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Assessment of Extent of Myocardial Ischemia in Patients with Non-ST Elevation Acute Coronary Syndrome Using Serum B-type Natriuretic Peptide Level

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Since B-type natriuretic peptide (BNP) concentration has been shown by recent studies to be elevated in patients presenting acute coronary syndrome (ACS) even in the absence of overt heart failure, other mechanisms for elevating plasma BNP (p-BNP) concentrations may be suggested to exist. We have studied the correlation between p-BNP level and the extent of myocardial ischemia (EMI) in non-ST elevation (NSTE) ACS and evaluated the BNP level as an objective marker of EMI. In 204 patients with NSTE ACS, we estimated the EMI by the echocardiographic wall motion score index (WMSI) and the coronary angiographic Gensini score. As the positive control group, 44 patients with stable angina were enrolled into the study. We compared their initial p-BNP levels with WMSI and the Gensini score. Additionally, peak troponin-T level was compared with p-BNP level in NSTE myocardial infarction (MI) patients. Using the multiple regression analysis, adjustments for age, left ventricle (LV) wall stress, LV mass amount and ejection fraction (EF) were made. Patients with LVEF $< 45\%$ or age > 75 years or underlying diseases that could elevate BNP levels were excluded from the study. P-BNP level was increased in NSTE ACS patients compared with stable angina patients (133.9 ± 87.4 vs. 12.2 ± 9.2 pg/ml, $p<0.05$). P-BNP levels were found to correlate with WMSI and the Gensini score in unstable angina (r=0.519, $p<0.01$; r=0.680, $p<0.01$) and NSTEMI (r=0.716, $p<0.01$; r=0.684, $p<0.01$) patients, respectively. Additionally, p-BNP levels correlated with the peak troponin-T level in patients with NSTEMI (r=0.700, $p<0.01$). P-BNP level might be a useful marker in the assessment of EMI.

Key Words: B-type natriuretic peptide, myocardial ischemia, acute coronary syndrome

INTRODUCTION

Patients presenting chest pain or similar symptoms suggestive of the acute coronary syndrome (ACS) today make up about 20% of all visit to the medical emergency department.[1] About 80% of these patients would have an electrocardiogram (ECG) non-diagnostic of acute myocardial infarction or unstable angina. In this category of patients, we assume the extent of myocardial ischemia based on echocardiography or peak plasma troponin level results. However, the echocardiography has limitations associated with echo window and the skill of investigator, besides, the troponin level would be normal in most patients with unstable angina. Since B-type natriuretic peptides (BNP) have shown by recent studies to be elevated in patients presenting unstable angina or myocardial infarction even in the absence of overt heart failure, other mechanisms elevating plasma BNP concentrations may be suggested to exist. To examine the plasma BNP as an independent marker of myocardial ischemia, we compared the plasma BNP level of non-ST elevation ACS patients with that of stable angina patients. Furthermore, we studied the relationship between the plasma BNP level and the extent of myocardial ischemia (by echocardiography, coronary angiography and cardiac enzyme) in non-ST

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elevation ACS, and evaluated the BNP level as an objective marker for evaluation of the extent of myocardial ischemia.

MATERIALS AND METHODS

Study population

Patients complaining of chest pain within 24 hours and diagnosed as non-ST elevation ACS, defined as an unstable angina pectoris or non-ST elevation myocardial infarction (NSTEMI) admitted to the emergency department of the Yongdong Severance Hospital from January 2002 to October 2003 were eligible for participation in this study. As a control group, stable angina patients were enrolled into the study. Unstable angina was defined as class IIIB of Braunwald's classification.[2] NSTEMI was defined as chest pain with troponin level above 0.1 ng/mL but non-ST elevation in ECG finding. All patients underwent echocardiography within 12 hours from admission and coronary angiography within 5 days from admission. The main exclusion criteria were age <20 or >75 years and the echocardiographic left ventricular ejection fraction (LVEF) $<45\%$. Additionally, patients with history of heart failure or diseases that could increase extracellular fluid, like pulmonary thromboembolism, acute and chronic renal failure, end stage renal disease, sepsis, liver cirrhosis, chronic obstructive lung disease, Cushing's syndrome, hyperthyroidism, primary aldosteronism, and adult respiratory distress syndrome were excluded from the study. All the clinical data were collected prospectively.

