Correlation of Plasma Concentrations of B-Type Natriuretic Peptide With Infarct Size Quantified by Tomographic Thallium-201 Myocardial Scintigraphy in Asymptomatic Patients With Previous Myocardial Infarction

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Background  Secretion of A-type (atrial) and B-type (brain) natriuretic peptides (ANP and BNP) increases in relation to left ventricular (LV) dysfunction in patients with myocardial infarction (MI). However, it is unknown what determines the concentrations of ANP and BNP in asymptomatic MI patients with preserved LV function, so the aim of the present study was to examine if they are associated with MI size.

Methods and Results  Plasma concentrations of ANP and BNP in the peripheral blood were measured in 88 asymptomatic (New York Heart Association class I) patients with previous MI. The infarct size was quantitatively calculated from rest thallium-201 myocardial single photon emission computed tomography. In multivariate linear regression analysis that included MI size, hemodynamic parameters, and age as covariables, only BNP concentrations had a significant association with MI size (p=0.0001). In contrast, ANP concentrations were not significantly correlated with MI size in either the univariate or multivariate analysis.

Conclusions  BNP but not ANP concentrations increased in proportion to the scintigraphic MI size despite the lack of heart failure in asymptomatic patients with previous MI. Thus, the increase in plasma BNP concentrations reflects the MI size, an important determinant of prognosis, in asymptomatic patients with MI.  (Circ J 2004; 68: 923 – 927)

Key Words: Heart failure; Myocardial infarction; Myocardial scintigraphy; Natriuretic peptides

A-type (atrial) natriuretic peptide (ANP) and B-type (brain) natriuretic peptide (BNP) are hormones with a wide range of potent biological effects, including natriuresis, diuresis, vasodilatation, and inhibition of the renin-angiotensin-aldosterone and sympathetic nervous systems. We and others have shown that ANP is mainly synthesized and secreted from the atria in adult mammals but it is also synthesized and secreted from the ventricles in patients with congestive heart failure. BNP is secreted mainly from the ventricles in normal adult humans as well as in patients with congestive heart failure, and the plasma concentrations of BNP are markedly increased in proportion to the severity of left ventricular (LV) dysfunction in patients with myocardial infarction (MI) or congestive heart failure. Plasma concentrations of ANP and BNP have been used to predict prognosis after MI.

It is widely accepted that asymptomatic post-MI patients have a high risk of progression to overt heart failure and death so it is clinically important to prevent their transition to a stage of accelerated progression of LV dysfunction. BNP concentrations are used to assess prognosis and therapeutic effects in asymptomatic MI patients as well as symptomatic patients and the expression of both ANP and BNP is increased in the localized myocardial infarct regions relative to the detrimental hemodynamic parameters in patients with MI. The increase in ANP and BNP concentrations precedes the development of symptoms in asymptomatic MI patients but it is unknown what determines the plasma concentrations of ANP and BNP in asymptomatic MI patients with relatively preserved LV function.

Therefore, the present study was designed to examine whether the plasma concentrations of ANP and BNP serve as a clinical indicator of the extent of MI, an important determinant of mortality. For these purposes we examined the relationship of plasma concentrations of ANP and BNP with the infarct size quantitatively calculated with thallium-201 single photon emission computed tomography (SPECT), a noninvasive and accurate method of assessment during the chronic phase of MI.
Table 1 Clinical and Hemodynamic Variables in Control Subjects and Patients With Myocardial Infarction

<table>
<thead>
<tr>
<th></th>
<th>Control (n=40)</th>
<th>Asymptomatic patients (n=88)</th>
<th>Symptomatic patients (n=27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>60±13</td>
<td>64±10</td>
<td>71±7</td>
</tr>
<tr>
<td>M/F</td>
<td>16/24</td>
<td>62/26</td>
<td>22/5</td>
</tr>
<tr>
<td>ANP (pg/ml)</td>
<td>16.6±10.2</td>
<td>36.0±26.5</td>
<td>149.0±132.3*†</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>12.3±10.5</td>
<td>74.7±63.1*</td>
<td>355.1±285.1*†</td>
</tr>
<tr>
<td>Location of MI (anterior/inferior/other)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-vessel disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scintigraphic extent score (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>8.2±1.7</td>
<td>8.2±3.9</td>
<td>12.8±8.3*†</td>
</tr>
<tr>
<td>CI (L/min per m²)</td>
<td>3.1±0.6</td>
<td>2.8±0.7</td>
<td>2.5±0.6*†</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>10.9±5.8</td>
<td>13.2±5.5</td>
<td>17.0±7.7*†</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>74.3±8.4</td>
<td>58.8±12.5*</td>
<td>37.0±17.5*†</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>64.8±15.4</td>
<td>65.7±22.9</td>
<td>110.2±52.0*†</td>
</tr>
<tr>
<td>LVESVI (mL/m²)</td>
<td>16.7±6.1</td>
<td>28.9±13.1*</td>
<td>69.0±48.2*†</td>
</tr>
</tbody>
</table>

