodeling	28(26.4)	13 (56.5)	0.005
Medication (%)			
HMG-CoA reductase inhibitors	60 (56.6)	10 (43.5)	0.252
ACEi	30 (28.3)	4 (17.4)	0.828
ARB	45 (42.5)	13 (56.5)	0.219
Beta-blocker	71 (67.0)	14 (6.9)	0.575
Diuretics	59 (55.7)	16 (69.6)	0.220

LDL: low density lipoprotein, CK-MB: creatinine kinase-MB, Ischemic time: time to reperfusion after onset of infarction, PCI: percutaneous coronary intervention, LV : Left

ventricle, HMG-CoA: beta-Hydroxy-beta-methylglutaryl coenzyme A, ACEi: angiotensin converting enzyme inhibitor,: ARB; angiotensin II receptor blocker,

Table 5. Angiographic and echocardiographic characteristics of patients in Non-MACE and MACE group

	Non-MACE group (n=106)	MACE group (n=23)	p value
Infarction territory (%)			0.473
Anterior	50 (47.2)	14 (60.9)	
Lateral	10 (9.4)	2 (8.7)	
Inferior	46 (43.4)	7 (30.4)	
Angiographic disease extent			0.085
1/2/3/Left main disease (%)	56.5/29.2/12.3/1.8	43.5/21.7/26.1/4.3	
LVEDV (mL)			
Initial	71.8±18.5	72.9±21.9	0.002
Follow-up	75.7±21.6	85.6±24.6	0.000
LVEF (mL)			
Initial	55.9±9.4	49.2±9.7	0.003
Follow-up	58.6±10.8	47.6±12.0	0.000
Wall motion scores			
Initial	23.0±5.2	25.3±5.0	0.048
Follow-up	21.5±5.6	26.1±6.7	0.001
E/E’			
Initial	11.2±3.9	14.4±6.2	0.027
Follow-up	7.7±2.8	14.6±7.8	0.000

LVEDV: left ventricular end-diastolic volume, LVEF: left ventricular ejection fraction, Initial: within 3 days after admission, Follow-up: at least 6 months after discharge.

3.5 Serial BNP and Major adverse events

The changes of BNP according to the presence or absence of MACE were also biphasic in both groups. Levels of BNP at acute, early and late phase were 208.0±382.3, 594.0±903.9 and 281.2±369.8 pg/mL in MACE group and 57.2±86.7, 110.4±141.0, 54.4±67.6 pg/mL in non-MACE group. The difference of BNP at each time was statistically significant within and between groups (p=0.000) and the difference between groups was greatest at early phase (Fig. 2).

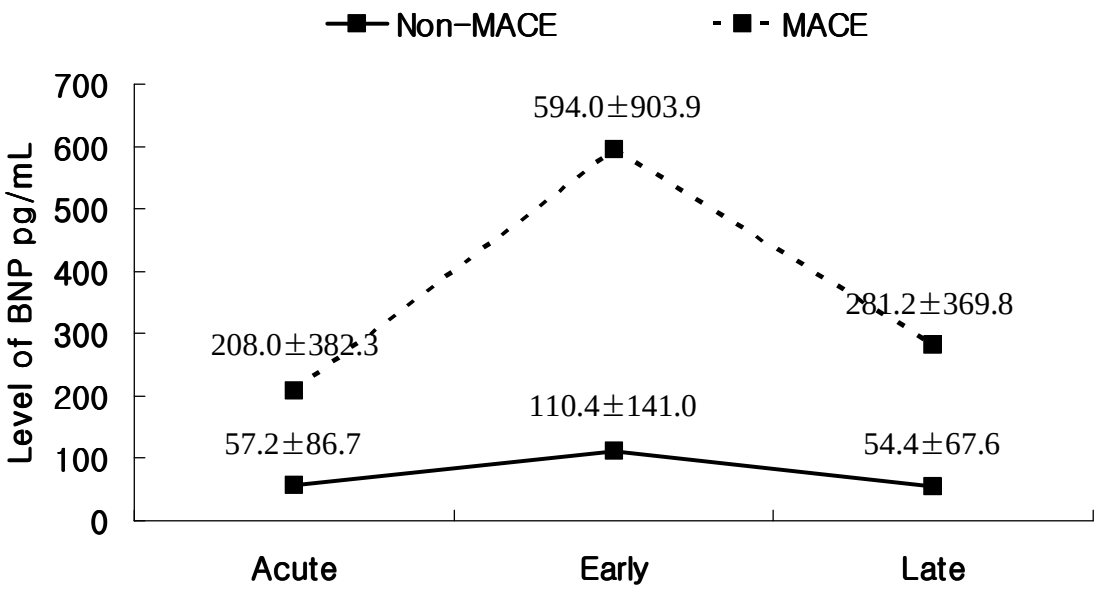

Fig.2. Serial change of BNP according to MACE. Repeated measures ANOVA analysis p=0.000.