Measurement of BNP levels and troponin T levels

Peripheral blood samples for plasma BNP were obtained within 2 hours on admission by direct venipuncture of the antecuital vein after the patient had been resting in the supine position for >30 minutes. Blood samples were kept at room temperature and analyzed within 4 hours after collection. Before the analysis, each tube was shaken/turned upside-down several times to ensure homogeneity of the specimen. The whole blood specimens were then analyzed in triplicate by Immunofluorescence BNP assay (Biosite Diagnostics, San Diego, CA, USA), which can measure BNP from 5 pg/mL to 5000 pg/mL. Levels below 5 pg/mL BNP were regarded as 2.5 pg/mL for the purposes of the statistics. Troponin-T levels were measured by ECLIA (electrochemiluminesence immunoassay, Roche, Basel, Switzerland) within 2 hours in all patients and measured every 12 hours until the peak level in NSTEMI patients.

Echocardiography

Echocardiographic examination was performed by an experienced investigator within 12 hours on admission to hospital. M-mode, 2D images, spectral and color flow Doppler recordings were obtained using commercially available instruments operating in range from 2.0 to 3.5 MHz. Two-dimensional imaging examinations were performed in the standard fashion in the parasternal long- and short-axis views and apical 4- and 2-chamber views. All the data were hard copied to a 1/2-in VHS videotape for subsequent playback, analysis, and measurement. Two-dimensional echocardiograms were subjected to careful visual analysis to detect regional contractile abnormalities. LV systolic, diastolic volumes and ejection fraction were derived from biplane apical (2- and 4-chamber) views, using a modified Simpson's rule algorithm. For the purposes of the regional wall motion analysis, we used a 16-segment.[3] Each segment was assigned a score, based on its contractility as assessed visually: normal 1; hypokinesis, 2; akinesis, 3; dyskinesis, 4; and aneurysm 5. On the basis of this wall motion analysis scheme, a WMSI is calculated to semiquantitate the extent of regional wall motion abnormalities. WMSI was calculated as the sum of the wall motion scores divided by the number of the visualized segments (Fig. 1). Meridional wall stress index (MWSI) was defined as being p (systolic LV pressure, dyne/cm^2 multiplied by r (LV systolic diameter, mm) divided by 2h (1+h/2r) (h being the posterior wall thickness (mm)). LV mass index (LV mass in g/m^2 body surface area) was estimated from the LV short-axis dimension and a simple geometric cube formula.[4] We defined LV