*p<0.05 vs control, †p<0.05 vs asymptomatic patients.

Methods

Study Patients

The study population consisted of a consecutive series of 115 patients with a first MI (84 men, 31 women; mean age, 63 years; range 32–83 years) admitted to Yamanashi University Hospital from January 2002 to December 2003. MI was diagnosed on the basis of chest pain persisting for at least 30 min, ST segment elevation of at least 0.1 mV in at least 2 contiguous leads, and elevation of serum creatine kinase-MB isozyme to more than twice the upper limit of normal range. Patients’ characteristics are shown in Table 1. This study was performed at 3–5 weeks after onset of the MI and was completed within 1 week. Based on the New York Heart Association (NYHA) classification of symptoms, 88 patients were categorized as class I, 17 as class II, and 10 as class III–IV. This study defined asymptomatic patients (n=88) as patients in NYHA class I and symptomatic patients (n=27) as the remaining patients in NYHA classes II–IV. Reperfusion therapies in the acute phase of MI were performed in 79 asymptomatic patients (percutaneous coronary intervention (PCI) in all patients with MI. The Swan-Ganz catheter technique was used for right heart catheterization and pulmonary capillary wedge pressure (PCWP) and cardiac output were measured as in our previous studies. LV ejection fraction (LVEF), LV end-systolic and diastolic volume indexes (LVESVI and LVEDVI) were determined from the left ventriculograms by area–length methods using computer-assisted analysis (Cardio 2000, Fukuda-denshi Corporation, Tokyo, Japan).

Cardiac Catheterization

Cardiac catheterization, including right heart catheterization, left ventriculography and coronary angiography, was performed after overnight fasting in all control subjects and patients with MI. The Swan-Ganz catheter technique was used for right heart catheterization and pulmonary capillary wedge pressure (PCWP) and cardiac output were measured as in our previous studies. LV ejection fraction (LVEF), LV end-systolic and diastolic volume indexes (LVESVI and LVEDVI) were determined from the left ventriculograms by area–length methods using computer-assisted analysis (Cardio 2000, Fukuda-denshi Corporation, Tokyo, Japan).

Thallium-201 Myocardial Scintigraphy

Rest thallium-201 myocardial scintigraphy was performed within 1 week before or after cardiac catheterization in all patients with MI. A bolus of 111 MBq (3 mCi) of thallium-201 was injected intravenously at rest and the imaging was begun 15 min later. The SPECT system consisted of a large-field-of-view gamma camera with a high-resolution, parallel-hole collimator mounted on a gantry (GCA-9300A/DI, Toshiba Corporation, Tokyo, Japan). Ninety projections taken every 4 degrees for 12 s each were obtained in a 360-degree arc around the long axis of the patient. The short-axis tomographic images encompassing the entire left ventricle were reconstructed at 6.4 mm intervals.

Quantitative Analysis of Defect Size on Scintigraphy

Computerized thallium-201 tomography was used to quantify the size of the perfusion defect. Circumferential profiles for each short-axis tomographic image were constructed from maximum-count values per pixel in each of 36 radii spaced at 10-degree intervals. Count values on each point in the profile were then normalized to the maximum counts in the profile of each image. The resulting profiles were arranged as a series of concentric circles forming a single 2-dimensional (D) polar map with the apex at the center and the base at the periphery. Then, extent polar maps were obtained by comparing normalized maximal count values per point on the generated 2-D polar map with the corresponding lower normal limits at 2.0 standard deviations below the mean derived from 20 (10 men, 10 women) normal subjects. The extent score for the...
size of perfusion defect was defined by calculating the number of points falling below the corresponding lower normal limits and by expressing this number as a percent of the total LV points on the extent polar map.

