Plasma Level of B-Type Natriuretic Peptide as a Prognostic Marker After Acute Myocardial Infarction
A Long-Term Follow-Up Analysis

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Background—Circulating levels of B-type natriuretic peptide (BNP), a cardiac hormone, reflect the severity of cardiac dysfunction. Because the plasma BNP level changes dramatically during the period after the onset of acute myocardial infarction (AMI), identification of a suitable sampling time is problematic. There have been several reports indicating that the plasma BNP level obtained in the acute phase of AMI can be used as a prognostic marker. We examined whether the plasma BNP level measured 3 to 4 weeks after the onset of AMI represents a reliable prognostic marker for patients with AMI.

Methods and Results—We analyzed 145 consecutive patients with AMI. Plasma BNP levels were measured during the 3 to 4 weeks after onset of AMI. Of those patients, 23 experienced fatal cardiac events during this study. The mean follow-up period was 58.6 months. Log BNP, left ventricular end-diastolic pressure, and pulmonary vascular resistance were all significantly higher in the cardiac death group, and there were more men and more patients with a history of heart failure in the cardiac death group. A Cox proportional hazards model analysis showed that log BNP was an independent predictor of cardiac death. The survival rate was significantly higher in patients with log BNP <2.26 (180 pg/mL) than in those with log BNP ≥2.26.

Conclusions—The plasma BNP level obtained 3 to 4 weeks after the onset of AMI can be used as an independent predictor of cardiac death in patients with AMI. (*Circulation. 2004;110:1387-1391.*)

Key Words: natriuretic peptides ■ myocardial infarction ■ prognosis
second peak are considered to be related to infarct expansion and subsequent ventricular remodeling.12,13

As mentioned above, the changing pattern of the plasma BNP level varies according to the cardiac condition after AMI. This raises the possibility that the plasma BNP level could reflect or predict prognosis after the onset of AMI. The changing pattern of the plasma BNP level after the onset of AMI is dynamic during the first month; therefore, identification of a suitable time frame for blood sampling for BNP measurement is an important issue. To exploit the plasma BNP level as a clinically useful prognostic marker after AMI in the future, it would be convenient to measure it 3 to 4 weeks after the onset of AMI. It is generally difficult to target the timing of the blood sampling to the formation of the second plasma BNP peak, although this strict time point may be better as a prognostic marker than the later phase, such as 3 to 4 weeks after the onset. According to our previous study, the plasma BNP level was still significantly higher in patients with the biphasic pattern than in those with the monophasic pattern at 3 to 4 weeks after onset of AMI,13 which suggests that sampling at this time would also be valuable for clinical use. In the present study, we examined whether the plasma BNP level measured 3 to 4 weeks after the onset of AMI represents a reliable prognostic marker after AMI by monitoring patients with AMI for a long-term period. The present study began just after the discovery of BNP, and therefore we were able to monitor the patients for approximately 5 years on average and as long as 13 years.

Methods

Study Patients

This study began in January 1990, just after the discovery of BNP, and an antibody for BNP was established by our research group.9,23–24 The end of the patient recruitment period was in March 1999. The final follow-up date was on May 31, 2003. During this time period, there were 403 admitted patients with AMI who underwent cardiac catheterization and in whom we were able to measure the plasma BNP level 3 to 4 weeks after the onset of AMI. We followed up 285 patients and were ultimately able to follow up 145 patients with highly reliable information about their prognosis from themselves, their families, and/or their affiliated hospitals. The 145 study patients consisted of 106 men and 39 women with a mean age of 65.1 years (range 31 to 90 years).

The diagnosis of AMI was made from clinical symptoms, including chest pain, ECG changes including ST elevation and ST depression, and an elevation of serum creatine kinase-MB isoenzyme to more than twice the normal upper level. In the present study, we defined the cardiac death group as patients who died of heart failure or sudden cardiac death and the non–cardiac-death group.9,23,24 The end of the patient recruitment period was in March 1999. The final follow-up date was on May 31, 2003. During this time period, there were 403 admitted patients with AMI who underwent cardiac catheterization and in whom we were able to measure the plasma BNP level 3 to 4 weeks after the onset of AMI. We followed up 285 patients and were ultimately able to follow up 145 patients with highly reliable information about their prognosis from themselves, their families, and/or their affiliated hospitals. The 145 study patients consisted of 106 men and 39 women with a mean age of 65.1 years (range 31 to 90 years).

