N-Terminal Pro-B-Type Natriuretic Peptide Predicts Significant Coronary Artery Lesion in the Unstable Angina Patients With Normal Electrocardiogram, Echocardiogram, and Cardiac Enzymes

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Background  Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are not specific for ventricular dysfunction and other cardiac processes, such as myocardial ischemia, may also cause elevation of these markers.

Methods and Results  To determine whether elevation of NT-proBNP without elevation of cardiac specific markers can predict coronary artery disease (CAD), the serum level of NT-proBNP was measured in 161 patients with unstable angina (61.0±8.1 years, male 54.0%) with normal ventricular function (left ventricular ejection fraction >55% and no regional wall motion abnormality by echocardiography) and normal troponin I level (<0.05 ng/ml). In these patients, levels of C-reactive protein and myoglobin were normal and none had Q wave on electrocardiographic (ECG). The NT-proBNP level was higher in patients with CAD (n=74) than in patients without CAD (n=87) (173.1±231.6 vs 68.1±62.5 pg/ml, p<0.001). At the standard cut-off point of >200 pg/ml, elevated NT-proBNP level shows high probability of CAD (odds ratio, 10.1; 95% confidence interval, 2.6–38.7, p=0.001). The NT-proBNP level positively correlated with the extent of CAD (r=0.329, p=0.001). In multivariate analysis, the NT-proBNP was an independent predictor of CAD.

Conclusion  These results suggested that NT-proBNP is a useful screening test for CAD in the unstable angina patients with normal ECG, echocardiogram and cardiac enzyme levels. (Circ J 2005; 69: 1472–1476)

Key Words:  Coronary artery disease; NT-proBNP; Unstable angina

Optimal risk stratification of patients with acute coronary syndromes is of paramount importance for delivering appropriate care according to risk category in patients with and without persistent ST-segment elevation. Risk prediction based on clinical, electrocardiographic (ECG), and biochemical (ie, cardiac troponin) markers, however, is relatively inaccurate.

Brain (B-type) natriuretic peptide (BNP) is a neurohormone synthesized and released from the cardiac ventricles in response to increased wall tension. It is increased in patients with heart failure, myocardial infarction and in unstable angina and the level increases in proportion to the degree of left ventricular (LV) dysfunction. BNP is produced as a prohormone, pro-BNP, which is enzymatically cleaved into BNP and the amino-terminal portion of the prohormone, N-terminal pro-brain natriuretic peptide (NT-proBNP). In heart failure patients, the proportional and absolute increase in NT-proBNP exceeds that of BNP, suggesting that NT-proBNP may be a more sensitive marker of LV function.

The aim of the present study was to determine whether elevation of NT-proBNP without elevation of cardiac specific markers could predict coronary artery disease (CAD).

Methods

Study Population  The study group comprised 161 patients (61.0±8.1 years, male 54.0%) complaining of chest pain that developed within the past 24 h and diagnosed as unstable angina who were admitted to the emergency department of the Chonnam National University Hospital from November 2003 to October 2004. Unstable angina was defined as angina pectoris with at least 1 of 3 features: (1) occurring at rest and usually lasting more than 20 min, (2) being severe and described as frank pain and of new onset (ie, within 1 month), and (3) having a crescendo pattern.

All patients underwent echocardiography within 12 h of admission and coronary angiography within 5 days. The

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main inclusion criteria were normal ventricular function (LV ejection fraction >55%), no regional wall motion abnormality on echocardiography, normal troponin I level (≤0.05 ng/ml), normal C-reactive protein (CRP), myoglobin, and other cardiac enzymes, normal ECG, and normal creatinine clearance rate. None had suffered a myocardial infarction or unstable angina prior to hospitalization. The main exclusion criteria were LV ejection fraction ≤55%, even one hypokinetic segment on echocardiography, troponin I >0.05 ng/ml, myoglobin >92.5 ng/ml, creatine kinase (CK)-MB >9.5 U/L, CRP >0.5 mg/dl, any pathologic Q wave or ST-T change on 12-lead ECG on admission, and calculated creatinine clearance rate <80 mL·min⁻¹·m⁻². All the clinical data were collected prospectively.

