Plasma Brain Natriuretic Peptide as a Prognostic Indicator in Patients With Primary Pulmonary Hypertension

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Background—Plasma brain natriuretic peptide (BNP) level increases in proportion to the degree of right ventricular dysfunction in pulmonary hypertension. We sought to assess the prognostic significance of plasma BNP in patients with primary pulmonary hypertension (PPH).

Methods and Results—Plasma BNP was measured in 60 patients with PPH at diagnostic catheterization, together with atrial natriuretic peptide, norepinephrine, and epinephrine. Measurements were repeated in 53 patients after a mean follow-up period of 3 months. Forty-nine of the patients received intravenous or oral prostacyclin. During a mean follow-up period of 24 months, 18 patients died of cardiopulmonary causes. According to multivariate analysis, baseline plasma BNP was an independent predictor of mortality. Patients with a supramedian level of baseline BNP (≥150 pg/mL) had a significantly lower survival rate than those with an inframedian level, according to Kaplan-Meier survival curves (P<0.05). Plasma BNP in survivors decreased significantly during the follow-up (217±38 to 149±30 pg/mL, P<0.05), whereas that in nonsurvivors increased (365±77 to 544±68 pg/mL, P<0.05). Thus, survival was strikingly worse for patients with a supramedian value of follow-up BNP (≥180 pg/mL) than for those with an inframedian value (P<0.0001).

Conclusions—A high level of plasma BNP, and in particular, a further increase in plasma BNP during follow-up, may have a strong, independent association with increased mortality rates in patients with PPH. (Circulation. 2000;102:865-870.)

Key Words: natriuretic peptides ▪ hypertension, pulmonary ▪ mortality
logue beraprost sodium (n=41).

The remaining 5 patients did not receive prostacyclin therapy; 3 patients could not tolerate it because of hypotension resulting from uncompensated right heart failure. 1 patient developed hypoxia during prostacyclin treatment, and 1 showed adverse effects. The study included 15 age-matched healthy control subjects (6 men and 9 women; mean age 40 years; range 25 to 65 years). All subjects gave informed consent.

**Blood Sampling and Assay**

Blood samples for baseline measurements were drawn from a peripheral vein in all patients at diagnostic catheterization while the patient was in a stable hemodynamic state and not receiving vasoactive drugs. Blood sampling was repeated in 53 patients after a mean follow-up period of 3±1 months. Forty-nine of the 53 patients received intravenous or oral prostacyclin therapy. Seven patients did not complete follow-up measurements; 1 patient died, 3 patients moved out of town before the second measurements, and 3 patients were dropped inadvertently.

Blood was immediately transferred into a chilled glass tube containing disodium EDTA (1 mg/mL) and aprotinin (500 U/mL) and centrifuged immediately at 4°C. Plasma BNP and atrial natriuretic peptide (ANP) were measured directly with highly sensitive and specific immunoradiometric assay kits (Shionogi Co, Ltd). Plasma norepinephrine (NE) and epinephrine (EPI) were measured by radioenzymatic assay (Amersham International). Plasma renin activity (PRA), plasma renin substrate (PRS), and plasma aldosterone were measured by radioimmunoassay (Amersham International). Plasma ANP was measured by specific immunoradiometric assay kits (Shionogi Co, Ltd). Plasma atrial natriuretic peptide (ANP) was measured directly with highly sensitive and specific immunoradiometric assay kits (Shionogi Co, Ltd).

Hemodynamic Studies

Diagnostic right heart catheterization was performed in all patients while they were in a stable condition during hospitalization. Baseline hemodynamic variables including mean pulmonary arterial pressure, mean right atrial pressure, pulmonary capillary wedge pressure, and RV end-diastolic pressure were measured in all patients. Cardiac output was measured by Fick’s method. Total pulmonary resistance was calculated by dividing mean pulmonary arterial pressure by cardiac output. Hemodynamic measurements along with BNP measurements were repeated in a subsample (n=40) of patients during prostacyclin therapy (3±1 months).