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Cardiac Catheterization

Cardiac catheterization was performed in 145 patients at 3 to 4 weeks after AMI. A Swan-Ganz catheter was inserted into the femoral or subclavian vein, and hemodynamic measurements were obtained, including pulmonary capillary wedge pressure, pulmonary artery pressure, right atrial pressure, and cardiac output. Cardiac output was determined in triplicate by the thermodilution technique. Blood samples that included BNP were obtained from either the femoral or subclavian vein.

After the Swan-Ganz catheterization procedure, aortic pressure and left ventricular end-diastolic pressure were measured; then, coronary angiography and left ventriculography were performed. The left ventricular ejection fraction was determined by left ventriculography.

Measurement of BNP Plasma Level

The plasma BNP concentration was measured with a specific radioimmunoassay for human BNP from 1990 to 1993,25,26 and then a specific immunoradiometric assay for human BNP from 1993 to 1999 (Shionoria BNP; Shionogi Inc.).27 There were no significant differences in the BNP values obtained by the radioimmunoassay and immunoradiometric assay methods.28

Statistical Analysis

Continuous values are expressed as the mean±SD. Statistical significance was defined as a probability value <0.05. A Cox proportional hazards regression analysis was performed to identify independent predictors of cardiac death by using variables including log BNP, left ventricular ejection fraction, history of heart failure, heart rate, male gender, anterior myocardial infarction, ACE inhibitor or β-blocker use, history of renal dysfunction, age, history of left ventricular hypertrophy, and revascularization. Because the BNP plasma level was not normally distributed, we selected log BNP for analysis. A log BNP cutoff point was selected to define a large patient group with a low risk of cardiac death. A Kaplan-Meier survival curve was used for survival comparisons between patient groups stratified according to this cutoff point.

Results

Follow-Up Periods

The mean follow-up period was 58.6 months (range 1 to 158 months) for all study patients, with mean follow-up periods of 41.3 months (range 1 to 127 months) for the cardiac death group and 61.9 months (range 1 to 158 months) for the non–cardiac-death group.

Prognosis of Patients and Causes of Death

Of the 145 patients, 115 survived and 30 died during the study period. Of the 30 patients who died, 8 (27%) died of sudden death, 15 (50%) had heart failure, and 7 (23%) died of other causes (2 of pneumonia, 2 of lung cancer, 1 of renal cell carcinoma, 1 of liver dysfunction, and 1 of blood dyscrasia).

Comparisons of Clinical Characteristics, Hemodynamic Parameters, and Plasma BNP Levels Between the Cardiac Death Group and the Non–Cardiac-Death Group

The clinical characteristics and hemodynamic parameters of the study patients are shown in Tables 1 and 2. Among all the patients, 72 (50%) had anterior infarction, and 73 (50%) had inferior or posterolateral infarction. Eighty-four (60%) had a history of smoking, 48 (35%) had a history of hypertension, 37 (27%) were obese, 62 (45%) had diabetes mellitus, and 57 (41%) had dyslipidemia (Table 1).

The number of male patients and patients with a history of heart failure was significantly higher in the cardiac death group than in the non–cardiac-death group. There were no significant differences for age, anterior myocardial infarction, coronary risk factors, history of left ventricular hypertrophy, history of renal dysfunction, revascularization, or pharmacotherapy between the cardiac death group and the non–cardiac-death group (Table 1).
TABLE 1. Patients' Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Non–Cardiac-Death (n=122)</th>
<th>Cardiac Death (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>64.7±11.1</td>
<td>66.7±7.9</td>
<td>NS</td>
</tr>
<tr>
<td>Male gender</td>
<td>70 (85/122)</td>
<td>91 (21/23)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anterior MI</td>
<td>47 (57/122)</td>
<td>65 (15/23)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking</td>
<td>60 (71/121)</td>
<td>65 (13/20)</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>37 (44/119)</td>
<td>20 (4/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Obesity</td>
<td>28 (33/119)</td>
<td>20 (4/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>46 (55/119)</td>
<td>35 (7/20)</td>
<td>NS</td>
</tr>
<tr>
<td>History of dyslipidemia</td>
<td>44 (52/119)</td>
<td>25 (5/20)</td>
<td>NS</td>
</tr>
<tr>
<td>History of heart failure</td>
<td>4 (5/117)</td>
<td>18 (4/22)</td>
<td>0.015</td>
</tr>
<tr>
<td>History of LVH</td>
<td>17 (20/117)</td>
<td>5 (1/22)</td>
<td>NS</td>
</tr>
<tr>
<td>History of renal dysfunction</td>
<td>19 (19/102)</td>
<td>33 (6/18)</td>
<td>NS</td>
</tr>
<tr>
<td>Revascularization*</td>
<td>53 (62/116)</td>
<td>52 (11/21)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Pharmacotherapy