3.6 Predictors of MACE

Univariate predictors of MACE were age, total cholesterol, LDL-cholesterol, pain to reperfusion time after AMI, LV ejection fraction, E/E' ratio, BNP levels at acute, early and late period. The independent predictors of MACE were BNP at early phase (Odd ratio 1.001, 95% CI 1.000-1.002) and LVEF (Odd ratio 0.944, 95% CI 0.899-0.991) in Cox proportional hazards regression analysis (Table 6). The optimal prognostic thresholds of BNP at early phase as assessed by receiver operating characteristics analysis, was 109 pg/mL (sensitivity 69.5%, specificity 68.9%) (Fig. 3). Kaplan-Meier survival curves in patients stratified according to level of BNP at early phase <109 pg/mL and ≥ 109 pg/mL revealed significant difference in MACE free survival (Fig. 4).

Table 6. Multivariate analysis of independent risk factors of MACE

Variables	Odd ratio	95% CI		p value
		Lower	Upper	
Age	1.024	0.982	1.068	0.269
Total Cholesterol (mg/dL)	1.001	0.974	1.028	0.939
LDL-Cholesterol (mg/dL)	0.990	0.965	1.016	0.433
Ischemic time (hours)	0.963	0.794	1.169	0.706
LVEF (%)	0.944	0.899	0.991	0.020
E/E'	0.991	0.883	1.111	0.874
LV Remodelling	1.195	0.399	3.575	0.750
BNP at acute phase (pg/mL)	0.999	0.997	1.001	0.190
BNP at early phase (pg/mL)	1.001	1.000	1.002	0.048
BNP at late phase (pg/mL)	1.001	0.998	1.003	0.625

LDL: low density lipoprotein, Ischemic time: time to reperfusion after onset of infarction, LVEF: left ventricular ejection fraction, LV: left ventricle, Acute phase: at admission (<24hous), Early phase:2-6 days after admission, Late phase: after at least 6 months following acute myocardial infarction.