Echocardiographic Assessment

Echocardiography was performed with a Toshiba SSH-120A within 1 week of diagnostic catheterization and during follow-up. Parasternal short-axis views were obtained at the level of the papillary muscles of the LV with the use of a 3.5-MHz sector transducer. The longest (L) and shortest (S) diameters of the LV cavity were measured at the time of maximal deformity in early diastole. The LV deformity index was calculated as L/S. The presence of pericardial effusion was also evaluated in the parasternal short-axis views in early diastole and graded as absent, small (separation <1 cm), or large (separation >1 cm). At one third of the length of the long axis from the base, RV end-diastolic dimension was obtained perpendicular to the long axis by means of the apical 4-chamber view.

Survival Estimates

Survival was estimated from the date of blood sampling to April 30, 1999, or cardiopulmonary death. No patient received lung or heart-lung transplantation during the follow-up period. No patient died of noncardiopulmonary causes. The follow-up rate was 100%.

Statistical Analysis

All data were expressed as mean value±SEM unless otherwise indicated. Log transformation was used to normalize the distribution of plasma hormone levels unless otherwise indicated. Comparisons of parameters between the 2 groups were made by Fisher’s exact test or unpaired Student’s t test. Comparisons of parameters among the 4 groups were made by means of 1-way ANOVA followed by Scheffe’s multiple comparison test. Correlation coefficients between plasma hormone levels and hemodynamic variables were calculated by linear regression analysis. The effects of vasodilator therapy on plasma BNP were analyzed by paired Student’s t test. The prognostic value of each variable was tested by univariate Cox proportional hazards regression analysis. With the use of a multivariate model, the prognostic power of plasma BNP was compared with that of other significant predictors in univariate analysis. Survival curves were derived by means of the Kaplan-Meier method and were compared by means of the log-rank test. Receiver operating characteristics were generated from multiple sensitivity/specificity pairs. A value of P<0.05 was considered statistically significant.

Results

Comparison of Patient Characteristics Between Survivors and Nonsurvivors

During a mean follow-up period of 24±2 months, 18 (30%) patients died of cardiopulmonary causes: 14 patients died of progressive RV failure, and 4 patients died suddenly. Baseline heart rate, mean pulmonary arterial pressure, total pulmonary resistance, and mean right atrial pressure were significantly higher in nonsurvivors than in survivors (Table 1). Cardiac output and mixed venous oxygen saturation were

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics in Patients With PPH According to Survival</th>
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<td>Variables</td>
</tr>
<tr>
<td>Age, y</td>
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<tr>
<td>Sex, male/female</td>
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<tr>
<td>NYHA functional class, n</td>
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<tr>
<td>III</td>
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<tr>
<td>IV</td>
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<tr>
<td>Hemodynamics</td>
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<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>mSAP, mm Hg</td>
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<tr>
<td>mPAP, mm Hg</td>
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<tr>
<td>CO, L/min</td>
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<tr>
<td>TPR, Wood units</td>
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<td>RAP, mm Hg</td>
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<tr>
<td>PCWP, mm Hg</td>
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<tr>
<td>Pulmonary function</td>
</tr>
<tr>
<td>Sao2, %</td>
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<td>SvO2, %</td>
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<td>PVC, % predicted</td>
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<tr>
<td>FEV1, % predicted</td>
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<tr>
<td>Medication use, n</td>
</tr>
<tr>
<td>Oral prostacyclin analogue</td>
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<tr>
<td>Intravenous prostacyclin</td>
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<td>Calcium antagonists</td>
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<td>Digitalis</td>
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<td>Diuretics</td>
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<td>Anticoagulant agents</td>
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</table>

mSAP indicates mean systemic arterial pressure; mPAP, mean pulmonary arterial pressure; CO, cardiac output; TPR, total pulmonary resistance; RAP, mean right atrial pressure; PCWP, pulmonary capillary wedge pressure; Sao2, arterial oxygen pressure; SvO2, mixed venous oxygen saturation; FVC, forced vital capacity; and FEV1, forced expiratory volume in 1 second. Data are mean±SEM.
significantly lower in nonsurvivors than in survivors. There was no significant difference in the use of the medications between survivors and nonsurvivors.