**Statistical Analysis**

Results are expressed as mean±SD. Differences in the plasma concentrations of ANP and BNP and the hemodynamic measurements between the patients with MI and the control subjects were compared by one-way ANOVA and a post hoc testing with Sheffe’s test. The correlation of ANP and BNP concentrations with the scintigraphic infarct size, hemodynamic parameters, and age was examined by linear regression analysis. Multivariate linear regression analysis was used to examine the relationship between the ANP or BNP and scintigraphic infarct size together with age and other hemodynamic parameters including PCWP, cardiac index (CI), LV end-diastolic pressure (LVEDP), LVEF, LVEDVI, and LVESVI. Statistical significance was defined as a p-value <0.05. Statistical analysis was performed with StatView 5.0 (SAS Institute, Cary, NC, USA).

**Results**

**Plasma Concentrations of ANP and BNP (Table 1)**

The BNP concentrations were increased in the asymptomatic patients (NYHA I) compared with control subjects, whereas the ANP concentrations did not differ between the 2 groups. The plasma concentrations of ANP and BNP were both higher in symptomatic patients with MI (NYHA II–IV) than in asymptomatic patients or control subjects.

**Comparisons of Scintigraphic Infarct Size and Hemodynamic Parameters Among Symptomatic and Asymptomatic Patients and Controls (Table 1)**

The thallium-201 scintigraphic extent scores ranged from 0% to 61% (mean 20±15%) and were significantly higher in the symptomatic patients than in the asymptomatic patients with MI. The asymptomatic patients had lower LVEF and higher LVESVI than controls, and other hemodynamic parameters, such as PCWP, CI, LVEDP, and LVEDVI, were comparable between the asymptomatic patients and controls.

**Correlations Between Scintigraphic Scores of MI Size and ANP and BNP Concentrations**

In the univariate linear regression analysis, BNP concentrations significantly correlated with the extent score in the asymptomatic patients (NYHA I) (Fig 1). Although the BNP concentrations had a non-Gaussian distribution, similar results were obtained when log-transformed values of the natriuretic peptides concentrations were statistically

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### Table 2  Correlation of Hemodynamic Parameters and Scintigraphic Extent Score With ANP and BNP Concentrations Using Univariate and Multivariate Linear Regression Analyses in Asymptomatic Patients With Myocardial Infarction (n=88)

<table>
<thead>
<tr>
<th></th>
<th>ANP</th>
<th></th>
<th>BNP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Univariate</td>
<td>Multivariate</td>
<td>Univariate</td>
<td>Multivariate</td>
</tr>
<tr>
<td></td>
<td>r p</td>
<td>Standardized regression coefficient</td>
<td>p</td>
<td>r p</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.22 0.03</td>
<td>0.15 0.63</td>
<td>0.26 0.04</td>
<td>0.21 0.42</td>
</tr>
<tr>
<td>Scintigraphic extent score (%)</td>
<td>0.19 0.08</td>
<td>0.26 0.12</td>
<td>0.45 &lt;0.0001</td>
<td>0.59 0.0001</td>
</tr>
<tr>
<td>PCWP (mmHg)</td>
<td>0.09 0.46</td>
<td>0.06 0.84</td>
<td>0.29 0.02</td>
<td>−0.19 0.48</td>
</tr>
<tr>
<td>CI (L/min per m²)</td>
<td>0.05 0.70</td>
<td>0.001 1.00</td>
<td>0.05 0.68</td>
<td>−0.13 0.54</td>
</tr>
<tr>
<td>LVEDP (mmHg)</td>
<td>0.05 0.68</td>
<td>0.25 0.30</td>
<td>0.23 0.04</td>
<td>0.04 0.84</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>−0.14 0.25</td>
<td>−0.04 0.92</td>
<td>0.23 0.04</td>
<td>0.04 0.84</td>
</tr>
<tr>
<td>LVEDVI (ml/m²)</td>
<td>0.18 0.14</td>
<td>0.16 0.63</td>
<td>0.15 0.21</td>
<td>0.26 0.40</td>
</tr>
<tr>
<td>LVESVI (ml/m²)</td>
<td>0.24 0.03</td>
<td>0.08 0.90</td>
<td>0.19 0.12</td>
<td>0.12 0.60</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.
analyzed (r=0.44, p<0.0001). Furthermore, in the asymptomatic patients, multivariate analysis showed that BNP concentrations had a significant association with the extent score only when extent score, PCWP, CI, LVEDP, LVEF, LVEDVI, LVESVI, and age were included as covariates (Table 2). Although ANP concentrations significantly correlated with the extent score in the entire patient population (symptomatic plus asymptomatic patients) in the multivariate linear regression analyses (standardized regression coefficient=0.23, p=0.03), they were not significantly correlated with the extent score in the asymptomatic patients in either the univariate or multivariate analysis (Fig 1, Table 2). Reperfusion therapies in the acute phase of MI and the extent of coronary artery disease had no influence on BNP concentrations in the asymptomatic patients (with reperfusion therapies 71±48 vs without reperfusion 78±82 pg/ml, p=NS; single-vessel disease 74±67 vs multi-vessel diseases 82±91 pg/ml, p=NS).

