Clinical Significance of Brain Natriuretic Peptide in Primary Pulmonary Hypertension

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OBJECTIVES
The aim of this study was to investigate the potential role of brain natriuretic peptide (BNP) levels in the assessment of functional status and right heart performance in primary pulmonary hypertension (PPH).

BACKGROUND
Primary pulmonary hypertension is a progressive disease leading to right heart failure and death. Right heart catheterization and maximal or submaximal exercise tests are employed to assess the course of the disease and the effect of therapeutic interventions. Additional noninvasive and reproducible parameters would be helpful to assess the status of patients with PPH. The natriuretic peptide system is up-regulated in PPH patients. Brain natriuretic peptide (BNP) is produced from the cardiac ventricles and elevated in PPH. The aim of our study was to evaluate the clinical significance of BNP in PPH patients.

METHODS
Correlation analysis was performed for plasma BNP levels of 28 PPH patients and World Health Organization (WHO) functional class (WHO-class), distance walked in 6 min, peak oxygen uptake (peak VO₂), and oxygen pulse during spiroergometry and various hemodynamic parameters, including pulmonary vascular resistance (PVR), pulmonary artery pressure (PAP), right atrial pressure (RAP), and cardiac index.

RESULTS
The BNP levels were inversely correlated with the 6-min walk (r = −0.70; p < 0.001) and peak VO₂ (r = −0.61; p < 0.01), and positive correlation was observed with WHO-class (r = 0.79; p < 0.001). Moreover, BNP levels were also correlated to PVR (r = 0.61; p < 0.01), PAP (r = 0.48; p < 0.05), and RAP (r = 0.78; p < 0.01), and were inversely related to cardiac index (r = −0.48; p < 0.05).

CONCLUSIONS
Our data suggest that plasma BNP levels are closely related to the functional impairment of PPH patients and parallel the extent of pulmonary hemodynamic changes and right heart failure. Serial measurements of plasma BNP concentrations may help improve the management of PPH patients.

Primary pulmonary hypertension (PPH) is a progressive disease leading to reduced functional status and a median survival of 2.8 years (1). According to our present understanding, vascular remodeling, vasoconstriction, and thrombosis in situ play a role in the development of PPH (2). Increased pulmonary artery pressures (PAPs) and elevated pulmonary vascular resistance (PVR) cause right heart failure with low cardiac output (CO) and elevated right atrial pressures (RAPs) (3). Progressive right heart failure results in an impaired patient's functional capacity (4–7). The clinical course of PPH is very variable; therefore, reliable parameters are needed to characterize the severity of the disease and to detect disease progression sensitively. For that reason, repetitive right heart catheterization and cardiopulmonary exercise testing, with submaximal (e.g., 6-min walk [6 MW]) or maximal (spirometry) tests, are employed for evaluation and follow-up of PPH patients (5). In addition, changes in exercise capacity have repeatedly been used to assess the effectiveness of different treatments (8–11).

However, simple noninvasive and examiner independent parameters could contribute significantly to the management of PPH patients. Natriuretic peptides are potential candidates in this respect. In left heart failure, high brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP) levels are associated with impaired exercise capacity (12) and a poor prognosis (13–17). In right heart failure resulting from PPH, limited data are available showing an involvement of the natriuretic peptide system (18–20). In particular, there are no data comparing serum peptide levels with the functional status of PPH patients. Thus, BNP is predominately secreted by the cardiac ventricles (21) and therefore is of special interest in this context.

The aim of our study was to establish BNP as a simple examiner-independent parameter for clinical assessment of disease severity in patients with PPH. For that purpose we performed correlation analysis for BNP levels and the World Health Organization functional class (WHO-class), the distance walked during the 6 MW, peak oxygen uptake (peak VO₂), and oxygen pulse (O₂-pulse) during spiroergometry as well as invasively measured hemodynamic parameters, during right heart catheterization in 28 patients with PPH.
METHODS

Twenty-eight patients (10 male, 18 female; mean age 46.9 years) with PPH were included in the study. Underlying causes for pulmonary hypertension were excluded according to the criteria established during the WHO conference at Evian, France, 1998 (5). Exclusion criteria were non-PPH, impaired renal function (serum creatinine $>1.3$ mg/dl and/or impaired creatinine clearance) or any other significant comorbidity. Vasodilative treatment at the time of enrollment included calcium channel blockers ($n = 7$), iloprost-aerosol (Ilomedin, Schering, Berlin, Germany) ($n = 16$) and Beraprost sodium (Dorer, Yamanouchi-Pharma, Tokyo, Japan) ($n = 2$), respectively. The study protocol was approved by the institutional review committee. The BNP data were blinded until after the exercise, and both hemodynamic data and functional class were recorded. Written informed consent was obtained from every patient. All procedures adhered to the institutional guidelines.