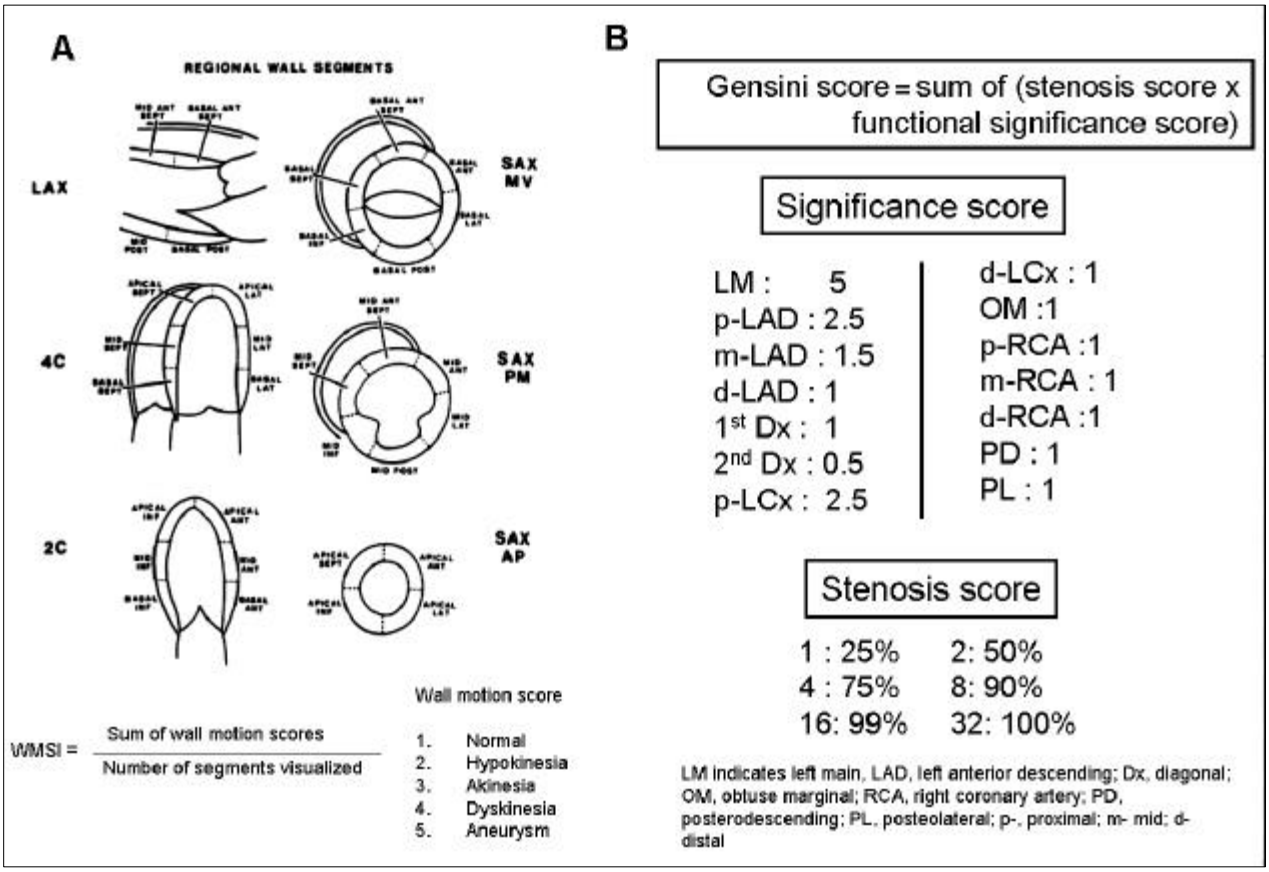

Fig. 1. Estimation of extent of myocardial ischemia by echocardiographic wall motion score index (A) and coronary angiographic jeopardy (Gensini) score (B).

mass 1.04[(LVID + PWT + IVST)3-LVID3] × 0.8 + 0.6, where LVID is the internal dimension, PWT is the posterior wall thickness, IVST is the thickness of the intraventricular septum, 1.04=specific gravity of the myocardium, and 0.8 is the correlation factor. All the measurements are made at the end-diastole (at the onset of the R wave) in centimeters.

Coronary angiography

Coronary angiography was performed by the Seldinger's technique. The angiograms were examined by an qualified cardiologist. The Gensini score, a measure of the extent of myocardial ischemia, was computed by assigning the severity score to each coronary stenosis, according to the degree of luminal narrowing and its geographic importance. Reduction in the diameter of the lumen, and the roentgenographic appearance of concentric lesions as well as eccentric plaques were evaluated (reductions of 25%, 50%, 75%, 90%, 99%, and complete occlusion values were given Gensini scores of 1, 2, 4, 8, 16, and 32, respectively). To each principal vascular segment a multiplier, according to the functional significance of the myocardial area supplied by this segment was assigned: the left main coronary artery, × 5; the proximal segment of the left anterior descending coronary artery (LAD), × 2.5; the proximal segment of the circumflex artery, × 2.5; the mid-segment of the LAD, × 1.5; the right coronary artery, the distal segment of the LAD, the posterolateral artery, and the obtuse marginal artery, × 1; and others, × 0.5 (Fig. 1).[5]

Statistical analysis

Statistical analyses were performed using a SPSS 11.0 for Windows. The data are expressed as

mean ± SD. The group comparison of BNP values were made using independent t-test. In the NSTEMI group, the correlation between the peak toroponin T and plasma BNP level was found. In both the unstable and NSTEMI groups, Pearson's correlation coefficients were computed between the extent of myocardial ischemia (WMSI and Gensini score) and plasma BNP level, respectively. Multiple regression analysis was performed between the plasma BNP level and many parameters which affect the basal plasma BNP level, such as age, LVEF, LV mass index, WMSI. A $p < 0.05$ was considered to be significant.