Discussion

The univariate statistical analysis conducted in the present study showed that BNP concentrations significantly correlated with MI size (extent score) in the asymptomatic patients. Furthermore, in multivariate linear regression analysis that included MI size, PCWP, CI, LVEDP, LVEF, LVEDVI, LVESVI, and age as covariates, only BNP concentrations had a significant association with MI size in the asymptomatic patients. These results suggest that BNP concentrations may directly reflect the MI size in asymptomatic post-MI patients and thus could serve as an important determinant of the prognosis in asymptomatic patients with preserved LV function, because the prognosis of MI is related to the extent of myocardial necrosis.16,17

Mechanisms of the Correlation Between Natriuretic Peptides Concentrations and MI Size

It has been reported that BNP concentrations in the anterior interventricular vein are higher in an anterior infarction than in an inferior infarction, suggesting that the secretion of BNP is significantly greater from the infarct region than from the non-infarct region in patients with MI. Furthermore, it has been shown that the immunoreactivity for ANP and BNP is markedly increased in the area surrounding the infarct region.18,19 The area surrounding a myocardial infarct is thought to suffer from a high level of regional wall stress, and regional wall stress has clearly been shown to be an important stimulus for secretion of ANP and BNP from the myocardium.20 Thus, the correlation between the infarct size and the concentrations of these peptides may be explained by an increase in regional wall tension or stretch in viable cells both within and surrounding the infarct area.

The present study showed that asymptomatic patients had a positive correlation between infarct size and BNP concentrations, but not with ANP concentrations, which is related to the finding that the cardiac secretion of BNP is predominantly derived from the left ventricle regardless of the presence or absence of LV dysfunction, whereas ANP secretion is mainly from the atria when the magnitude of LV dysfunction is insignificant.20 These results are consistent with previous reports8,11,21 showing that BNP concentrations are a better predictor of prognosis after MI. Although we did not measure N-terminal pro-ANP concentrations, the increased clearance of ANP compared with BNP may possibly contribute to the disparity in the significance of the correlation between ANP and BNP concentrations.

Clinical Implications

Screening for high-risk asymptomatic MI patients is very important21 because they may benefit from early treatment. An elevated BNP concentration in the absence of detrimental LV hemodynamic parameters does not represent a false-positive result, but might reflect a larger MI size in an asymptomatic patient with a prior MI. Therapeutic efforts should also be directed to preventing the progression of LV remodeling and dilation that occurs before symptomatic heart failure.22

Study Limitations

Serial measurement of serum concentrations of cardiac markers was widely used for estimating MI size in the pre-reperfusion era; however, coronary artery reperfusion dramatically changes the washout kinetics of the cardiac markers, thus limiting their usefulness as a measure of infarct size. Also, assessment of MI size using thallium-201 myocardial scintigraphy has several limitations, such as artifacts and showing the relative distribution, not the absolute distribution, of myocardial perfusion. Nevertheless, CT using the profile technique can provide quantitative data on MI size more readily than other noninvasive methods.23 Although the BNP concentrations did not differ between those with single-vessel disease and those with multi-vessel disease in the present study, we did not estimate the extent of myocardial ischemia that potentially elevates the BNP concentration and could affect the present results.

Conclusions

In patients with a previous MI, the BNP but not the ANP concentrations were increased in proportion to the size of the MI, estimated by thallium-201 SPECT, despite the lack of symptoms of heart failure. Thus, the plasma BNP concentrations are a marker of MI size in asymptomatic patients with MI.

Acknowledgments

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References


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BNP Concentration and MI Size

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