Elevated plasma brain natriuretic peptide levels in chronic respiratory failure with cor pulmonale

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Elevated plasma brain natriuretic peptide (BNP) levels have been described in patients with congestive heart failure and acute myocardial infarction. We measured plasma BNP levels in patients with chronic respiratory failure to evaluate the correlation between plasma BNP levels and pulmonary hemodynamics. Plasma BNP levels were measured in 28 patients with chronic respiratory failure accompanied by three underlying diseases [14 with chronic obstructive pulmonary disease (COPD), seven with sequelae of pulmonary tuberculosis (sequela Tbc) and seven with diffuse panbronchiolitis (DPB)] by immunoradiometric assay methods (IRMA). Twenty-one of 28 patients had already received oxygen supplementation and 16 of 21 patients were treated as outpatients with home oxygen therapy. Plasma BNP levels were significantly elevated in patients with chronic respiratory failure complicated by cor pulmonale (81.5 ± 13.1 pg ml⁻¹) compared to patients without cor pulmonale (13.3 ± 2.7 pg ml⁻¹, P<0.001). As controls, plasma BNP levels in 10 patients with primary lung cancer were studied, and the results (3.5 ± 1.0 pg ml⁻¹) were not significantly different from those of patients with chronic respiratory failure without cor pulmonale. Plasma BNP levels in 12 healthy subjects were also studied, and the results (7.2 ± 1.0 pg ml⁻¹) were not significantly different from those of the control subjects. Plasma BNP levels showed a weak linear correlation with systolic pulmonary arterial blood pressure, estimated by Doppler echocardiography (r=0.43; P=0.068), but there was no significant correlation between BNP levels and the degree of hypoxaemia (r=0.30; P=0.138). Plasma atrial natriuretic peptide (ANP) levels in patients with chronic respiratory failure were also measured using the same samples. Plasma ANP levels were also significantly elevated in patients with chronic respiratory failure complicated by cor pulmonale (80.8 ± 12.1 pg ml⁻¹) compared to patients without cor pulmonale (26.1 ± 4.4 pg ml⁻¹, P=0.003). A significant correlation was found between plasma BNP and ANP levels (r=0.68; P<0.001). Our results suggest that the plasma BNP or ANP level may be a useful indicator for detecting the presence of cor pulmonale in patients with chronic respiratory failure.

Introduction

Brain natriuretic peptide (BNP), a recent addition to the family of natriuretic peptides, has been isolated from porcine brain (1–3). In humans, a major source of circulating BNP is cardiac tissue. BNP is produced in ventricular tissue, unlike atrial natriuretic peptide (ANP), which is produced in the atrium. ANP has a role in regulating pulmonary vascular tone and may be involved in the pathophysiology of pulmonary hypertension (4,5). A recent study has suggested that the measurement of plasma ANP levels is useful for evaluating pulmonary hypertension (6). However, although elevated plasma BNP levels have been reported in patients with congestive heart failure (left ventricular failure), acute myocardial infarction and in normal subjects after sodium loads (7–10), the role of BNP in the pulmonary circulation is not fully understood. A recent study suggests that BNP blunts hypoxic pulmonary vasoconstriction in isolated perfused rat lung models (11). In humans, Cargill et al. (12) have shown that BNP blunts hypoxic pulmonary vasoconstriction in both healthy volunteers and in patients with cor pulmonale. Studies have also shown elevated plasma BNP levels in patients with chronic obstructive pulmonary disease (13). Therefore, BNP may also play an important role in the pathophysiology of pulmonary hypertension and cor pulmonale.

Although some controversy still exists as to the precise definition of cor pulmonale (14,15), cor pulmonale is defined by the World Health Organization (WHO) as enlargement of the right ventricle (dilation and/or hypertrophy) secondary to pulmonary hypertension from diseases of the lungs or pulmonary circulation (16). As right ventricular failure is not necessary for a diagnosis of cor pulmonale and no specific symptoms are attributable to...
Table 1. Characteristics of patients with chronic respiratory failure