Baseline Hormone Levels With Reference to NYHA Functional Class and Hemodynamic Variables
Baseline plasma BNP and ANP increased significantly with the severity of New York Heart Association (NYHA) functional class (Figure 1). Plasma NE differed significantly between functional classes II and IV and between classes III and IV but not between classes II and III. Baseline plasma BNP and ANP correlated positively with mean pulmonary arterial pressure and negatively with cardiac output, thus showing a strong positive correlation with total pulmonary resistance (Table 2). Plasma BNP and ANP correlated positively with mean right atrial pressure but not with pulmonary capillary wedge pressure. In contrast, neither plasma NE nor EPI was significantly correlated with any hemodynamic variable.

Baseline and Follow-Up Hormone Levels in Survivors and Nonsurvivors
Baseline plasma BNP, ANP, and NE but not EPI were significantly higher in nonsurvivors than in survivors (Figure 2). The plasma BNP level in survivors decreased significantly during prostacyclin therapy, whereas that in nonsurvivors increased significantly despite treatment. Consequently, there was a marked difference in follow-up plasma BNP level between survivors and nonsurvivors. Plasma ANP in survivors decreased significantly, whereas that in nonsurvivors remained elevated. Neither plasma NE nor EPI changed significantly during follow-up.

Plasma BNP Level and Hemodynamic Alterations During Prostacyclin Therapy
Changes in plasma BNP correlated closely with changes in total pulmonary resistance ($r=0.72$, $P<0.001$) and RV end-diastolic pressure ($r=0.78$, $P<0.001$) during prostacyclin therapy. However, changes in plasma BNP did not always reflect changes in RV dimension ($r=0.38$, $P<0.05$) or mean pulmonary arterial pressure ($r=0.43$, $P<0.05$). Interestingly,

<table>
<thead>
<tr>
<th>Neurohormones</th>
<th>mPAP</th>
<th>CO</th>
<th>TPR</th>
<th>RAP</th>
<th>PCWP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma BNP</td>
<td>0.42†</td>
<td>−0.51†</td>
<td>0.59†</td>
<td>0.55†</td>
<td>0.16</td>
</tr>
<tr>
<td>Plasma ANP</td>
<td>0.42†</td>
<td>−0.49†</td>
<td>0.52†</td>
<td>0.55†</td>
<td>0.22</td>
</tr>
<tr>
<td>Plasma NE</td>
<td>−0.09</td>
<td>−0.29*</td>
<td>0.24</td>
<td>0.23</td>
<td>0.03</td>
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<tr>
<td>Plasma EPI</td>
<td>0.05</td>
<td>0.04</td>
<td>0.00</td>
<td>0.08</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Abbreviations as in Table 1.

* $P<0.05$; † $P<0.001$. 

Figure 1. Baseline plasma BNP, ANP, NE, and EPI in patients with PPH according to NYHA functional class. *$P<0.05$ vs control; †$P<0.05$ vs NYHA class II; ‡$P<0.05$ vs NYHA class III.

Figure 2. Changes in plasma BNP, ANP, NE, and EPI in survivors and nonsurvivors during follow-up. *$P<0.05$ vs baseline value in survivors; †$P<0.05$ vs follow-up value in survivors.
although there was no significant change in RV dimension in survivors (2%) or nonsurvivors (1%) during prostacyclin therapy, plasma BNP changed significantly in survivors (254%) and nonsurvivors (175%). In addition, the marked increase in plasma BNP in nonsurvivors was not associated with changes in mean pulmonary arterial pressure (0%).