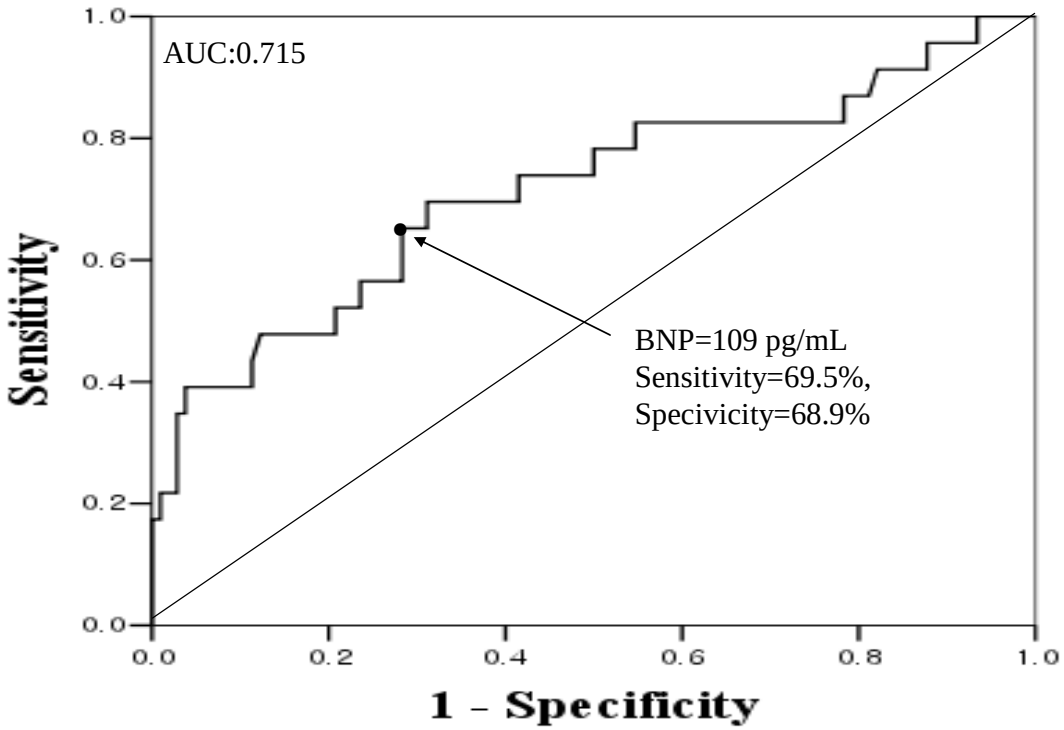

Fig.3. The ROC curve of BNP to predict MACE.

The AUC of early period BNP concentration for predicting MACE in patients with acute myocardial infarction was 0.715 (sensitivity 69.5%, specificity 68.9%), and optimum cut-off point was 109 pg/mL ($p<0.001$). ROC: receiver operating characteristic, AUC: area under the

curve, BNP: B-type natriuretic peptide, MACE: major adverse cardiac

event

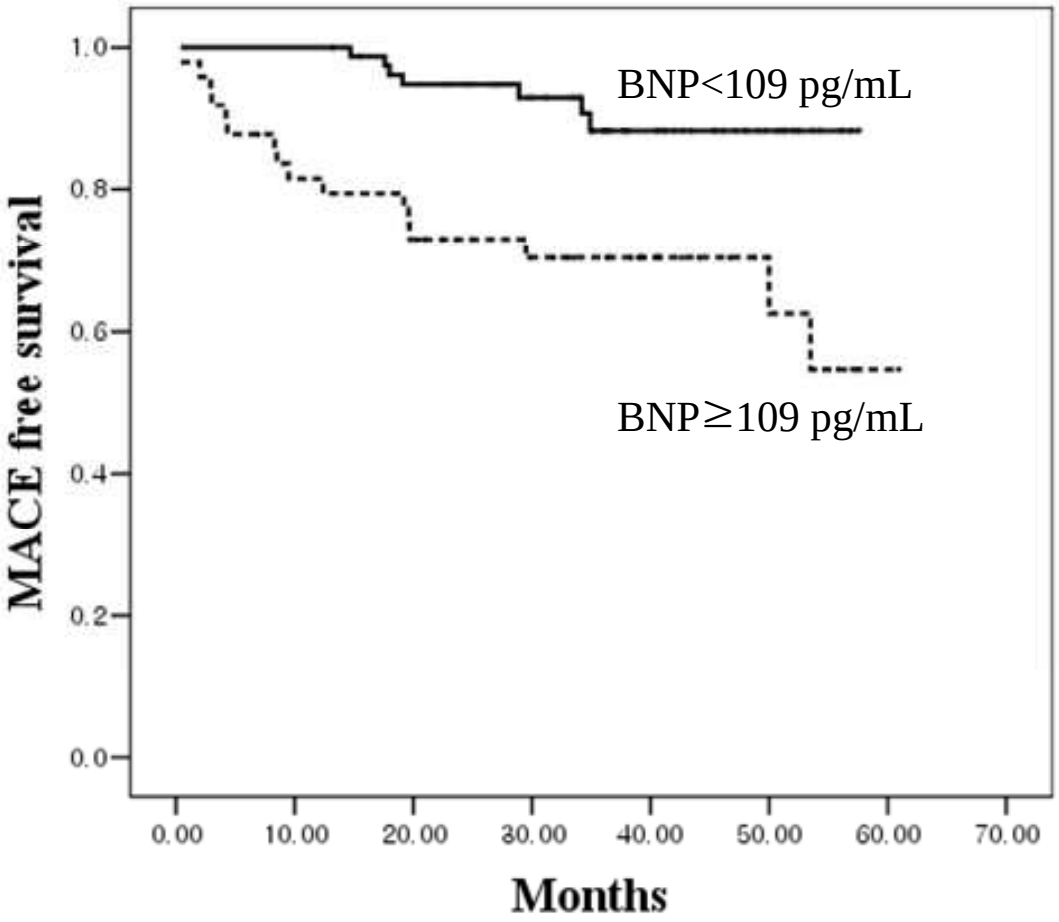

Fig.4. Kaplan-Meier survival curve of cumulative survival rates in patients with acute myocardial infarction divided into 2 groups according to BNP concentration. Patients with BNP ≥ 109 pg/mL differed meaningfully from patients with BNP<109 pg/mL. p=0.001. BNP: B-type natriuretic peptide.

