PLASMA BRAIN NATRIURETIC PEPTIDE LEVELS IN CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITHOUT PULMONARY HYPERTENSION

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ABSTRACT

BACKGROUND

It has long been known that pulmonary hypertension (PH) leads to rise in brain natriuretic peptide (BNP) in patients with Chronic Obstructive Pulmonary Disease (COPD). However, data on BNP level in COPD patients without PH is limited. This study was carried out to evaluate the change in BNP level in COPD patients without PH or cor-pulmonale during exacerbation and after remission.

MATERIALS AND METHODS

The study involved 90 subjects; 60 patients with COPD and 30 age matched healthy subjects without COPD (15-smokers and 15-non-smokers). In all the patients, history and clinical exam, pulmonary function test, BNP level measurement, electrocardiography and echocardiography were performed. In COPD patients, BNP level was measured during exacerbation and after remission and at only once in healthy subjects.

RESULTS

Levels of BNP were significantly higher in COPD patients (37.54 ± 15.1 pg/mL) compared to control (19.12 ± 4.61 pg/mL) and increased further during exacerbation (67.59 ± 38.4 pg/mL). BNP levels during exacerbation were significantly higher in patients with COPD grade III-IV (88.76 ± 37.54 pg/mL) compared to grade II (55.88 ± 7.6 pg/mL) and grade I (37.66 ± 8.76 pg/mL). It was a significantly inversely related to post FEV1%. Moreover, Comparing the baseline PO2 and PCO2 in COPD patients, PO2 decreased and PCO2 increased significantly as the severity of COPD class increased.

CONCLUSION

Plasma BNP can be used as a useful diagnostic and prognostic biomarker of COPD and a good predictor of exacerbation.

KEYWORDS

Pulmonary Hypertension, Brain Natriuretic Peptide (BNP), COPD.

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BACKGROUND

COPD is characterized by progressive air flow limitation due to chronic inflammatory response in the airways and the lung parenchyma to noxious particles or gases. Repeated exacerbations and associated comorbidities contribute to the overall morbidity and mortality in these patients.[1]

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Since the first description from porcine brain in 1988, brain natriuretic peptide (BNP) was soon found to originate mainly from the heart.[1,2] BNP is synthesized as a prehormone (pro-BNP). 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. Therefore, NT-pro BNP plasma values are approximately six times higher than BNP values.[1,3]

The main stimulus responsible for release of BNP is myocardial wall stretch, ventricular dilation, and increased pressures from circulatory volume overload. BNP levels are elevated several-fold in patients with COPD with PH and cor-pulmonale (COR-P), presumably due to right atrial stretch in response to increased right ventricular afterload.[4,5] The biological role of BNP is probably to attenuate the pulmonary

vasopressor response to alveolar hypoxia.[6] Studies have reported usefulness of measurement of plasma BNP levels as a biomarker for the detection and follow-up of heart diseases and a risk factor for death independent of COPD.[6,7]

Studies related to BNP levels in Stable COPD patients without PH or COR-P however, are limited.[2,8,9] The aim of the present study was to investigate the use of plasma BNP levels as a prognostic marker in patients with stable COPD during exacerbation and after remission.

MATERIALS AND METHODS

Ours was a prospective observational study. The study was performed in department of internal medicine, civil hospital, Ahmedabad, Gujarat, India. The study was approved by ethics committee of our hospital and informed and written consent was obtained from all the patients. Patients who consented were included in the study.

Study included 60 patients with varying severity of COPD who presented to our hospital with exacerbation. For comparison, 30 healthy age matched adults were included. They were divided into 2 groups:

Group 1(n=60): COPD with exacerbation. They were further grouped based on severity of COPD.

- Group 1-A (n = 20): Patients with COPD GOLD class I (FEV1 $\geqslant$ 80% of predicted).
- Group 1-B (n = 20): Patients with COPD GOLD class II (50% $\leqslant$ FEV1 < 80%).
- Group 1-C (n = 20): Patients with COPD GOLD class III–IV (FEV1<50% of predicted).

Group 2 (n =30): Healthy subjects. Fifteen patients were non-smokers and 15 patients were asymptomatic smokers.

Inclusion Criteria

Patients with COPD diagnosed according to GOLD 2016 criteria.