<table>
<thead>
<tr>
<th></th>
<th>COPD (n=14)</th>
<th>Seq Tbc (n=7)</th>
<th>DPB (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>75.3 ± 1.2</td>
<td>68.3 ± 2.2</td>
<td>64.4 ± 4.8</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>13:1</td>
<td>5:2</td>
<td>1:6</td>
</tr>
<tr>
<td>VC (ml)</td>
<td>2794 ± 235</td>
<td>1450 ± 217</td>
<td>1620 ± 27</td>
</tr>
<tr>
<td>FEV₁ (ml)</td>
<td>1090 ± 196</td>
<td>905 ± 66</td>
<td>640 ± 27</td>
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<td>FEV₁/VC⁻¹ (%)</td>
<td>37 ± 6</td>
<td>67 ± 8</td>
<td>40 ± 3</td>
</tr>
<tr>
<td>% FEV₁</td>
<td>57.2 ± 10.3</td>
<td>52.6 ± 4.3</td>
<td>40.8 ± 2.6</td>
</tr>
<tr>
<td>P AO₂ (Torr)</td>
<td>74.2 ± 3.3</td>
<td>70.4 ± 5.5</td>
<td>66.0 ± 4.4</td>
</tr>
<tr>
<td>P CO₂ (Torr)</td>
<td>50 ± 2.9</td>
<td>61.9 ± 5.5</td>
<td>53.0 ± 4.3</td>
</tr>
<tr>
<td>Patients with complicated cor pulmonale (n)</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>O₂ treatment</td>
<td>9</td>
<td>5</td>
<td>7</td>
</tr>
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</table>

COPD: chronic obstructive pulmonary disease; Seq Tbc: sequelae of pulmonary tuberculosis; DPB: diffuse panbronchiolitis; M: male; F: female; VC: vital capacity; FEV₁: forced expiratory volume in 1 sec; % FEV₁: predicted forced expiratory volume in 1 sec; PAO₂: arterial oxygen tension; P CO₂: arterial carbon dioxide tension.

diagnosis is based on physical signs, radiographical studies, electrocardiography, echocardiography, radionuclide studies and cardiac catheterization of only these (17,18). However, cardiac catheterization can document pulmonary hypertension unambiguously and hence can unequivocally admit a diagnosis of cor pulmonale.

In this study, we measured plasma BNP and plasma ANP concentrations in patients with chronic respiratory failure, some of whom did and some of whom did not have cor pulmonale. Our goal was to determine whether the plasma BNP concentration correlated with the existence of cor pulmonale. We also measured the BNP concentration longitudinally in individuals with cor pulmonale to investigate whether changes in the BNP concentration correlated with changes in the clinical course.

Methods

Patients

Twenty-eight patients (nine women, 19 men; mean age 70.5 years, range 42-81 years) with chronic respiratory failure were investigated after informed consent. Underlying diseases included (Table 1): chronic obstructive pulmonary disease (COPD) in 14, sequelae of pulmonary tuberculosis (sequelae Tbc) in seven and diffuse panbronchiolitis (DPB) in seven. Twenty-one patients were treated with oxygen supplementation and 16 of these were treated as outpatients with home oxygen therapy at a mean flow rate of 1.6 1 min⁻¹ for a mean of 50 months (range 10-120 months). The remaining four patients were admitted as inpatients during periods of acute deterioration. Eighteen of the 28 patients were treated with diuretics, five patients were treated with digitalis and all patients were clinically stable according to physical and laboratory findings during the time of study except for the four patients who acutely deteriorated. Patients with systemic hypertension, renal diseases or ischaemic heart diseases were excluded. As control subjects, 10 inpatients with primary lung cancer (three women, seven men), who had not been treated, were studied. The mean age of control subjects was 69.2 years (range 62-76 years). They were clinically stable according to physical and laboratory findings [vital capacity (VC) 2992 ± 225 ml; forced expiratory volume in 1 sec (FEV₁) 2010 ± 270 ml]. We also measured plasma BNP levels in 12 normal subjects (two women, 10 men; mean age 29.3 years, range 22-35 years). Patients were requested to rest quietly for at least 30 min before measurement and the arterial blood gas was drawn from the brachial artery. Spirometric tests were performed to evaluate respiratory function. Echocardiography was performed to assess systolic (ejection fraction) and diastolic (mitral inflow E/A ratio) function. Left-sided heart failure was defined according to the following criteria: ejection fraction less than 60% and E/A ratio less than 1 or over 2. Chronic respiratory failure, using the criteria of the Respiratory Failure Research Group in Japan, was defined as an arterial oxygen tension (PAO₂) of less than 60 Torr on room air, for a period of at least 1 month (19). A clinical diagnosis of cor pulmonale was based on documentation of peripheral oedema with or without elevated jugulovenous pressure, a right ventricular heave on palpitation in the left parasternal area or increased intensity of the pulmonary component of the second heart sound on auscultation. In addition, diagnoses were made by chest roentgenograms which showed enlargement of the pulmonary artery in the hilar regions, electrocardiograms which showed right axis deviation and tall P waves (>2.5 mV) in standard lead II and echocardiograms which showed increased right ventricular dilatation and/or wall thickness in the subxiphoid approach in all cases. Cor pulmonale was present in 13 of 28 patients with chronic respiratory failure. As 19 patients had triicuspid regurgitation on Doppler echocardiography, we estimated right
ventricular systolic (pulmonary artery systolic) pressure (Pasp) using the following formula: \( Pasp = 4 \times V^2 + Pr_a \), where \( V \) is the maximum velocity of tricuspid regurgitant flow and \( Pr_a \) is the jugular venous pressure (20). Pulmonary hypertension was diagnosed using an estimated Pasp greater than 40 mmHg.

