Prognostic value of plasma brain natriuretic peptide in patients with stable chronic obstructive pulmonary disease

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Abstract Introduction: Early detection of pulmonary hypertension or cor pulmonale could be beneficial in managing patients with chronic obstructive pulmonary disease (COPD) because the prognosis of these conditions is poor. Plasma brain natriuretic peptide (BNP) levels are elevated in patients with PH secondary to chronic lung diseases.

Aim: The aim of the present study was to investigate the use of plasma BNP levels as a prognostic marker in patients with stable COPD.

Methods: Plasma BNP was measured in controls and patients with stable COPD stage II, III and IV (according to the Global Initiative for Chronic Obstructive Lung Disease classification). Echocardiography, arterial blood gas analysis, and spirometry were also performed for COPD patients.

Results: The study included 57 male patients with stable COPD; 19 had stage II COPD, 21 had stage III COPD, and 17 had stage IV COPD. Twenty age-matched healthy male smokers were enrolled as a control group. The plasma BNP levels were significantly higher in COPD patients compared to controls. The plasma BNP levels in COPD patients increased with disease severity. Plasma BNP levels significantly correlated with FEV1%, PaCO2, PaO2 and pulmonary artery systolic pressure.

Conclusions: Plasma BNP levels increased significantly with disease severity, progression of chronic respiratory failure, and secondary pulmonary hypertension in patients with stable COPD. These results suggest that plasma BNP can be a useful prognostic marker to monitor COPD progression and identify cases of secondary pulmonary hypertension in patients with stable COPD.

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for increasing BNP level is myocardial wall stretch. Circulating BNP levels are elevated several-fold in patients with cor pulmonale, presumably due to right atrial stretch in response to increased right ventricular afterload [2]. The biological role of BNP is probably to attenuate the pulmonary vasopressor response to alveolar hypoxia [3].

Several large trials have found that the most frequent cause of death among patients with COPD is cardiac, rather than respiratory, complications [4,5]. Therefore, secondary pulmonary hypertension and cor pulmonale are important causes of death and poor prognosis in COPD patients [6,7].

Right heart catheterization has been used for diagnosis and assessment of the severity of PH and cor pulmonale. However, recent studies have not demonstrated any sustained benefits of right heart catheterization for the monitoring of heart failure, and some have even suggested harm due to adverse events related to this invasive procedure [8,9].

Plasma BNP is a noninvasive biomarker for the diagnosis and monitoring of cardiac diseases and heart failure [10,11]. In addition, it is well known that plasma BNP levels are elevated in patients with cor pulmonale [2]. Although increased BNP level was reported as a risk factor for death independent of chronic lung disease [12], few studies have assessed the prognostic value of BNP for determining COPD severity and identifying the possibility of progression to secondary pulmonary hypertension. Therefore, the aim of the present study was to investigate the use of plasma BNP levels as a prognostic marker in patients with stable COPD.

Materials and methods

Subjects

Patients with stable COPD were enrolled, all were males. The inclusion criteria were a history of smoking, FEV1/FVC ratio <70%, and an FEV1 < 80% of predicted values. Patients with conditions altering the levels of plasma BNP were excluded such as respiratory disorders other than COPD, pulmonary embolisms, infectious diseases, malignancy, recent surgery, and cardiac, endocrine, hepatic, or renal dysfunction. Age-matched healthy smoker males were enrolled as a control group.

Spirometry

Spirometry was performed for patients and controls using a computer spirometer (Jaeger, Germany). Spirometry was performed 3 times and the best effort of FEV1 was recorded.

Arterial blood gases analysis

Arterial blood was drawn from COPD patients after a rest period of 10 min. Arterial partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2) were measured immediately using an automatic blood gas analyzer.

Echocardiography

Transthoracic echocardiography was performed for COPD patients by a cardiologist. The pulmonary artery systolic pressure (PASP) was analyzed in terms of tricuspid regurgitation peak velocity (TRPV) and right atrial pressure (RAP) using a color-Doppler technique (PASP = 4 × TRPV + RAP) [13].