<table>
<thead>
<tr>
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<th>Non–Cardiac-Death (n=122)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>45 (50/111)</td>
<td>45 (9/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Digitalis</td>
<td>3 (3/111)</td>
<td>5 (1/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Furosemide</td>
<td>17 (19/111)</td>
<td>25 (5/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>3 (3/111)</td>
<td>5 (1/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>80 (88/111)</td>
<td>75 (15/20)</td>
<td>NS</td>
</tr>
<tr>
<td>Nitrate</td>
<td>59 (65/111)</td>
<td>60 (12/20)</td>
<td>NS</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>20 (22/111)</td>
<td>30 (6/20)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Log BNP was significantly higher in the cardiac death group than in the non–cardiac-death group (2.44±0.57 versus 1.91±0.59, P<0.0001; Table 2).

Univariate and Multivariate Predictors of Cardiac Death

Table 3 shows the results of univariate and multivariate Cox proportional hazards model analyses for cardiac death. In the univariate analysis, log BNP, left ventricular ejection fraction, history of heart failure, heart rate, and male gender were significant predictors. In the multivariate analysis, log BNP was the only independent predictor of cardiac death.

Kaplan-Meier Survival Analysis

We examined the sensitivity and specificity of various cutoff values of log BNP for predicting survival and created receiver operating characteristic curves. The best value of log BNP with the highest sensitivity and specificity was 2.26, equivalent to a BNP level of up to 180 pg/mL (Figure 1). Figure 2 shows that the survival rates were significantly higher in patients with log BNP <2.26 than in patients with log BNP ≥2.26.

Discussion

During the follow-up period, 23 patients died of cardiac death. The plasma BNP level 3 to 4 weeks after the onset of AMI was significantly higher in the cardiac death group (n=23) than in the non–cardiac-death group (n=122). We examined the sensitivity and specificity of various cutoff values of log BNP for predicting survival. We created

TABLE 2. Hemodynamic Parameters and BNP Levels

<table>
<thead>
<tr>
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<th>Cardiac Death (n=23)</th>
<th>P</th>
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<tbody>
<tr>
<td>Log BNP</td>
<td>1.91±0.59 (81±4 pg/mL)</td>
<td>2.44±0.57 (277±4 pg/mL)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Hemodynamics

<table>
<thead>
<tr>
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<th>Non–Cardiac-Death (n=122)</th>
<th>Cardiac Death (n=23)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate, bpm</td>
<td>71±13</td>
<td>80±25</td>
<td>NS</td>
</tr>
<tr>
<td>Mean blood pressure, mm Hg</td>
<td>97±15</td>
<td>95±23</td>
<td>NS</td>
</tr>
<tr>
<td>SVR, dyne · s · cm⁻²</td>
<td>1786±52</td>
<td>2209±1039</td>
<td>NS</td>
</tr>
<tr>
<td>PVR, dyne · s · cm⁻²</td>
<td>141±76</td>
<td>223±127</td>
<td>0.0280</td>
</tr>
<tr>
<td>LVEDP, mm Hg</td>
<td>11±6</td>
<td>18±5</td>
<td>0.0002</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>56±17</td>
<td>44±16</td>
<td>0.0064</td>
</tr>
<tr>
<td>CI, L · min⁻¹ · m⁻²</td>
<td>2.3±0.5</td>
<td>2.8±0.6</td>
<td>0.0040</td>
</tr>
</tbody>
</table>