4. Discussion

Our study evaluated the relationship between serial change of BNP and LV remodeling or long-term prognosis in patients with successful reperfusion therapy to determine the optimal time of sampling of BNP after acute myocardial infarction. Compared with previous studies, this study is distinctive as follow up duration was relatively long and analyzed serial BNP change including relatively long time elapsed after acute myocardial infarction. Our study clearly shows that the change of BNP after AMI was biphasic and only early phase (2-6 days after admission) BNP was an independent predictor of left ventricular remodeling and MACE after acute myocardial infarction.

In previous reports, the changing pattern of the plasma BNP level in patients with AMI is dynamic and biphasic.[9] The plasma level of BNP was significantly increased on admission in patients with acute myocardial infarction and reached the peak level after 4-7 days, and thereafter, the level decreased.[9] The mechanism for the formation of the first acute phase plasma BNP peak was shown to be due to the genetic characteristics of BNP.[10] The BNP is one of the acute-phase reactants hat are released in response to acute tissue injuries. The levels

of plasma BNP in the acute phase of acute myocardial infarction did not correlate significantly with the hemodynamic parameters. This suggests that the synthesis and secretion of BNP may be stimulated by myocardial necrosis, local mechanical stress, or both on ventricular myocytes even when global hemodynamic parameters are within normal ranges.[9] Plasma BNP concentration in subacute phases of myocardial infarction correlated significantly with pulmonary capillary wedge pressure, cardiac index, stroke volume, left ventricular ejection fraction and left ventricular end diastolic pressure.[11] In subacute phase, increased wall stress after myocardial infarction mostly derives from stretch in the border zone between infarct and non-infarct sites. BNP synthesis is presumably enhanced, as shown in experimental animals[12] and in humans.[13] From one to six months, the concentration of plasma BNP and of BNP released from the infarct site decreased significantly due to functional recovery after fibrotic scar formation.[14]

4.1 Serial change of BNP and LV remodeling after acute myocardial infarction

In this study, LV remodeling was occurred in 31.8% patients. All levels of BNP at each time were significantly higher in remodeling group, and the difference of early phase BNP was most prominent. In multivariate analysis, early phase BNP and wall motion scores

were independent predictors of LV remodeling.

LV remodeling after AMI is a dynamic process of progressive changes in LV chamber size, shape, muscle mass, and function.[15] In previous report, LV dilatation and increased wall stress after MI is associated with increased LV secretion of BNP. Furthermore, BNP concentration can be used as a predictor of subsequent LV dilatation.[3] Talwar et al reported that N-terminal pro-brain natriuretic peptide at 73–120 h was the best independent predictor of wall motion index during hospitalization and at 6 weeks.[16] These results may explain that especially early phase BNP is the most powerful predictor of LV remodeling after acute myocardial infarction among serially checked BNP.

4.2 Serial change of BNP and long term prognosis after acute myocardial infarction

In our study, there were 23 MACEs (17.8%) during follow-up. In patients with MACE, levels of BNP at each time were higher and the difference was greatest at early phase. The independent predictors of MACE were LVEF and early phase BNP. The optimal prognostic threshold of BNP at early phase was 109 pg/mL (sensitivity 69.5%, specificity 68.9%). MACE free survival was significant higher in patients with level of early phase BNP<109 pg/mL.

LV systolic function is a major prognostic indicator after AMI.[17] BNP and NT-proBNP

differ from other biomarkers used for risk stratification in ACS such as troponins and CRP in that BNP is a counterregulatory hormone that plays an active role in the response to ischemic injury. There have been several reports indicating that in addition to LV ejection fraction, the plasma BNP level obtained in the acute phase of AMI can be used as a prognostic marker for patients with AMI.[18-20] Because the plasma BNP level changes dramatically during the period after the onset of AMI, identification of a suitable sampling time is problematic. Talwar et al reported that plasma N-terminal pro-brain natriuretic peptide measured later in hospitalization better predicts poor outcome following myocardial infarction than when it is measured in the immediate post infarction period.[16] Suzuki et al reported that plasma levels of BNP measured at 3 to 4 weeks after AMI were a prognostic marker statistically.[21]

In the present long-term follow up study, plasma level of BNP measured at 2 to 6 days after admission due to acute myocardial infarction was unique independent predictor of LV remodeling and long-term prognosis after acute myocardial infarction. The results of the present study revealed that a sampling time at 2-6 days after the admission due to AMI would provide prognostic insights. However, the sample size was limited and the time interval from onset of acute myocardial infarction to first sampling of BNP was variable. Thus, it might be

necessary to perform analysis on a larger scale in another series of studies.