RESULTS

The study population consisted of 204 patients: 113 were enrolled as unstable angina group and 91 were NSTEMI group. The mean age was 61 years in the unstable angina group and 64 years in NSTEMI patients, respectively. Forty percent were women. Patients with history of hypertension were 34%, diabetes 26%, dyslipidemia (LDL-cholesterol >160 mg/dl or HDL- cholesterol <35 mg/dl) 27%, obesity 42% and smoking were 49% of total. On coronary angiographic findings, percentage of the left anterior descending artery involvement was 57% (unstable angina was 59% and NSTEMI was 56%). As a positive control, 44 patients with stable angina were enrolled into the study. There were no significant differences in multiple parameters between the stable angina group and NSTE ACS group, such as history of hypertension (stable angina vs. NSTE ACS; 19% vs. 34%), diabetes (31% vs. 26%), dyslipidemia (LDL-cholesterol >160 mg/dl or HDL-cholesterol <35 mg/dl) (21% vs. 27%), smoking (42% vs. 49%), obesity (32% vs. 42%) and incidence of angiographic involvement of the left anterior descending artery (43% vs. 57%). The basic characteristics, echocardiographic parameters, plasma BNP level and angiographic Gensini scores are shown in Table 1. Plasma BNP levels were more elevated in the unstable angina (70.2 ± 53.3 pg/mL vs. 12.2 ± 9.2 pg/mL, $p < 0.05$) and NSTEMI (213.1 ± 204.9 pg/mL vs. 12.2 ± 9.2 pg/mL, $p < 0.05$) group compared with the stable angina group. Coronary angiographic Gensini score (24.1 ± 16.7 vs. 8.4 ± 5.1, $p < 0.05$) and WMSI (1.35 ± 0.81 vs. 1.06 ± 0.09,

Table 1. Basic Characteristics, Ehchocardiographic and Coronary Angiographic Parameters of Study Population

	Stable angina (n=44)	Unstable angina (n=113)	NSTEMI (n=91)
Age (years)	60.2 ± 8.8	61.7 ± 9.5	64.2 ± 12.0
BSA (m2)	1.7 ± 0.1	1.7 ± 0.2	1.7 ± 0.2
Male /female	26/18	74/39	58/33
History of HiBP (n)	19	38	32
LVEF (%)	65.4 ± 7.4	61.4 ± 9.2	56.2 ± 8.8
LV mass index (g/m2)	296.9 ± 60.1	326.2 ± 140.2	341.3 ± 97.4
Wall stress index (dyne/cm2)	100076.2 ± 57959.0	199197.8 ± 50048.1	190050.7 ± 78325.6
Peak troponin-T* (ng/mL)			4.67 ± 4.94
BNP (pg/mL)	12.2 ± 9.2	70.2 ± 53.3†	213.1 ± 204.9†
WMSI	1.06 ± 0.09	1.24 ± 0.19†	1.50 ± 0.38‡
Gensini score	8.4 ± 5.1	19.6 ± 14.2†	29.9 ± 22.0†
LAD culprit (%)	43	56	59

NESTEMI indicates non-ST elevation myocardial infarction; HiBP, hypertension; LVEF, left ventricular ejection fraction; BSA, body mass index; WMSI, wall motion score index; LAD, left anterior descending artery; *only in NSTEMI group; †$p<0.05$, ‡$p<0.01$ vs. stable angina.
All other $p \geq 0.05$.

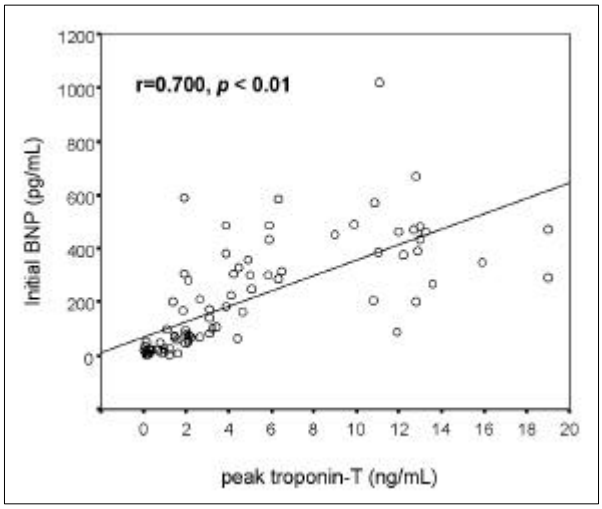

Fig. 2. Peak troponin T level was positively correlated with plasma BNP level in NSTEMI group.