Univariate and Multivariate Predictors of Mortality

By univariate analysis, NYHA functional class, heart rate, LV deformity index, the severity of pericardial effusion, mean pulmonary arterial pressure, cardiac output, mean right atrial pressure, and mixed oxygen saturation at diagnostic catheterization were all related to mortality in PPH (Table 3).

As shown in Table 3, baseline plasma levels of BNP, ANP, and NE but not EPI were significantly correlated with mortality in PPH. Follow-up plasma levels of BNP, ANP, and NE also showed a significant correlation with mortality in PPH. Among significant noninvasive baseline predictors in univariate analysis, only baseline plasma BNP was an independent predictor of mortality in patients with PPH by multivariate analysis (P<0.05, Table 4). In addition, only BNP provided independent prognostic information even after mean pulmonary arterial pressure and cardiac output were included as covariates in multivariate analysis (P<0.05). When follow-up variables during prostacyclin therapy were included in multivariate analysis, only follow-up BNP was an independent predictor of mortality (P<0.05).

Kaplan-Meier Lifetime Analysis

Kaplan-Meier survival curves according to the median value of baseline and follow-up BNP are shown in Figure 3. Patients with a baseline plasma BNP ≥150 pg/mL had a significantly lower survival rate than those with a baseline plasma BNP <150 pg/mL (log-rank test, P<0.05). However, a more distinct separation of survival curves was demonstrated for the median value (180 pg/mL) of follow-up plasma BNP (log-rank test, P<0.0001).

Receiver Operating Characteristics

Receiver operating characteristic analysis demonstrated that the prognostic value of baseline plasma BNP was comparable...
or even superior to that of mean pulmonary arterial pressure or cardiac output at diagnostic catheterization (Figure 4). As expected, the prognostic accuracy of follow-up plasma BNP was superior to that of baseline plasma BNP.

Discussion

In our assessment of the prognostic value of plasma BNP, we demonstrated that (1) baseline plasma BNP was an independent predictor of mortality by multivariate analysis, and (2) patients with a supramedian level of baseline BNP had a significantly lower survival rate than those with an inframedian level, according to Kaplan-Meier survival curves. We also demonstrated that (3) plasma BNP in survivors decreased significantly during vasodilator therapy, whereas that in nonsurvivors increased despite treatment, and thus, (4) survival was strikingly worse for patients with a supramedian follow-up BNP level than for those with an inframedian level.

Baseline Plasma Hormone Levels

Baseline plasma BNP and ANP were significantly higher in nonsurvivors than in survivors. These peptides were both significantly related to mortality in univariate Cox proportional hazards regression analysis. The significant relation between plasma BNP and ANP and RV hemodynamics may support the significance of these peptides as prognostic indicators. Interestingly, however, among noninvasive variables correlated significantly with mortality in univariate analysis, only plasma BNP was an independent predictor of mortality by multivariate analysis. The superiority of BNP over ANP may be attributed to the synthesis and secretion pattern of each peptide. ANP is released mainly from stored granules in atrial tissue through a regulated pathway and is easily affected by blood pressure, sodium intake, and postural change.\(^ {11,20}\) In contrast, BNP is secreted predominantly from cardiac ventricles through a constitutive pathway and is affected by the degree of myocardial stretch, damage, and ischemia in the ventricle.\(^ {5,7,21}\) Our previous study demonstrated that plasma BNP correlated inversely with RV ejection fraction in patients with pulmonary hypertension.\(^ {11}\) Thus, plasma BNP may be more suitable than plasma ANP for the evaluation of RV dysfunction and thereby the prediction of mortality in patients with PPH.

A recent study demonstrated the close relation between plasma NE and mortality in patients with PPH.\(^ {22}\) In the present study, plasma NE but not plasma EPI was significantly higher in nonsurvivors than in survivors. Sympathetic nervous system activation, indicated by a high plasma NE level, may be associated with mortality in patients with PPH. Although univariate analysis in the present study confirmed the relation between plasma NE and mortality, NE measurement provided no additional prognostic information after introduction of plasma BNP as a covariate in a multivariate model. Thus, plasma BNP may be superior to plasma NE for prediction of mortality in patients with PPH.