Plasma NT-proBNP

BNP is synthesized as a prehormone (proBNP). Upon release into circulation it is cleaved into equal amounts of biologically active C-terminal fragment (BNP), and the biologically inactive N-terminal fragment (NT-proBNP). The half-life of BNP is 20 min, whereas NT-proBNP has a half-life of 120 min. This explains why NT-proBNP plasma values are approximately six times higher than BNP values, even though both molecules are released in equimolar proportions. Peripheral blood samples were collected in tubes containing ethylenediamine tetra-acetate (EDTA). Measurements were performed using a commercial kit (Roche Diagnostics Corp., Indianapolis, IN, USA) and an electrochemiluminescent method with an Elecsys 2010 Automated Analyzer (Roche Diagnostics). The results are presented as pg/ml.

Statistical analysis

All data are expressed as mean and standard error of the mean (±SEM). One way ANOVA was used to compare variables among groups. Correlations were determined by Spearman’s rank correlation test. A p value < 0.05 was considered significant. Data were analyzed with the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA).

Results

Clinical characteristics of patients and controls

The study included 57 male patients with stable COPD; 19 had stage II COPD, 21 had stage III COPD, and 17 had stage IV COPD. Twenty age-matched healthy male smokers were enrolled as a control group. There were no significant differences in age, smoking history (pack-years), or body mass index among subjects with different stages of COPD and controls (Table 1).

Plasma BNP levels

The plasma BNP level in COPD patients was significantly higher than that in normal subjects. The levels of plasma BNP were significantly higher in patients with stage IV > stage III > stage II COPD (Table 2). Plasma BNP levels significantly correlated with FEV1% (r = −0.489; P < 0.01), PaCO2 (r = 0.501; P < 0.05), PaO2 (r = −0.443; P < 0.05) and PASP (r = 0.489; P < 0.01).

Discussion

The present study tested the prognostic value of plasma BNP levels in patients with stable COPD to predict COPD severity, and complications (pulmonary hypertension). Plasma BNP levels in patients with stable COPD increased significantly with disease severity and significantly correlated with pulmonary artery systolic pressure.

Plasma BNP levels in patients with stable COPD increased significantly with disease severity. The levels of plasma BNP
were significantly higher in patients with stage IV > stage III > stage II COPD. There have been few studies that examined plasma BNP levels in patients with stable COPD. Rutten et al. [14] demonstrated that the overall diagnostic utility of BNP is lower for detecting heart failure in patients with chronic dyspnea and COPD than in individuals with acute dyspnea presenting at the emergency department. Stolz et al. [15] showed that plasma BNP levels are significantly elevated during acute exacerbation of COPD compared to recovery. Inoue et al. [16] reported that plasma BNP levels in patients with stable COPD were significantly higher than those of healthy subjects and patients with severe asthma, and the level increased significantly with disease severity. A high plasma BNP level was shown to be an independent risk factor for exacerbation but not mortality [16].

The mechanism underlying high plasma BNP levels in patients with stable COPD is not clear. Stolz et al. [15] hypothesized that the elevation of BNP levels is at least partly due to hypoxia-mediated contraction of small pulmonary arterioles, resulting in increased pulmonary arterial pressure and subsequent cardiac stretch. However, this group failed to show a significant correlation between plasma BNP levels and PaO₂, PaCO₂, or FEV₁ [15]. In the present study, we observed significant differences in plasma BNP levels among patients at different stages of COPD with significant correlations between plasma BNP levels and FEV₁%, PaO₂, PaCO₂ and PASP. This result can be explained by the fact that decreased FEV₁ may lead to increased air-trapping and hyperinflation of the lung. Such hyperinflation is associated with decreased cardiac function and may result in an increase of plasma BNP. Another explanation might be related to chronic hypoxia in patients with COPD resulting in contraction of the small pulmonary arterioles, increased PASP and subsequently plasma BNP levels.

In conclusion, we demonstrated that plasma BNP levels significantly increased with COPD severity, progression of chronic respiratory failure, and the presence of secondary pulmonary hypertension in patients with stable COPD. Our results suggest that plasma BNP can be a useful prognostic marker of COPD progression. This factor may also help identify cases of secondary pulmonary hypertension in patients with stable COPD.

References