5. Conclusions

We investigated the relationship between serial measurement of BNP and LV remodeling, or long-term prognosis in patients with acute myocardial infarction. Plasma levels of BNP at each phase were significantly higher in remodeling group and MACE group. The difference of the level of BNP was most prominent at early phase among serially checked BNP (Fig 1, 2). Independent predictors of left ventricular remodeling were BNP at early phase and wall motion scores and those of long term prognosis were BNP at early phase and left ventricular ejection fraction (Table 3, 6).

In conclusion, BNP measured at 2 to 6 days after the admission among serially checked BNP is unique significant predictor of LV remodeling and long-term prognosis after acute myocardial infarction.

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국문 요약

급성 심근경색환자에서 연속적으로 측정한 BNP와 급성 심근경색 후 좌심실 재형성 및 장기예후와의 관계

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안 민 수

배경: B-type natriuretic peptide (BNP)는 급성 심근경색 이후 중요한 예후 인자이다. 그러나 급성 심근경색 발병 이후에 혈중 BNP치는 극적으로 변하기 때문에 적합한 채혈 시간을 정하는 것이 문제가 되었다. 이에 저자는 급성 심근경색 환자에서 연속적으로 BNP를 측정하여 시간에 따른 각각의 BNP치가 좌심실의 재형성 및 장기 예후에 대한 예측인자로 작용하는지 알아보고자 하였다. 방법: 2003년 4월부터 2006년 6월까지 ST 분절 상승 심근경색으로 내원한 334명의 환자들 중, 내원 후 3일 이내 그리고 퇴원 최소 6개월 이후에 전향적으로 심초음파를 시행한 129명의 환자들의 정보를 후향적으로 분석하였다. BNP는 급성기 (내원 당시), 초기 (입원 후 2-6일), 후기 (퇴원 후 최소 6개월 이후)에 연속적으로 측정하였다. 좌심실 재형성은 초기와 추적관찰에서 시행한 심초음파에서 좌심실 확장기말 부피가 15%이상 증가한 것으로 정의 하였다. 장기 주요심장사건은 심인성 사망, 심근경색, 심부전으로 인한 재입원으로

정의하여 조사하였다. 결과 : 대상 환자의 평균 연령은 59.7±11.7세였고 남성이 71.3%였다. 평균 추적관찰 기간은 35.9±11.8 개월이었다. 급성 심근경색 이후 BNP의 변화는 이상성을 보였다. 재형성이 발생하였던 군의 급성기, 초기, 후기 BNP치는 재형성이 발생하였던 군에서는 168.1±300.0, 451.1±700.7 and 205.5±293.2 pg/mL였고 재형성이 발생하지 않은 군에서는 44.9±68.6, 78.1±104.6, 43.2±57.1 pg/mL였다(p=0.000). 재형성에 대한 독립적인 예측 인자는 초기 BNP (비교위험도 1.006, 95% 신뢰구간 1.001-1.010)와 국소벽 운동장애 점수 (비교 위험도, 95% 신뢰구간 1.022-1.413)이었다. 주요 심장사건이 발생한 군에서 BNP치는 208.0±382.3, 594.0±903.9 and 281.2±369.8 pg/mL이었고 주요 심장사건이 발생하지 않은 군에서 는 57.2±86.7, 110.4±141.0, 54.4±67.6 pg/mL이었다. 주요심장사건에 대한 독립적인 예측인자는 Cox proportional hazards regression 분석에서 초기 BNP (비교위험도 1.001, 95% 신뢰구간 1.000-1.002)와 좌심실 구혈율 (비교위험도 0.944, 95% 신뢰구간 I 0.899-0.991)이었다. 결론: 본 논문의 결과로 보아 급성심근경색 2-6일 후 초기에 측정한 BNP 값이 급성심근경색 환자의 장기예후와 좌심실 재형성을 추정하는 인자로서 의미 있을 것으로 생각한다.

핵심단어: B-type natriuretic peptide; 급성심근경색; 재형성; 예후