Characterization of Brain Natriuretic Peptide in Long-term Follow-up of Pulmonary Arterial Hypertension*

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Study objectives: **Pulmonary arterial hypertension (PAH) leads to substantial morbidity and mortality. Noninvasive parameters in the follow-up assessment of PAH could be helpful in clinical decision making. The brain natriuretic peptide (BNP) has been shown to correlate with the functional status and prognosis of these patients and could be a valuable parameter in this respect. The aim of our study was to investigate whether BNP levels could reflect clinical and hemodynamic changes, including the response to therapy during long-term follow-up in patients with PAH.**

Study design: **We measured pulmonary hemodynamics, functional parameters including the 6-min walk distance (6MWD), and plasma BNP levels at baseline and after a mean (± SEM) follow-up period of 12.6 ± 1.5 months in patients with PAH.**

Results: **In group A (n = 18), with decreasing BNP levels mean pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) decreased (PAP, 60.89 ± 3.44 to 53.47 ± 3.24 mm Hg; PVR, 1,207.47 ± 111.75 to 942.35 ± 103.15 dyne · s · cm^{-5}; p < 0.01) and 6MWD increased (408.24 ± 29.57 to 470 ± 25.54 m; p < 0.01). In group B (n = 12), with increasing BNP levels mean PAP and PVR increased (PAP, 52 ± 3.31 to 60.17 ± 5.03 mm Hg; PVR, 946.13 ± 115.35 to 1,236.6 ± 180.23 dyne · s · cm^{-5}; p < 0.01) and mean 6MWD decreased from 463.64 ± 27.77 to 367.27 ± 38.87 m (p < 0.05). Comparing groups revealed statistically significant differences regarding changes in PAP (group A, −11.58 ± 3.57%; group B, +13.29 ± 5.44%; p = 0.001) and PVR (group A, −19.21 ± 5.87%, group B, +30.35 ± 7.72%; p < 0.001). Correlations existed between the changes in BNP levels and pulmonary hemodynamics.**

Conclusion: **We concluded that BNP levels parallel changes in pulmonary hemodynamics and functional parameters, including the 6MWD, in PAH patients. Consequently, we suggest BNP as a parameter for the follow-up assessment of PAH patients.** ***(CHEST 2005; 128:2368–2374)***

Key words: exercise; hypertension; natriuretic peptides; pulmonary

Abbreviations: BNP = brain natriuretic peptide; CI = cardiac index; CO = cardiac output; 6MWD = 6-min walk distance; PAH = pulmonary arterial hypertension; PAP = pulmonary arterial pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; $S\bar{v}O_2$ = mixed venous oxygen saturation; WHO = World Health Organization

Pulmonary arterial hypertension (PAH) is a progressive disease that leads to substantial morbidity and mortality without adequate treatment.[1] New treatment options have been shown[2–7] to positively influence pulmonary hemodynamics and to improve exercise capacity. Nevertheless, these new treatments are not unequivocally effective in every patient. In patients with progressive disease, the escalation of medical therapy and even a combination therapy with different vasodilators have been suggested.[4,8,9] In this context, it seems to be of crucial importance to recognize disease progression. A number of surrogate markers of disease progression have been proposed such as pulmonary hemodynamics measured by repetitive right heart catheterization, the determination of the World Health Organization (WHO) functional class, and the 6-min walk distance (6MWD).[10] However, there is a need for sensitive

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biological markers that are objective, independent of examiner and patient, and noninvasive.

The natriuretic peptide system may be a candidate in this respect. The atrial natriuretic peptide and brain natriuretic peptide (BNP) have been shown to significantly correlate with the degree of right ventricular overload in patients with pulmonary hypertension.[11–14] BNP seems to be of special interest as it is secreted by the cardiac ventricles[15] and has been shown to be inversely related to prognosis in patients with acute pulmonary thromboembolism.[16,17] However, variations in secretion patterns among individuals have been observed and may be at least partially explained by genetic factors.[18] In addition, there is a need for further long-term follow-up data in patients with PAH.