Exclusion Criteria

1. Pulmonary hypertension, COR-P or other chronic respiratory disease.
2. Exacerbations due to pneumothorax or cardiac failure without acute exacerbation of COPD.
3. Patients with a history for cardiac, renal, hepatic, endocrine, neurological and psychological disease.
4. Malignancy, pulmonary embolisms, infectious diseases and recent surgery.

All subjects were submitted to the following-

1. Detailed history including history of smoking, chest symptoms and co-morbidities.
2. General and respiratory examination, chest X-ray postero-anterior and lateral views.
3. Complete blood count, hepatic and renal function tests and fasting blood sugar, pulmonary function test (spirometry) before and after bronchodilation. Spirometry was performed 3 times and the best effort of FEV1 was recorded. These investigations were performed to exclude the presence of associated disease.
4. Arterial blood gases analysis for partial pressure of oxygen (PaO2) and carbon dioxide (PaCO2). Sample was drawn in COPD patients after 15 minutes of rest period.
5. Transthoracic Echocardiography was performed to exclude the presence of PH and other associated cardiac lesions.
6. Plasma NT-proBNP: Peripheral blood samples were collected in tubes containing ethylenediamine tetra-acetate (EDTA). Measurements were performed using an electro chemiluminescent method with an Elecsys 2010 Automated Analyzer (Roche Diagnostics). The results were presented as pg/ml.

Statistical Analysis

The collected data were analysed using SPSS version 16 for windows. Categorical data were presents as number and percentage while continuous variables were presented as mean and SD if parametric, and as median and range if non-parametric, chi square, paired t-test and spearman's correlation coefficients were used as tests of significance. Two-sided p <0.05 value was considered significant.

RESULTS

The study included 90 patients, 60 male patients with stable COPD and 30 age-matched healthy males without COPD as controls. As shown in table 1, there were no significant differences in age or body mass index among subjects with different stages of COPD and controls. Duration of smoking was significantly less in control group compared to study group (p<0.05). Comparing the baseline PO2 and PCO2 in COPD patients, PO2 decreased and PCO2 increased significantly as the severity of COPD class increased. (Table-1).

	Control Group (n=30)	Group A (n= 20)	Group B (n=20)	Group C (n=20)	P Value
Male (n) (%)	30 (100%)	20 (100%)	20 (100%)	20 (100%)	-
Age (years) (Range)	54.6 ± 6.32 (42.5–69)	53.3 ± 6.43 (43.5-67)	56.4 ± 5.68 (46–69.5)	57.8 ± 5.5 (45-67)	0.092
Smoking (pack-years)	38.1 ± 7.7	43.0 ± 4.0	51.7 ± 9.3	49.4 ± 8.4	<0.0001
BMI (Range)	25.8 ± 3.3 (20–33.6)	25.2 ± 4.7 (19-34.9)	24.2 ± 4.2 (19.7–34.7)	25.8 ± 3.9 (17.8-34.5)	0.510

	Control Group (n=30)	Group A (n= 20)	Group B (n=20)	Group C (n=20)	P Value
FEV1 (Range)	86.8 ± 6.9 (74–100)	83.8 ± 5.9 (81–94)	71 ± 8.4 (54 – 78)	45.7 ± 10.3 (26–50)	<0.0001
FEV1/FVC% (Range)	79.7 ± 5.97 (72–87)	65.3 ± 7.1 (53 – 68.4)	60.6 ± 11.4 (38–67)	58.3 ± 6.7 (43 – 65)	<0.0001
PaO_2 (mmHg)		81.2 ± 8.8	77.9 ± 4.1	61.8 ± 6.3	<0.0001
$PaCO_2$ (mm Hg)		39.2 ± 4.8	46.2 ± 6.1	69.2 ± 7.8	<0.0001

Table 1. Demographic Data of Studied Group

BMI: Body Mass Index; FEV1: Forced expiratory volume; FVC: forced vital capacity.

Mean BNP levels in COPD patients in stability were significantly higher compared to controls. (19.12 ± 4.61 pg/ml vs 37.54 ± 15.1 pg/ml; p<0.0001) Further, in COPD patients, the BNP levels increased significantly during exacerbation compared to during stability. Comparing the three COPD groups, BNP levels increased significantly with increasing severity of COPD class and it further increased significantly in all three classes during exacerbation. (Group A = 24.77 ± 3.27 pg/ml; Group B= 33.87 ± 7.45 pg/ml; Group C=48.75 ± 22.6 pg/ml; p<0.0001, respectively) Comparing the smoker and non-smoker patients in the controls, BNP levels were significantly higher in smokers compared to non-smokers. (25.32 ± 3.1 pg/ml vs. 19.44 ± 4.92 pg/ml; p<0.0001).