$p<0.05$) were more elevated in non ST elevation ACS group compared with stable angina group. Table 2 represents the correlation between multiple parameters and plasma BNP level with the multiple linear regression analysis. This result showed that WMSI and Gensini score positively correlated with plasma BNP level (r=0.857; $p<0.05$, r=0.754; $p<0.05$). Peak troponin T level positively correlated with the extent and severity of myocardial ischemia, such as WMSI (r=0.822; $p<0.01$) and Gensini score (r=0.637; $p<0.01$) in the NSTEMI group. Additionally, peak troponin T level positively correlated with plasma BNP level in the NSTEMI group (r=0.700; $p<0.05$) (Fig. 2). WMSI, as the extent of myocardial ischemia assessed by an echocardiography, and Gensini score, as the severity and extent of myocardial ischemia assessed by coronary angiography, also correlated positively with the plasma BNP level in the unstable angina and NSTEMI groups, respectively (Fig. 3).

DISCUSSION

Recently, the plasma BNP and NT-proBNP concentrations have been shown to provide prognostic information about the development of heart failure after the acute myocardial infarction, and they also are regarded as prognostic markers of morbidity and mortality in patients with ACS.[6,7] Possible mechanisms may involve elevated BNP that may reflect a permanent LV dysfunction, and it in turn may also reflect a temporary LV dysfunction secondary to transient ischemic episodes, exposing to risk a large part of the myocardium. Additionally, BNP elevation is associated with an advanced age of the patient, renal impairment, left ventricular hypertrophy, and preexisting LV systolic or diastolic dysfunction. Other numerous factors can also affect this result. But the pathophysiologic mechanism responsible for this strong association still has not been revealed. So there are two concerns which should be clarified. One is to reveal the main mechanism of BNP elevation that deteriorates the prognosis. In the present study, we have made adjustments for the age, LV mass amount, wall stress and global LV systolic function to plasma BNP level; according to the present

Table 2. Correlation between Plasma BNP Level and Multiple Parameters by Multiple Linear Regression Study in Non ST Elevation ACS Patients

	Correlation (r)	Significance (p)
Age	0.688	0.552
LVEF	-0.003	0.994
WMSI	0.857	0.023*
Gensini score	0.754	0.045*
Wall stress index	0.543	0.610
LV mass index	0.352	0.355

LVEF indicates left ventricular ejection fraction; LV, left ventricle; WMSI, wall motion score index.
*$p<0.05$.

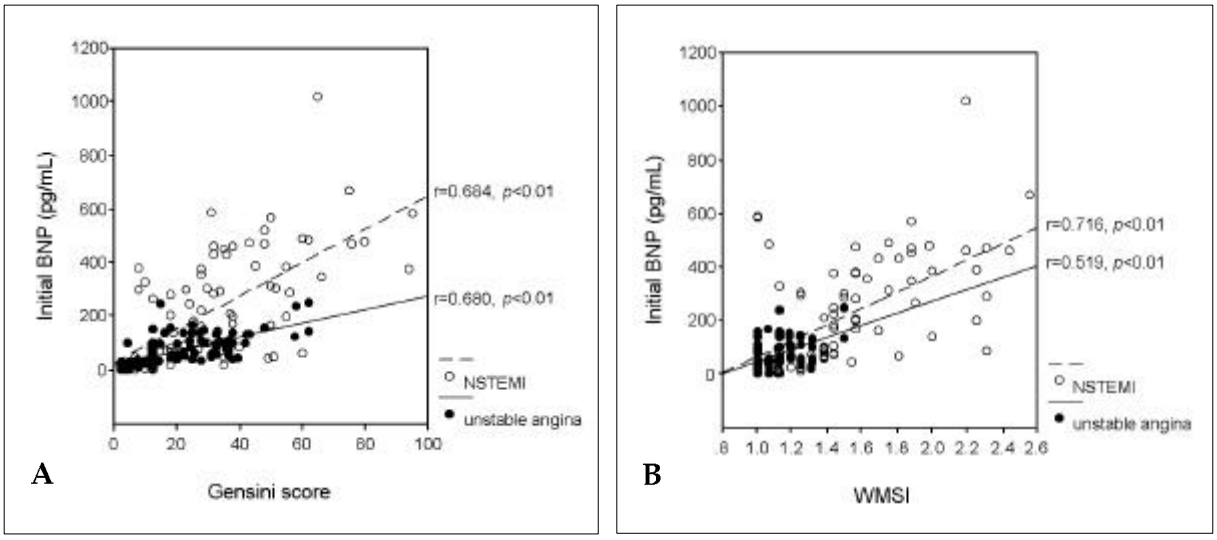

Fig. 3. WMSI (A) as an extent of myocardial ischemia assessed by an echocardiography and Gensini score as a severity and extent of myocardial ischemia assessed by coronary angiography were positively correlated with plasma BNP level in unstable angina and NSTEMI group, respectively.