**MEASUREMENT OF PLASMA BNP AND ANP LEVELS**

Plasma samples were obtained from the brachial artery at the same time that the blood gas was drawn. They were immediately transferred to glass tubes containing Na₂FDTA (1 mg ml⁻¹) and aprotinin (1000 KIU ml⁻¹), and centrifuged at 4°C. The plasma was immediately frozen and stored at −80°C until the assay. Plasma BNP and ANP levels were determined using an immunoradiometric assay method (IRMA) (Shionoria ANP and BNP, Shionogi & Co, Ltd, Osaka, Japan) (21), which is available commercially (SRL Inc., Tokyo, Japan). In brief, a mixture of standard BNP (4–2000 pg ml⁻¹, 100 µl) or sample (100 µl) ¹²⁵I-labelled monoclonal antibody (200 µl) and a bead bearing another immobilized monoclonal antibody which recognizes the human BNP regions which maintain the integrity of both the C-terminal region and the disulphide bond-mediated ring structure, was incubated at 4°C for 20 h. After removing the supernatant by aspiration, we washed the antibody bead twice with 2 ml of buffer. The radioactivity count in relation to the level of BNP calibrator was used to estimate the level of plasma BNP. In this assay, the minimum detectable quantity of human BNP was 0.5 fmol ml⁻¹. The degree of cross-reactivities with other natriuretic peptides were as follows: for the ANP assay, human ANP 100% and human BNP 0.001%, and for the BNP assay, human BNP 100% and human ANP 0.001%. The intra-assay and interassay variations were less than 10% in this assay system.

**DATA ANALYSIS**

Results are expressed as mean ± SEM. Serum BNP and ANP levels in patients with chronic respiratory failure with or without cor pulmonale, control subjects, and normal subjects were compared using the Mann-Whitney U-test. Linear regression analysis and statistics between plasma BNP and ANP levels and systolic pulmonary arterial blood pressure or blood gas analysis data (\( P_{aO_2} \), \( P_{aCO_2} \)) were performed using Stata Statistical Software 5.0 (Stata-Corp., College Station, TX, U.S.A.). Values of \( P<0.05 \) were considered to be statistically significant.