Measurement of Serum NT-proBNP and Troponin I Levels

Peripheral blood samples for serum NT-proBNP were obtained within 2 h of admission by direct venipuncture of the antecubital vein after the patient had been resting supine for 30 min. Blood samples were collected in tubes without anticoagulant, centrifuged, and the serum was stored frozen in aliquots at −70°C within 30 min of collection. The serum NT-proBNP level was measured by an electrochemiluminescence “sandwich” immunoassay (ECLIA) method for NT-proBNP using an Elecsys® 2010 analyzer (Roche Diagnostics, Mannheim, Germany). This ECLIA detects photons using polyclonal antibodies (a biotinylated antibody and a ruthenium derivative-labeled antibody) in 2 voltage electric fields. It has a high sensitivity, specificity, and a large detection range: for NT-proBNP it extends from 5 to 35,000 ng/L. The reference value is variable according to age and sex at our institute, the reference value is <88 pg/ml for males and <153 pg/ml for females.

Troponin-I levels were also measured by ECLIA within 2 h in all patients and measured every 12 h until the peak level was observed.

Coronary Angiography

All patients underwent coronary angiography using a common technique. The coronary angiograms were assessed by 2 experienced angiographers unaware of NT-proBNP levels, using a validated quantitative coronary angiographic system (Philips H5000, Philips Medical Systems, Andover, MA, USA, or Allula DCI program, Philips Medical System, Best, The Netherlands). We estimated the extent of CAD using the Gensini score4 which is a measure of the extent of myocardial ischemia and is computed by assigning a severity score to each coronary segment 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) (Fig 1). To each principal vascular segment a multiplier, according to the functional significance of the myocardial area supplied by this segment was assigned: left main coronary artery, ×5; proximal segment of the left anterior descending coronary artery (LAD), ×2.5; proximal segment of the circumflex artery, ×2.5; mid-segment of the LAD, ×1.5; right coronary artery, distal segment of the LAD, posterolateral artery, and obtuse marginal artery, ×1; and others, ×0.5 (Fig 1).

Statistical Analysis

All metric variates were described as mean±standard deviation. Differences in the metric variates between groups

Table 1 Baseline Clinical Characteristics of the Patients With Chest Pain

<table>
<thead>
<tr>
<th></th>
<th>CAL (n=74)</th>
<th>No CAL (n=87)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61±8.8</td>
<td>60±8.0</td>
<td>0.236</td>
</tr>
<tr>
<td>Male gender (n, %)</td>
<td>49 (66.2)</td>
<td>38 (43.7)</td>
<td>0.004</td>
</tr>
<tr>
<td>Hypertension (n, %)</td>
<td>39 (52.7)</td>
<td>44 (50.6)</td>
<td>0.788</td>
</tr>
<tr>
<td>Diabetes (n, %)</td>
<td>18 (24.3)</td>
<td>8 (9.2)</td>
<td>0.009</td>
</tr>
<tr>
<td>Smoking (n, %)</td>
<td>20 (27.0)</td>
<td>8 (9.2)</td>
<td>0.444</td>
</tr>
<tr>
<td>Dyslipidemia (n, %)</td>
<td>47 (65.5)</td>
<td>19 (21.8)</td>
<td>0.000</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>67±6±6.8</td>
<td>69±6±6.6</td>
<td>0.171</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>108±2.2</td>
<td>90±4.2</td>
<td>0.100</td>
</tr>
<tr>
<td>C-reactive protein (mg/dL)</td>
<td>0.3±0.1</td>
<td>0.3±0.1</td>
<td>0.997</td>
</tr>
<tr>
<td>Troponin I (ng/ml)</td>
<td>0.02±0.01</td>
<td>0.01±0.01</td>
<td>0.544</td>
</tr>
<tr>
<td>CK-MB (U/L)</td>
<td>3.3±2.1</td>
<td>3.9±2.8</td>
<td>0.143</td>
</tr>
<tr>
<td>Myoglobin (mg/ml)</td>
<td>37.5±14.0</td>
<td>33.9±13.2</td>
<td>0.096</td>
</tr>
<tr>
<td>Homocysteine (mmol/L)</td>
<td>9.3±3.3</td>
<td>7.9±2.3</td>
<td>0.005</td>
</tr>
</tbody>
</table>

CAL, coronary artery lesion; CK-MB, MB fraction of creatine kinase.
were analyzed using Student’s t-test. Correlations between NT-proBNP and parameters were described with Pearson’s correlation. Prediction power of NT-proBNP for coronary artery lesions was calculated by multivariate logistic regression analysis. All statistical processes were done using SPSS-PC 11.0 (SPSS-PC Inc, Chicago, IL, USA). A p-value of less than 0.05 was considered significant.