study, the extent of myocardial ischemia is the main decisive prognostic factor. These results may help set up initial treatment modalities, such as early aggressive treatment with neurohormonal antagonism (such as angiotensin-converting enzyme inhibitors and beta blockade) and an early revascularization procedure in addition to an intense antithrombotic treatment. And BNP level could be a useful guideline for medical treatment. The other concern is to reveal whether pure myocardial ischemia without hemodynamic changes can elevate the plasma BNP level and, if possible, what mechanisms are responsible for it. According to the current study, myocardial ischemia without homodynamic changes can increase the plasma BNP level, and the plasma BNP level can reflect the extent of the myocardial ischemia. Several other studies have supported these results. In the previous animal model of transmural infarction, the level of expression of the BNP gene in the left ventricle was elevated about three-fold within four hours after coronary ligation, and the tissue levels of BNP were increased even in non- infarcted segments as well as in infarcted areas.[8] Several small cross-sectional studies have shown that the level of BNP is higher in the unstable angina than stable angina or healthy control groups.[9] Goetze et al. have reported that the ventricular BNP gene expression is upregulated by myocardial hypoxia, resulting in augmented plasma concentration of BNP and proBNP in human myocardium.[10] Thus, elevated concentrations of BNP and proBNP do not always reflect heart failure, whether in relation with myocardial ischemia. The mechanisms of production of these peptides in myocardial ischemia are not clear. We could assume that myocardial ischemia may increase the regional ventricular wall stretch owing to local depression of myocardial contraction. Mechanical stretch can activate the JAK/STAT pathway and may stimulate BNP secretion and augment the gene expression of IL-6 and cardiotrophin-1.[11,12] Alternatively, cardiotrophin-1 may, directly promote myocardial gene transcription of BNP.[13] Another recent study has shown that BNP and its signaling system are involved in the induction of matrix metalloproteinases (MMPs). Furthermore, crosstalk of BNP with ET-1 (endothelin-1) and TNF-α (tissue necrosis factor-α) occurs on modulating MMP-2 abundance.[14] It is possible that increased BNP may trigger the MMP expression in atheromatous plaque which may add to the plaque vulnerability and propagate the plaque breakdown. This vicious cycle may provide a clue of the cor-

relation between the severity of myocardial ischemia and plasma BNP level. Additionally, this result may explain the recurrent ischemic event in ACS patients with elevated initial plasma BNP levels. Future studies should be focused on the exact role of BNP in myocardial ischemia.

The present study have some limitations, although we have made adjustments for major factors which may affect the plasma BNP level, but the effect of minor factors, such as smoking history, current medication could not be excluded completely. One shortcoming is that BNP was measured during only the first 2 hours after admission. Previous study has reported that BNP and NT-proBNP continues to increase in patients with AMI, during the first 24 hours after chest pain onset.[15] Thus serial measurement might be of additional value. Another shortcoming is the fact that we could not know the exact extent of myocardial ischemia in patients with non-ST ACS but combined with echocardiographic WMSI and coronary angiographic jeopardy score (Gensini score), we could improve the accuracy of it. BNP as a cardiac biomarker, it might help clinicians select an appropriate therapeutic regimen. For example, patients with elevated levels of BNP after ACS may derive benefit from intensive antiplatelete and antithrobotic medication, neurohormonal antagonisms, such as beta-blockers and angiotensin-convering-enzyme inhibitors, and early revascularization procedure. Similarly, in patients who present low levels of BNP after an ACS, a less intensive management approach may be appropriate, in order to avoid the cost and risk related to unnecessary treatment modalities. These findings suggest that BNP might be helpful in patients with ACS in the aspect of establishment of the severity and prognostic factors of myocardial ischemia as well as selection of the therapeutic modality.

In conclusion, we can see that the plasma BNP level closely correlates with the extent of myocardial ischemia in patients with non-ST elevation ACS. Although further study is necessary , plasma BNP level could be an objective marker in assessing the patients with ACS.

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