**Results**

The clinical data are summarized in Table 1. There was no significant intergroup difference in age or \( P_{aO_2} \) between controls, patients with cor pulmonale and patients without cor pulmonale. The male:female ratio was different in the DPB group compared with the other two groups. Twenty-six patients had their systolic pulmonary arterial blood pressure estimated by Doppler echocardiography; the systolic pulmonary arterial blood pressure could not be estimated in seven patients because of a tricuspid regurgitant jet. Thirteen patients (46.4%) were diagnosed with cor pulmonale. Although the systolic pulmonary arterial blood pressure could be estimated in all patients with cor pulmonale (57.6 ± 4.3 mmHg), we could estimate the systolic pulmonary arterial blood pressure in only six of 15 patients without cor pulmonale (26.6 ± 5.3 mmHg) \( (P=0.0021) \). There was no correlation between plasma BNP levels and age. Plasma BNP and ANP levels in healthy subjects, control subjects, patients without cor pulmonale and patients with cor pulmonale are shown in Fig. 1. The mean BNP level in patients with chronic respiratory failure complicated by cor pulmonale (81.5 ± 13.1 pg ml⁻¹) was significantly higher than in healthy subjects (7.2 ± 1.0 pg ml⁻¹), the control group (3.5 ± 1.0 pg ml⁻¹), or patients without cor pulmonale (13.3 ± 2.7 pg ml⁻¹) \( (P<0.001) \). However, no differences were observed between the healthy group, the control group and patients without cor pulmonale. The mean ANP level in patients with chronic respiratory failure complicated by cor pulmonale (80.8 ± 12.1 pg ml⁻¹) was significantly higher than in patients without cor pulmonale (26.1 ± 4.4 pg ml⁻¹) \( (P=0.003) \). Relationships between the plasma BNP levels and systolic pulmonary arterial blood pressure estimated by Doppler echocardiography and plasma ANP levels are shown in Fig. 2a and b. There was a weak correlation between plasma BNP levels and systolic pulmonary arterial blood pressure \((r=0.43; \ P=0.068)\). In addition, there was a significant correlation between plasma BNP levels and ANP levels \((r=0.68; \ P<0.001)\), but not \( P_{aO_2} \) \((r=0.30; \ P=0.138)\) (Fig. 3). Relationships between the plasma ANP levels and systolic pulmonary arterial blood pressure estimated by Doppler echocardiography and \( P_{aO_2} \) are shown in Fig. 4(a) and (b). There was a weaker correlation between plasma ANP levels and systolic pulmonary arterial blood pressure \((r=0.36; \ P=0.062)\), but not \( P_{aO_2} \) \((r=0.01; \ P=0.627)\). Yasue et al. (22) showed that plasma BNP and ANP levels in 420 healthy subjects were less than 20 pg ml⁻¹ (maximum 18.4 pg ml⁻¹, mean 5.9 pg ml⁻¹) and less than 40 pg ml⁻¹ (maximum 27.5 pg ml⁻¹, mean 11.3 pg ml⁻¹), respectively, using the same methods. Our data also showed that the plasma BNP level was less than 20 pg ml⁻¹ in each healthy subject. Therefore, we set the normal BNP and ANP levels at less than 20 pg ml⁻¹ and less than 40 pg ml⁻¹, respectively. The sensitivity, specificity, positive predictive values and negative predictive values of plasma BNP and ANP are shown in Table 2. The sensitivity of BNP was higher than that of ANP, but its specificity was lower. We evaluated the regression of plasma BNP and ANP levels after treatment in four patients with acute exacerbations (Fig. 5). All four patients were treated with oxygen supplementation, diuretics and antibiotics. Subsequently, the mean \( P_{aO_2} \) and the mean systolic pulmonary arterial pressure improved from 53.5 Torr to 66.3 Torr, and from 62.0 mmHg to 60.0 mmHg, respectively. Although plasma ANP levels did not decrease in three cases, plasma BNP levels decreased rapidly after treatment in all cases.
FIG. 1. Plasma BNP (a) and ANP (b) levels by IRMA in healthy subjects, controls, patients without cor pulmonale and patients with cor pulmonale. Error bars are means. The BNP and ANP concentrations in the patients with cor pulmonale were significantly higher when compared with the concentrations in healthy subjects or in patients without cor pulmonale.

FIG. 2. Correlations of plasma BNP levels and systolic pulmonary arterial blood pressure (a) and plasma ANP levels (b). Linear correlations were found between plasma BNP concentrations and the systolic Ppa ($r=0.43; P<0.001$) and plasma ANP levels ($r=0.68, P<0.001$). Ppa: pulmonary arterial blood pressure.

Discussion

In our study, plasma BNP concentrations were higher in patients with chronic respiratory failure complicated by cor pulmonale than in healthy subjects, control subjects or patients without cor pulmonale. In addition, a weak linear correlation was found between plasma BNP concentrations and systolic pulmonary arterial blood pressure estimated by Doppler echocardiography in patients with chronic respiratory failure. Increased plasma BNP levels have been
reported in patients with predominantly left-sided heart failure (8,9). Hang et al. (23) demonstrated a weak linear correlation between plasma BNP levels and diastolic pulmonary arterial pressure or pulmonary capillary wedge pressure, a very close non-linear correlation with left ventricular end-diastolic pressure and a negative linear correlation with ejection fraction. However, the relationship between plasma BNP levels and pulmonary circulation has not been fully studied. Our data demonstrate that the plasma BNP level is a good indicator of pulmonary hypertension and cor pulmonale.