**Right heart catheterization.** In 27 patients a Swan-Ganz catheter (Cordis, Johnson & Johnson, Miami, Florida) were inserted into the right femoral vein and artery, respectively. Hemodynamic measurements were performed in recumbent position. Continuous hemodynamic monitoring included heart rate (HR), systemic and pulmonary (PAP) artery blood pressures and transcutaneous oxygen saturation. Oxygen saturation was measured in arterial and mixed venous blood samples (Hemoximeter, Radiometer, Copenhagen, Denmark). Additionally, blood gas analysis was performed in arterial blood samples (ABL 520, Radiometer, Copenhagen, Denmark). Additional parameters were pressures in wedge position and right atrium. Cardiac output was obtained, using triplicate measurements with the thermodilution method (cardiac output computer, Edwards Laboratories, Santa Ana, California). Cardiac index, PVR, and systemic vascular resistance were calculated using standard formulas.

**The 6-min walk test.** The 6-min walk test was performed in 26 patients using a standardized protocol in accordance to the American Thoracic Society statement 2002 (22). Patients walked along an enclosed-level corridor; length to first turnaround point was 40 m. Techniques did not escort but encouraged patients using standard phrases such as “You are doing well,” “Keep up the good work,” and were instructed not to use other encouragement. All patients were told to use their own pace, but to cover as much ground as possible in 6 min.

**WHO functional class assessment.** The functional class of each patient was determined using a standardized protocol according to the classification of Evian 1998 (5), including questions concerning the patient’s daily life.

**Spiroergometry.** Spiroergometry was performed by 20 patients using a standardized protocol (23). All patients performed a progressively increasing working rate (10 W·min$^{-1}$) to a maximum tolerated level on a electromagnetically braked cycle ergometer. Blood gases were analyzed during the pre-exercise rest, exercise, and postexercise rest. Heart rate and pulse oximetry were monitored continuously, and noninvasive blood pressure was taken every 3 min. The maximum work rate was recorded. Oxygen uptake ($\text{VO}_2$), minute ventilation, and $\text{CO}_2$-output were calculated breath by breath, interpolated, and averaged over 10-s periods. Peak oxygen uptake (peak $\text{VO}_2$) and oxygen pulse ($\text{O}_2$-pulse) were calculated as described by Wasserman et al. (23).

**Lung function test.** The complete set of pulmonary function tests included blood gas analysis in arterialized capillary blood from the ear lobe, spirometry, body plethysmography, and single-breath diffusing capacity.

**Blood sampling and assay.** In all patients ($n = 28$) blood samples were drawn and analyzed for routine laboratory parameters (including renal function) and BNP. Blood samples were drawn from the antecubital vein after at least 30 min of supine rest. The BNP samples were kept at 4°C until centrifugation within 1 h; the plasma obtained was kept at $-20$°C until analysis. Plasma BNP concentrations were quantified as described before (15) using a sandwich radioimmunoassay (Shionoria BNP, CIS, Gif-sur-Yvette, France). The kit uses two different monoclonal antibodies; the first antibody recognizes the C-terminal region of the BNP molecule and is coated onto beads as the solid phase. The second antibody recognizes the intramolecular ring structure of BNP and is radiolabeled with iodine-125 as a tracer. Incubation is performed overnight. During a seven-month period and 31 analytical series, a coefficient of variation of $7.7\%$ was found for a low concentration quality-control sample (mean 5.55 pmol/ml), and of 4.0% for a high concentration sample (mean 85.83 pmol/ml). The cross-reactivity of the assay toward ANP is specified as $<1 \times 10^{-5}\%$.