Follow-Up Plasma Hormone Levels

Recently, long-term therapy with intravenous prostacyclin or an orally active prostacyclin analogue was shown to significantly lower pulmonary vascular resistance and thereby improve the survival of patients with PPH in comparison to conventional therapy alone.\(^ {12-17}\) Nevertheless, some patients ultimately require heart-lung or lung transplantation.\(^ {4}\) We have shown that plasma BNP may be a potential marker for the efficacy of vasodilator therapy in patients with PPH.\(^ {11}\) Thus, in the present study, BNP measurement was repeated during vasodilator therapy to try to predict patients who would be refractory to treatment. Plasma BNP in survivors significantly decreased during prostacyclin therapy, whereas that in nonsurvivors increased despite treatment. We found poor correlations between changes in plasma BNP and changes in mean pulmonary arterial pressure or RV dimension during prostacyclin therapy. In contrast, changes in plasma BNP were associated with changes in RV end-diastolic pressure and total pulmonary resistance. These results are consistent with our previous findings that plasma BNP correlated independently with RV end-diastolic pressure and RV ejection fraction but not pulmonary arterial pressure or RV volume.\(^ {11}\) Thus, changes in plasma BNP by prostacyclin therapy may reflect changes in RV wall stress resulting from high pulmonary vascular resistance in PPH. Multivariate analysis demonstrated a high follow-up BNP level to be strongly associated with increased mortality. It should be noted that follow-up BNP showed a more distinct separation of survival curves than baseline BNP. It is possible that progressive RV dysfunction despite vasodilator therapy, as indicated by the high follow-up BNP level, may be associated with poor outcome in patients with PPH. Thus, repeated measurements of BNP may be helpful for prediction of mortality in patients with PPH.

In the present study, invasively determined RV hemodynamic parameters such as mean pulmonary arterial pressure and cardiac output were related to prognosis, which is consistent with the results of earlier studies.\(^ {3,5}\) The question may arise whether these invasive parameters can serve as sufficient prognostic indicators, and plasma BNP may add little information regarding prognosis or treatment effects. However, BNP measurement provided independent prognostic information even after introduction of mean pulmonary arterial pressure and cardiac output as covariates in multivariate analysis. In addition, receiver operating characteristic analysis demonstrated that the prognostic power of baseline
BNP was comparable to or even superior to that of these hemodynamic parameters. Furthermore, the prognostic accuracy of follow-up BNP was superior to that of baseline BNP. Plasma BNP may provide supplementary prognostic information by reflecting myocardial factors, which are not always reflected by hemodynamic measurements alone. Thus, plasma BNP, in particular, follow-up BNP, may serve as a noninvasive prognostic indicator of PPH, which may complement invasive standard prognostic markers.

Clinical Implications
Measurement of plasma BNP is simple, noninvasive, and relatively inexpensive. Baseline plasma BNP at diagnostic catheterization may be an early predictor of outcome in patients with PPH. A second measurement of plasma BNP during administration of prostacyclin or its analogues may identify patients refractory to treatment. Thus, repeated measurement of plasma BNP may be helpful as part of the evaluation of treatment in patients with PPH and, in particular, as a guide to the selection and timing for alternative therapies.

Study Limitations
Patients with kidney failure were excluded from this study because of potentially marked elevation of plasma BNP. Thus, it remains unknown whether plasma BNP level can also be used to predict survival in such patients. Therapy was not controlled in this study. Nevertheless, 55 (92%) patients received prostacyclin therapy: intravenous prostacyclin or an oral prostacyclin analogue, both of which have beneficial effects on survival in PPH. In addition, there was no significant difference regarding medication use in survivors and nonsurvivors.

Conclusions
A high level of plasma BNP, and in particular, a further increase in plasma BNP during follow-up, may have a strong, independent association with increased mortality rates in patients with PPH.

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References
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