We found no significant differences between plasma BNP levels in patients with COPD, sequelae Tbc or DPB, which are the most common causes of chronic cor pulmonale due to parenchymal lung diseases in Japan. Also, no differences were observed between the healthy group, control group and patients without cor pulmonale. Our data suggest that plasma BNP levels may rise in cases of cor pulmonale which result from various parenchymal lung diseases. Although cor pulmonale is most often caused by parenchymal lung disease, problems with the ventilatory drive, the respiratory pumping mechanism or the pulmonary vascular bed may also result in right ventricular hypertrophy and dilatation. Prasad et al. (24) reported elevated plasma BNP levels in cases of pulmonary arterial hypertension secondary to recurrent thromboembolism.

Because the clinical manifestations of cor pulmonale are quite diverse, the diagnosis and assessment of patients is difficult. Patients with suspected pulmonary hypertension or cor pulmonale may benefit from complete cardiac catheterization to confirm its presence and determine its severity. Because this technique is invasive, non-invasive tests such as electrocardiography, chest radiography and spirometric tests are sometimes used instead. Perreault et al. (6) have suggested that measurement of plasma ANP is useful for diagnosing pulmonary hypertension. The most sensitive non-invasive test for diagnosing pulmonary hypertension is echocardiography (25). Although these studies often are non-specific in evaluating pulmonary hypertension, and the value of any single test is limited, the use of two or more independent non-invasive tests increases diagnostic accuracy and reliability (18). In the present
study, the specificity and sensitivity of the plasma BNP concentration for detecting cor pulmonale were 73.3 and 100%, respectively. Compared with the specificity and sensitivity of other non-invasive tests, including chest radiography (specificity 94%, sensitivity 36%), electrocardiography (specificity 98%, sensitivity 57%) and echocardiography (specificity 94%, sensitivity 69%) as established in the WHC Multicenter Study (16), the plasma BNP concentration appears to be a more sensitive, although less specific, measure. However, specificity was improved by combining the plasma BNP and plasma ANP levels (specificity 100%, sensitivity 69-2%). Therefore, although it may be difficult to evaluate the presence of pulmonary hypertension using BNP levels alone, the measurement of both BNP and ANP may help to diagnose cor pulmonale.

A recent study has suggested that some differences exist between ANP and BNP secretion and metabolism (26). We also observed differences in the response of BNP and ANP levels in four cases of acute exacerbation. Jin et al. (27) suggested that endogenous ANP modulated the subacute, but not the acute, phase of hypoxic pulmonary hypertension. Mukoyama et al. (8, 10) have shown that plasma BNP levels increase rapidly and markedly compared to ANP levels in congestive heart failure and within hours of the onset of an acute myocardial infarction. In addition, Lang et al. (13) have shown that plasma BNP levels are elevated in patients with acute exacerbations of COPD. Our data show that plasma BNP levels change rapidly after treatment. On the other hand, Cargill et al. (28) have shown that acute pulmonary vasoconstriction is associated with release of ANP but not BNP, and that there is a strong correlation between ANP release and the degree of hypoxic pulmonary vasoconstriction. These response patterns of plasma BNP and ANP suggest that they play complementary roles in the regulation of the pulmonary vascular response. Adachi et al. (29) have observed in rats that ANP mRNA levels in the right ventricle increase from day 3 to day 7 after pulmonary arterial banding and that BNP mRNA levels increase from day 1 through day 7 in right ventricular hypertrophy. Our data suggest that plasma BNP levels may be useful for following the course of individuals in whom cor pulmonale has already occurred, especially during acute exacerbations.

We found no correlation between the plasma BNP concentrations and the degree of hypoxaemia. Although the mechanism responsible for BNP release is not yet understood, some studies have shown that the plasma BNP concentration increases with worsening hypoxaemia (13). These differences may occur because of the influence of oxygen supplementation. The $\text{PaO}_2$ data in our study were
collected while patients were in a chronic steady-state with stable oxygen supplementation, except for the four patients experiencing an acute exacerbation. Thus it was difficult to determine the relationship between the plasma BNP concentration and the degree of hypoxaemia in this study.

In conclusion, although measuring the central haemodynamics invasively would have improved the authority of this study, current data strongly suggest that an elevation in the plasma BNP concentration correlates with presence of cor pulmonale. A larger study, testing whether the plasma BNP concentration is able to discriminate between patients with respiratory failure who do and do not have cor pulmonale, is needed. Longitudinal studies in patients with cor pulmonale correlating changes in the BNP concentration with the clinical course of the disease also are required.

References