**Statistical analysis.** Data are shown as mean ± SEM. The statistical software used was SPSS 11.0 for Windows. The Pearson correlation coefficient was calculated for BNP and for all other parameters, and was tested for two-sided significance. Comparison between groups was tested for significance using the nonparametric Mann-Whitney test. In general, $p$ values $<0.05$ were considered statistically significant.
significant. Correlations between hemodynamic and functional parameters and BNP were only performed in those patients who underwent the respective tests.

**RESULTS**

**Hemodynamic parameters at rest.** All patients had significant precapillary pulmonary hypertension (mean PAP 52.9 ± 3.1 mm Hg); wedge pressure 7.8 ± 0.6 mm Hg; PVR 1.058.6 ± 118.5 dyne·cm⁻¹·s⁻¹, and impaired cardiac index (2.1 ± 0.1 l/min·m²). The RAP was 7.6 ± 1.3 mm Hg. The WHO-class was distributed as follows: I (n = 1), II (n = 19), III (n = 6), and IV (n = 2) (Table 1).

**Plasma BNP levels in PPH patients.** Plasma BNP levels were significantly elevated in PPH patients (range, 1.16 to 267.33 pmol/ml; mean, 50.37 ± 11.21 pmol/ml). The BNP concentrations showed significant correlations with the mean PAP, PVR, and RAP obtained during right heart catheterization. Cardiac index was inversely related to plasma BNP levels (Table 1, Figs. 1 and 2). Correlation between plasma BNP levels and WHO-class was strong. The 6 MW ranged from 180 to 600 m and was inversely correlated to plasma BNP levels. Peak VO₂ ranged from 5.2 to 18.8 ml·kg⁻¹·min⁻¹ and was also inversely related to plasma BNP levels. Oxygen pulse also correlated inversely (r = −0.49; p < 0.05) with BNP levels.

**Comparison between WHO functional classes.** The number of patients with WHO functional class I (n = 1) and class IV (n = 2) was too small for further analysis. Comparison of WHO functional class II and class III showed significant differences in BNP levels (p < 0.001), 6 MW (p < 0.001), and peak VO₂ (p < 0.01). In contrast, RAP (p < 0.05) was the only hemodynamic variable that significantly differed between these two groups (Table 1, Fig. 3).

**Correlation analysis of exercise and hemodynamic parameters.** A strong inverse correlation existed between 6 MW test and WHO functional class. Peak VO₂ (r = 0.73; p < 0.001) and oxygen pulse (r = 0.57; p < 0.05) were positively correlated with the 6 MW. Even with high 6 MW test results between 400 and 500 m, we observed a positive correlation with peak VO₂ (data not shown). With regard to hemodynamic parameters, the 6 MW correlated inversely with PVR (r = −0.48; p < 0.05) and positively with cardiac index (r = 0.41; p < 0.05). In addition, the 6 MW distance showed an inverse correlation with the RAP (r = −0.68; p < 0.001) (Table 1, Fig. 3).

Peak VO₂ during spirometry was inversely correlated with the functional class (r = −0.73; p < 0.001). The RAP was significantly inversely correlated with peak VO₂ (r = −0.61; p < 0.01). In addition, oxygen pulse showed a

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<th>Characteristics</th>
<th>All</th>
<th>WHO II</th>
<th>WHO III</th>
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<tr>
<td>PVR (dyne·cm⁻¹·s⁻¹)</td>
<td>1,058.6 ± 118.5</td>
<td>924.3 ± 102.7</td>
<td>1,224.5 ± 102.7</td>
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<tr>
<td>Mean PAP (mm Hg)</td>
<td>52.9 ± 3.1</td>
<td>50.4 ± 3.3</td>
<td>59.6 ± 3.0</td>
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<tr>
<td>RAP (mm Hg)</td>
<td>7.6 ± 1.3</td>
<td>4.6 ± 0.6</td>
<td>13.8 ± 1.4*</td>
</tr>
<tr>
<td>PCWP (mm Hg)</td>
<td>7.8 ± 0.6</td>
<td>7.9 ± 0.6</td>
<td>8 ± 0.8</td>
</tr>
<tr>
<td>CI (l/min·m²)</td>
<td>2.1 ± 0.1</td>
<td>2.2 ± 0.1</td>
<td>2.1 ± 0.2</td>
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**Exercise performance**