DISCUSSION

BNP levels are increasing being used as marker of heart failure. However, its utility in stable COPD patients and in diagnosis of COPD exacerbation is still limited. In our study, Plasma BNP level was found to be significantly higher in COPD patient (37.54 ± 15.1 pg/mL) compared to controls (19.12 ± 4.61 pg/mL). Our results are in agreement with study by Inoue et al (10) who found that plasma BNP levels in patients with stable COPD (41 ± 6.6 pg/mL) were significantly higher than those of healthy subjects (14.8 ± 2.7 pg/mL) and the level increased significantly with disease severity.

Also, it was found that BNP level was significantly higher in COPD patients during exacerbation (67.59 ± 38.4 pg/mL) than after stability (37.54 ± 15.1 pg/mL) and the difference between them was statistically highly significant (p<0.001). Further, BNP level increased significantly with increasing severity of COPD class. Our results are in agreement with Inuoe et al,[10] Nishimura et al[11] and El Gazzar et al[2] where they measured plasma BNP level in patients with increasing severity of COPD and found that it was high at hospitalization with acute exacerbation of COPD and it reduced significantly after stabilization of their COPD. This difference was statistically highly significant in all the studies (p < 0.005). Studies have found the elevated levels of BNP as a predictor of mortality in patients admitted to the hospital with acute exacerbation of COPD. In a study by Patolia et al,[12] they found BNP levels to be significantly elevated during acute exacerbation (86.96 pg/mL) of COPD. They also found that elevation of BNP level suggested higher severity of COPD and was associated with increase mortality and hospital length of stay.

The reason why BNP level rise in patients with COPD is not clearly understood. There are two possible mechanisms that have been proposed. First, in stable COPD there is pulmonary hyperinflation that is further aggravated during exacerbation of COPD due to acute air trapping and hyperinflation. Pulmonary hyperinflation in COPD patients may adversely affect the cardiovascular function leading to stretching of right atrium and right ventricle. It is possible that BNP is released as a result of this atrial and ventricular stretching rather than intrinsic myocardial dysfunction. Second, BNP level may be a marker of systemic or lung inflammation during acute exacerbation of COPD that is qualitatively or quantitatively different from stable COPD. This modification of inflammation may be related to LV preload through systemic vasoconstriction, or alternatively lung hyperinflation or inflammation may be causing the increase in BNP levels via an increase in left ventricular wall stress.[2]

In our study, COPD patients had significantly higher BNP level compared to patients without COPD irrespective of whether they were smokers or non-smokers. Further, comparing the patients without COPD, BNP levels were higher in smoker compared to non-smoker. This agrees with Otsuka et al[13] who found significantly higher BNP levels in current smokers (21.7 ± 2.3 pg/ml) compared to in never smokers (17.9 ± 2.1 pg/ml) (p <0.001). Further, current smokers had an increased odds ratio (3.04, 95% for elevated NT-pro-BNP >54.5 pg/ml) for increased NT-pro-BNP compared to never smokers. The probable mechanism is that cigarette smoking impairs arterial function and promotes atherosclerosis. This may result in increased cardiac overload which may result in increased secretion of BNP. Further, smoking cessation ameliorates these conditions. The studied by Omer et al[7] with 75 healthy habitual smokers (40 females, 35 males, mean age 36.5 ± 8.5 years), and 73 nonsmokers (45 females, 28 males, mean age 34.6 ± 7.2 years). Additionally, found that smoking resulted in an increase NT-pro-BNP levels and there was a significant positive correlation observed between the duration of smoking and NT-pro-BNP levels. They stated that nicotine in cigarette smoking increased the risk of acute

cardiac event related with endothelial dysfunction, increase sympathetic activity, coronary vasoconstriction and platelet aggregation.

CONCLUSION

Plasma BNP level was significantly higher in COPD patients than in control groups. It was significantly higher in grade (IV, III) than grade (II, I) and was significantly higher in grade (II) than grade (I) COPD patients. BNP level was significantly higher during exacerbation than during remission of COPD. So, plasma BNP can be used as a useful biomarker in prognosis of COPD. There is a significant and direct correlation between BNP level and both of S.I. (smoking index) and paCO2 and a non-significant negative correlation between BNP and paO2 in COPD patients.

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