The aim of our study was to investigate whether BNP levels could reflect clinical and hemodynamic changes and the response to therapy during long-term follow-up in patients with PAH. We performed a prospective longitudinal study in patients with PAH, investigating plasma BNP levels, 6MWDs, and WHO functional class as indicators of changes in pulmonary hemodynamics.

Materials and Methods

Subjects

Thirty patients with PAH (12 men and 18 women; mean [± SEM] age, 46.93 ± 2.8 years), as established according to the WHO classification,[19] were included in the study. Twenty-five subjects received diagnoses of idiopathic PAH. PAH was associated with HIV infection (n = 1), appetite suppressants (n = 1), Gaucher disease (n = 1), capillary hemangiomatosis (n = 1), and corrected atrial septal defect (n = 1).

Exclusion criteria were impaired renal function (serum creatinine level, > 1.3 mg/dL; and/or creatinine clearance rate, < 50 mL/min), age > 65 years, decreased left heart function, and atrial fibrillation. Also, patients were excluded from the study if they showed signs of acute right heart decompensation or volume overload.

The study protocol was approved by the institutional ethics committee. Written informed consent was obtained from every patient.

Right Heart Catheterization

All patients underwent routine right heart catheterization at the beginning of the study and after a mean observation period of 12.6 ± 1.5 months. Patients received no medications by mouth, and the inhalation therapy was paused on the morning of the procedure, resulting in a discontinuation of treatment with medication of about 12 h. Right heart catheterization was performed as described previously.[20]

6-Min Walk Test

Patients performed the 6-min walk test, and the distance was recorded using a standardized protocol in accordance with the American Thoracic Society 2002 guidelines.[21] All patients walked along an enclosed level corridor and were told to proceed at their own pace but to cover as much ground as possible in 6 min. The distance to the first turnaround point was 40 m. The preceptors of the test were blinded to the hemodynamic results.

Blood Sampling and Assay

Blood samples were drawn before right heart catheterization and the 6-min walk test were performed. Samples were analyzed for routine laboratory parameters (including renal function) and BNP levels in all patients (n = 30), as described previously.[11] In general, blood samples were drawn in the morning hours. The normal value obtained during a 7-month period and 31 analytical series was 5.2 pmol/mL. A coefficient of variation of 7.7% was found for a low-concentration quality control sample (mean, 5.55 pmol/mL); 4.0% for a high-concentration sample (mean, 85.83 pmol/mL). The BNP data were blinded until after the 6-min walk test results and hemodynamic data were recorded.

Statistical Analysis

The data were presented as the mean ± SEM. A statistical software package (SPSS, version 11.0 for Windows; SPSS; Chicago, IL) was used for the analysis. Patients were assigned to two different groups regarding the development of BNP concentration during follow-up. Group A consisted of 18 patients with decreasing BNP levels during follow-up. Group B included 12 patients who showed an increase in BNP concentrations. The measured variables were compared in both groups using the Student *t* test for unpaired probes. For analysis of the follow-up data within one group, the Student paired *t* test was used.

The relative changes during the follow-up period compared to baseline values were calculated for BNP levels, pulmonary hemodynamic variables, and the 6MWD. To compare the absolute and relative changes, correlation analysis was performed using the Pearson correlation index. Correlation analysis was performed only in those patients who underwent the respective tests.

All results were tested for two-sided significance. In general, p values < 0.05 were considered to be statistically significant.

Results

Patients Characteristics

Vasodilative treatment included calcium channel blockers (n = 5), bosentan (Tracleer; Actelion; Allschwil, Switzerland) [n = 12], beraprost sodium (Dorner; Yamanouchi-Pharma; Tokyo, Japan) [n = 2], and iloprost-aerosol (Ilomedin; Schering; Berlin, Germany) [n = 6]. Five patients were treated with a combination therapy of either iloprost-aerosol plus calcium channel blockers (n = 3) or beraprost plus calcium channel blockers (n = 2). No additional specific therapy was added, and the medication dosage was kept constant during the study period. The mean follow-up time was 12.6 ± 1.5 months.

Hemodynamics, Functional Parameters, and BNP Concentrations at Baseline

All patients showed severe PAH (*ie*, mean pulmonary artery pressure [PAP], 57.33 ± 2.54 mm Hg;