<table>
<thead>
<tr>
<th>All</th>
<th>WHO II</th>
<th>WHO III</th>
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<tr>
<td>6 MW (m)</td>
<td>442.3 ± 25</td>
<td>494.4 ± 12.9</td>
</tr>
<tr>
<td>Peak VO₂ (ml/kg·min⁻¹)</td>
<td>12.5 ± 0.8</td>
<td>13.3 ± 0.6</td>
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<tr>
<td>Oxygen pulse (ml·beat⁻¹)</td>
<td>7.3 ± 0.5</td>
<td>7.3 ± 0.4</td>
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<tr>
<td>BNP</td>
<td>50.37 ± 11.21</td>
<td>23.03 ± 5.06</td>
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**Spirometry**

| FEV₁ (% predicted) | 89.5 ± 3.3 | 92.6 ± 3.5 | 81.7 ± 2.6 |
| VC (% predicted) | 90.4 ± 3.1 | 93.9 ± 3.2 | 83.0 ± 2.3 |
| DLCO (% predicted) | 69.1 ± 4.2 | 66.1 ± 4.8 | 72.8 ± 2.7 |
| PO₂ (mm Hg) | 60.3 ± 2.3 | 59.7 ± 2.4 | 58.3 ± 2.4 |

Table 1. Patient Characteristics Including Hemodynamic Parameters, Exercise Tests, BNP Levels, and Spirometry

Comparison WHO II vs. WHO III: *p < 0.05; †p < 0.01; ‡p < 0.001.

BNP = brain natriuretic peptide; CCB = calcium channel blockers; CI = cardiac index; DLCO = diffusing capacity; FEV₁ = forced expiratory volume in 1 s; mean PAP = mean pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; peak VO₂ = peak oxygen uptake; PO₂ = arterial partial oxygen pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; 6 MW = 6-minute walk; VC = vital capacity; WHO = World Health Organization functional class.
significant correlation with cardiac index ($r = 0.63; p < 0.001$) and an inverse correlation with PVR ($r = -0.60; p < 0.05$) (Table 1, Fig. 3).

**Comparison of treatment and lung function groups.** Comparing different treatments with regard to BNP levels or any other parameter we observed no statistically significant differences or correlations between these groups (data not shown). Lung function test showed no correlation with BNP levels in any parameter, including spirometry and the diffusion capacity (data not shown).

**DISCUSSION**

In this study we tried to establish plasma BNP as a simple, noninvasive, and observer-independent parameter for assessing disease severity in patients with PPH. We found robust correlations between BNP levels and WHO-class, the distance walked during the 6 MW test, and peak VO$_2$ during spiroergometry. Additionally, we could demonstrate significant correlations between BNP levels and hemodynamic parameters obtained during right heart catheterization. Based on our results we conclude that plasma BNP concentration is an excellent marker for assessing the functional impairment in PPH patients due to right heart failure.

Plasma BNP levels have been shown to be related to hemodynamic parameters and are suggested to be of prognostic value in patients with left or right heart failure. The majority of data from different investigators show that plasma BNP levels are linked to hemodynamic indices of left ventricular function (14,24–26). Moreover, in chronic left heart failure and myocardial infarction, elevated plasma BNP levels have been associated with a poor prognosis (15,16). Only few reports deal with BNP levels in the context of right ventricular dysfunction complicating pulmonary artery hypertension of different etiologies (18,24). Moreover, there are no data relating BNP to the functional capacity of patients with pulmonary hypertension.

Our results are in line with the hypothesis that the natriuretic peptides are part of a physiologic counterregulatory system in PPH patients with progressive right

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**Figure 1.** (A to D) Correlation of resting hemodynamic parameters with brain natriuretic peptide (BNP) levels in primary pulmonary hypertension (PPH). (A) Pulmonary vascular resistance (PVR) vs. BNP; $r = 0.61; p = 0.001$; (B) mean pulmonary artery pressure (PAP) vs. BNP; $r = 0.49; p = 0.01$; (C) right atrial pressure (RAP) vs. BNP; $r = 0.78; p < 0.001$; (D) cardiac index (CI) vs. BNP; $r = -0.48; p < 0.05$. 