Values are mean±SD. SVR indicates systemic vascular resistance; PVR, pulmonary vascular resistance; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; and CI, cardiac index.
receiver operating characteristic curves and concluded that the best cutoff value of log BNP was 2.26, equivalent to a plasma BNP level of 180 pg/mL. The Cox proportional hazards model analysis showed that plasma BNP level was an independent predictor of cardiac death. The survival rate was significantly higher in the patients with log BNP <2.26 (equivalent to a plasma BNP level of up to 180 pg/mL) than in those with log BNP ≥2.26. This plasma BNP level for predicting cardiac events is almost the same as in previous reports.29–32

The present study began just after the discovery of BNP, and an antibody for BNP was created by our research group.2,23 Thus, we were able to follow up patients for a mean period of 58.6 months for all patients, with mean follow-up periods of 41.3 months for the cardiac death group and 61.9 months for the non–cardiac-death group. We demonstrated that the plasma BNP level measured at 3 to 4 weeks after AMI onset was a significant prognostic marker of AMI in this long-term follow-up study.

There have been several reports indicating that the plasma BNP level obtained in the acute phase of AMI can be used as a prognostic marker for patients with AMI.13,37,38,43 However, there are no reports on sampling at 3 to 4 weeks after the onset of AMI. In the present study, we performed BNP sampling at 3 to 4 weeks after AMI onset. Because the changing pattern of the plasma BNP level in patients with AMI is dynamic,13 the timing of the blood sampling is an important matter. The first peak of plasma BNP was shown 20 hours after AMI onset, and the second peak was shown at approximately the fifth day after onset. Plasma BNP levels in the second peak would reflect the degree of ventricular remodeling after AMI.13 We considered that timing the blood sampling to occur just at the second peak might be ideal to predict prognosis; however, it is quite difficult to obtain the blood sample just at the second peak, because the authentic second peak of plasma BNP varies among patients with AMI. Given this background, a sampling point of 3 to 4 weeks after AMI onset appears better, because plasma BNP levels would be quite stable during this phase, as shown in our previous report.13 The results of the present study revealed that a sampling time at 3 to 4 weeks after the onset of AMI in addition to the acute phase would provide prognostic insights, as previously speculated.31,38

In the present study, the number of patients taking ACE inhibitors (ACEIs) and/or β-blockers appears to be relatively low compared with recent studies.39–43 It seems that historical background plays a role in accounting for this. There were many patients who participated in the present study around 1995; the rate of calcium channel blocker prescriptions was very high in Japan during that time. We prescribed calcium channel blockers for many patients with AMI, in part because we expected calcium channel blockers to prevent coronary artery spasm, which commonly occurs in Japanese patients.44 Of course, the use of ACEIs or β-blockers in addition to calcium channel blockers is increasing even now in Japan. It has been reported that ACEIs are useful in the treatment of heart failure after AMI.49–52; thus, it would be highly recommended that an ACEI be prescribed, or that the dose of the ACEI be increased, if the plasma BNP level is elevated 3 to 4 weeks after the onset of AMI. In addition, an aldosterone antagonist would be useful in the treatment of AMI.53 In the present study, baseline medications, such as ACEIs or β-blockers, were not related to plasma BNP levels (data not shown) or the prognosis of the study patients (Table 3).

In our previous report, we stated that the biphasic pattern of the plasma BNP level indicated poor ventricular function after AMI, whereas the monophasic pattern did not.13 Plasma BNP levels at 3 to 4 weeks after AMI onset were higher in the biphasic pattern than in the monophasic pattern. This observation and the present data suggest that the biphasic pattern would indicate a poor prognosis after AMI.

In the present long-term follow-up study, we found that plasma levels of BNP measured at 3 to 4 weeks after AMI were a prognostic marker statistically; however, the sample size was limited. Thus, it might be necessary to perform analysis on a larger scale in another series of studies. It is also necessary to examine how BNP levels at 3 to 4 weeks after the onset of AMI affect the subsequent treatment, including medical therapies and implantation of an internal defibrillator.

In conclusion, the plasma BNP level measured 3 to 4 weeks after the onset of AMI is a significant prognostic marker of AMI, as determined by this long-term follow-up study.

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