**Results**

The detailed baseline characteristics of the study population are given in Table 1. No significant differences in age or LV ejection fraction were observed between the subgroups with and without coronary artery stenosis. However, male gender, diabetes, and dyslipidemia were more prevalent in the patients with CAD. Laboratory findings of creatinine, CRP, troponin I, CK-MB, and myoglobin were not different between the subgroups (Table 1).

The level of NT-proBNP according to the severity of CAD is shown in Table 2. In patients with less than 50% diameter stenosis it was 56.5±56.0 pg/ml, between 50% and 74% 72.5±50.8 pg/ml, between 75% and 89% 171.2±292.5 pg/ml, between 90% and 98% 171.8±222.2 pg/ml, 99% 249.5±115.4 pg/ml, and 100% 251.0±176.3 pg/ml. The level of NT-proBNP according to the number of involved vessels with more than 50% diameter stenosis is shown in Table 3: in patients with no critical stenosis it was 58.1±57.6 pg/ml, 1-vessel disease 132.5±206.5 pg/ml, 2-vessel disease 110.1±127.3 pg/ml, and 3-vessel disease 324.9±303.8 pg/ml. The level of NT-proBNP in the patients with significant coronary stenosis was significantly increased compared with the patients with no critical coronary artery stenosis (173.1±231.6 vs 68.1±62.5 pg/ml, p<0.001) (Fig 2). The level of NT-proBNP was positively correlated with the extent of significant CAD (r=0.329, p=0.001) (Fig 3). Gensini score stratified according to the NT-proBNP level is positively correlated with the extent of coronary artery disease (r=0.329, p=0.001) (Fig 4). The correlation between NT-proBNP and multiple parameters was positive by Gensini score (r=0.329, p=0.001) and age (r=0.260, p=0.001), and negative by ejection fraction (r=–0.195, p=0.028) (Table 4). Multivariate logistic regression analyses of the association between coronary artery stenosis and multiple parameters are shown in Table 5. At the standard cut-off value of...
>200 pg/ml, elevated NT-proBNP showed a high probability of CAD (odds ratio, 10.1; 95% confidence interval, 2.6–38.7; p=0.001). In multivariate analysis, the NT-proBNP was a predictor of CAD independent of age, gender, ejection fraction, antecedent hypertension or diabetes, creatinine, total cholesterol, and other inflammatory markers. The most powerful parameter for predicting coronary artery stenosis was NT-proBNP.

Discussion

BNP, a type of neurohormone, is released from the cardiac ventricle whenever it is stretched. This prohormone is cleaved to BNP and NT-proBNP in plasma. BNP is broadly involved in blood pressure, circulating volume, natriuresis, vasodilation, inhibition of the rennin – angiotensin system, and inhibition of the sympathetic nervous system. It is well known that BNP and NT-proBNP are useful markers in the diagnosis, evaluation of treatment effectiveness, and prediction of prognosis in heart failure patients, and recently, their usefulness in predicting LV dysfunction after myocardial infarction has been reported.

The increase in NT-proBNP is larger than that of BNP as an absolute and a relative value when the left ventricle is strained, a difference that suggests that NT-proBNP is a more sensitive index of LV dysfunction possibly because of its longer half life (3–6-fold) and more stable plasma concentration. Several studies have reported that NT-proBNP and BNP are increased not only in necrotic myocardial tissue but also in non-necrotic myocardial tissue, such as with unstable angina, and that they reflect the severity of myocardial damage and thus have a relationship with diagnosis and prognosis. In particular, NT-proBNP is sensitive enough to detect myocardial ischemia and predict prognosis in patients without LV dysfunction.