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**Table 1.**

<table>
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<th>Parameter</th>
<th>BNP (pmol/l)</th>
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<tr>
<td>Pulmonary Vascular Resistance (PVR)</td>
<td>0.61</td>
</tr>
<tr>
<td>Mean Pulmonary Artery Pressure (PAP)</td>
<td>0.49</td>
</tr>
<tr>
<td>Right Atrial Pressure (RAP)</td>
<td>0.78</td>
</tr>
<tr>
<td>Cardiac Index (CI)</td>
<td>-0.48</td>
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heart failure. In this context, activation of the natriuretic peptide system will ameliorate pulmonary hypertension owing to the direct vasodilatory properties of ANP and BNP (27) and indirectly by fluid loss. Both, ANP and BNP are peptide-hormones and act via ANP receptors (ANP-A, ANP-B, ANP-C). The ANP-A and ANP-B receptors activate particulate guanylate cyclase and thus induce formation of cyclic guanosine monophosphate (cyclic GMP). The cyclic GMP serves as a second messenger and results in vasodilation, inhibition of the renin angiotension aldosterone system, and inhibition of sympathetic activation (28). However, in left heart failure this linkage is more complex in advanced disease. It has been described that BNP levels are elevated to a higher degree than cyclic GMP levels in severe congestive heart failure (13). Although this cannot be directly transferred to right heart failure in pulmonary hypertension, there seems to be a threshold of BNP above which cyclic GMP no longer increases despite rising BNP production. This
could explain why increasing BNP levels are associated with disease progression and a bad prognosis. In the context of PPH, ANP (19) plays a role in progressive right heart failure as it is highly activated in these patients. Moreover, its secretion is decreased by application of the pulmonary vasodilator iloprost (29) underlining sensitive regulation of the natriuretic peptides.

Predominant vasoconstrictors (30–32) and vascular remodeling lead to increased pulmonary pressures in PPH (2). Moreover, PAP and PVR increase further during exercise, owing to impaired pulmonary vasodilation and recruitment (33). As a result, submaximal and maximal exercise capacity (4) are decreased in PPH. For these reasons the 6 MW test and spiroergometry have been of great value in identifying therapeutic effects of different vasodilators and in assessing a patient’s functional status (7,8,11,34,35). In this context, peak VO₂ has been used as an excellent marker of exercise capacity in a variety of cardiopulmonary diseases as it integrates maximal CO, the potential of the exercising muscle to extract oxygen and the patient’s ventilatory capacity (6). Peak VO₂ has repeatedly been shown to be decreased in PPH (6,23,36). Introduction of oxygen pulse allows correction of oxygen uptake for the heart rate and is a suitable parameter to describe exercise limitations caused by diseases of the pulmonary circulation (23). Consequently, our data describe a close linkage between hemodynamics and maximal exercise impairment. In particular, RAP, a marker of right heart failure, showed significant correlation to peak VO₂. In addition, oxygen pulse correlated significantly with cardiac index and inversely with PVR.

In contrast to spiroergometry, the 6 MW test can be performed in advanced disease stage as it is a submaximal exercise test. We found the distance during the 6 MW to be significantly correlated to cardiac index and inversely correlated to PVR and RAP. This finding confirms previous data from Miyamoto et al. (4).

To the best of our knowledge, there are no data showing correlations between the natriuretic peptides and impaired functional status resulting from right heart failure in PPH. Our results demonstrated robust correlations between plasma BNP levels and clinical status as well as functional parameters derived from maximal and submaximal exercise testing. Additionally, only BNP levels, 6 MW, and peak VO₂ showed a statistically significant difference between functional WHO class II and class III. In contrast, hemodynamics measured during right heart catheter were not significantly different in these groups, except for the RAP.

Finally, long-term observational studies are necessary to evaluate BNP as a marker of disease progression and its role in the assessment of treatment efficiency in PPH and other forms of pulmonary hypertension as this information cannot be drawn from our study. Thus far, our data suggest that BNP is a simple and clinically helpful parameter in the evaluation of PPH patients.

REFERENCES