Jernberg et al reported that NT-proBNP is strongly associated with mortality in patients with suspected or confirmed unstable CAD and, combined with a marker of inflammation, seems helpful in identifying those with greatest benefit from an early invasive strategy. Some authors have reported that elevated plasma NT-proBNP concentrations are associated with the severity of CAD and mortality in patients with non-ST elevation acute coronary syndrome and it may be a useful predictor of complete occlusion of the coronary artery. Katayama et al reported that BNP is a reliable predictor of mortality in patients with acute myocardial infarction complicated by cardiogenic shock and successfully treated by direct percutaneous coronary intervention, as assessed by the acute-phase plasma concentration of adrenomedulin, peak CK value, and ventricular fibrillation.

In the present study of unstable angina patients with normal ECG, echocardiogram, and cardiac enzymes, the level of NT-proBNP was higher in patients with defined coronary artery lesions than in those without. Unfortunately, we did not investigate patients’ mortality, and the CRP did not relate significantly to coronary artery stenosis compared with NT-proBNP. Therefore, in this patient population, NT-proBNP was better able to predict the severity of CAD than CRP. The results of this study suggest that the response of NT-proBNP to the stimuli of myocardial ischemia is very rapid and that it acts as an acute phase reactant.

Nishikimi et al reported that N-terminal pro atrial natriuretic peptide (ANP) may be associated with clinically important coronary artery stenosis in patients with normal LV systolic function, but its clinical usefulness may be limited. In their study, BNP had no relation to coronary artery stenosis, although NT-proBNP was not measured. Nakagawa et al reported that BNP but not ANP levels increased in proportion to the scintigraphic myocardial infarction size despite the lack of heart failure in asymptomatic patients with previous myocardial infarction. Choi et al reported that the BNP level correlated with echocardiographic wall motion score index and Gensini score in unstable angina and non-ST elevation myocardial infarction patients, respectively. In the present study, NT-proBNP had a significant Pearson’s correlation with Gensini score and may be a useful marker of the extent of myocardial ischemia.

Study Limitations

First, although the protocol was to sample the blood of the patients as soon as possible, it was not always done at the same time for each patient. Therefore, these data can not reflect the acute phase concentration of NT-proBNP. However, NT-proBNP has a longer half-life and better stability in plasma than BNP and so this limitation may be partially overcome. Second, there were more men in the CAD group and generally, NT-proBNP is lower in males. Nevertheless, the NT-proBNP levels in the CAD group were significantly higher than those of the non-CAD group. Third, the clinical implication of NT-proBNP in the treatment of response was not evaluated. Fourth, there is poor evidence in setting the cut-off value of NT-proBNP at 200 pg/ml and calculations of the specificity and sensitivity at various levels of NT-proBNP and a valid cutoff value are needed. Fifth, diastolic function was not investigated in this study. Because systolic dysfunction is preceded by diastolic dysfunction during the course of cardiac failure, it would be valuable to investigate whether BNP or NT-proBNP concentrations reflect the diastolic dysfunction. The fact that...
elevated NT-proBNP is detected in myocardial ischemia with preserved LV systolic function suggests that myocardial ischemia itself or ventricular stress in myocardial ischemia promotes the release of NT-proBNP. Therefore, more studies of the mechanisms involved in this phenomenon are needed.

Of the patients enrolled in our hospital for the most recent 6 months, we performed first coronary angiography in 1,165 patients and there were 347. Cases of acute myocardial infarction (29.8%), unstable angina 480 (41.2%), and stable angina 338 (29.0%). In the patients with unstable angina, 253 (21.7%) were unstable angina with normal ECG, echocardiogram, and cardiac enzymes while 227 (19.5%) had unstable angina with abnormal ECG or elevated cardiac enzymes. Of the patients with unstable angina with normal ECG, echocardiogram, and cardiac enzymes, 140 (55.3%) have a significant coronary artery stenosis. We considered unstable angina from the viewpoint of the patients’ symptoms and therefore patients with atypical chest pain could be included.

The population of this study had normal troponin I, CRP, ECG findings, and renal function, which makes it very difficult to predict coronary artery stenosis before coronary angiography. However, we predicted more than 50% coronary artery stenosis when NT-proBNP was over than 200 pg/ml, so the results of this study suggest that NT-proBNP would be a useful screening test for CAD in patients with unstable angina and normal ECG, echocardiogram, and cardiac enzymes.

References