Plasma brain natriuretic peptide levels in COPD without pulmonary hypertension

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ABSTRACT

Introduction: It has long been known that COPD causes elevation in BNP level caused by hypoxia present in cases of pulmonary hypertension in COPD.
The aim of this study: This study was carried out to evaluate the changes in BNP level in COPD patients without pulmonary hypertension or cor pulmonale during exacerbation and after remission.
Subjects and methods: This study was created on 50 subjects, 30 COPD patients according to inclusion and exclusion criteria (BNP level will be measured during exacerbation and after remission) plus 20 age matched apparently healthy control subjects, ten of them are non smokers and ten are asymptomatic smokers. For all subjects, history taking, full clinical exam done. PFT (spirometry), BNP level measurement on human serum by ELIZA, routine labs (CBC, liver and renal function). ECG. echocardiography.
Results: Levels of BNP were significantly higher in COPD patients with mean (60.52 ± 30.98 pg/mL) than control with mean (21.13 ± 4.61 pg/mL) and higher during exacerbation (60.52 ± 30.9 pg/mL) than during remission (35.65 ± 16.54 pg/mL), BNP was significantly higher in grade (III, IV) with mean (86.94 ± 40.19 pg/mL) than grade (II) (56.76 ± 6.2 pg/mL) and grade (II) was significantly higher than grade (I) with mean (37.86 ± 8.81 pg/mL) and it was a significantly inversely related to post FEV1% and post FEF 25–75% and significantly direct correlated to paco2 and non significant negative correlation to pao2.
Conclusion: Plasma BNP can be used as a useful prognostic biomarker of COPD and a good predictor of exacerbation, As BNP level was significantly higher in COPD patients than in control groups, (p < 0.005) and also significantly higher in grade (IV, III) than grade (II) and was significantly higher in grade (II) than grade (I) COPD patients, BNP level significantly higher (p < 0.005) during exacerbation than during remission of COPD patients.

Introduction

COPD is a common preventable and treatable disease that is characterized by persistent air flow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity in individual patients [1].

Acute exacerbation of chronic obstructive pulmonary disease is defined as acute event characterized by a worsening of the patients respiratory symptoms that is beyond normal day to day variations and leads to a change in medications [1].

Natriuretic peptides are peptides that are released from the heart in situations of pressure and volume overload of the ventricles. There are 3 types of natriuretic peptides: atrial natriuretic peptide, B-type natriuretic peptide (BNP), and C-type natriuretic peptide. Atrial natriuretic peptide is released predominantly from the atria, BNP from the ventricles, and C-type natriuretic peptide from the endothelium [2].

Release of NPs results from cardiac wall stretch, ventricular dilation, or increased pressures from circulatory volume overload. The effects of NPs result in lowering blood volume and pressure [3].

Plasma brain natriuretic peptide (BNP) is a useful biomarker for the detection and follow up of heart diseases [4].
Plasma BNP level is elevated in patients with pulmonary hypertension (PH) and chronic lung disease with right ventricular over-load [5]. Plasma BNP levels in Stable COPD patients without PH or cor pulmonale have not been studied well [6].

**Aim of the work**

This study was carried out to evaluate the changes in BNP level in COPD patients without pulmonary hypertension or cor pulmonale during exacerbation and after remission.

**Subjects and methods**

**Study design**

Prospective case control study.

**Subjects**

This study was performed in Benha University Hospital Chest Department on 50 subjects. They were divided into 2 groups:

1. Group A: included (30) patients with acute exacerbation of chronic obstructive pulmonary disease and will be classified according to grading into Group [A] 1: (10) patients grade I (FEV1 ≥ 80% of predicted).
   Group [A] 2: (10) patients grade II (50% ≤ FEV1 < 79%).
   Group [A] 3: (10) patients grade III–IV (30% ≤ FEV1 < 49% of predicted. FEV1<30% of predicted) respectively.
2. Group B: included (20) healthy subjects, (10) of them are non smokers and (10) are asymptomatic smokers.

**Inclusion criteria**

Patients with COPD diagnosed according to GOLD (2016) criteria.

**Exclusion criteria**

1. Pulmonary hypertension, cor pulmonale or other chronic respiratory disease.
2. Exacerbations due to pneumothorax or cardiac failure without acute exacerbation chronic obstructive pulmonary diseases.
3. Patients with a history of symptoms and medication for cardiac, renal, neurological and psychological disease.
4. Malignancy.

All subjects were submitted to the following:

1. History taking: History of smoking, chest symptoms and any other co-morbidities.
2. Clinical examination: both general and local examination.
3. Radiological examination: Plain chest X ray postero-anterior and lateral views.
4. Pulmonary function tests (spirometry) before and after bronchodilatation.
5. Routine investigations as: Electrocardiography, complete blood count, liver function tests, kidney function tests and fasting blood sugar.
6. Measuring the oxygen saturation in the blood by pulse oximetry.
7. Electrocardiography (ECG) A 12 lead ECG including 3 bipolar limb leads, 3 unipolar limb leads and 6 unipolar precordial leads was performed.
8. Echocardiography was done to exclude pulmonary hypertension cases.
9. Plasma Brain natriuretic peptide B type measurement [7].

Using commercially available enzyme-linked immunosorbent assay (ELISA) were used according to the manufacture’s instruction (Human NPPB (BNP) ELISA Kit, Thermo Scientific).

**Statistically analysis**

The collected data were analyzed 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**

Table 1 show that (100%) were males COPD patients.

The mean age for patients was (47.9 ± 6.48) years old and for control was (49.1 ± 5.01) years.

FEV1% and FVC% were significantly higher in control group than case group.

Table 2 and Fig. 1 show that BNP level significantly higher in COPD patients than control group.

Table 3 and Fig. 2 Show that BNP level significantly higher in COPD patients during exacerbation than after stability.

Table 4 and Fig. 3 show that BNP level was significantly higher in Group A3 than Group A1 and Group A2 and in Group A2 than Group A1 and that it was higher during exacerbation than during remission of COPD patients.

Table 5 and Fig. 4 show that BNP level significantly higher in Group (A) COPD patients than group (B) control smokers and non smokers. And significantly higher in control healthy smoker than control non smoker.

Table 6 and Fig. 5 show a significant direct correlation between BNP level and smoking index in COPD patients.

Table 7 and Fig. 6a and b show a Significant direct correlation between BNP level and paco2 and a non significant negative correlation between BNP and pao2.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic data of studied group.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Case group</td>
</tr>
<tr>
<td>Sex n &amp; %</td>
<td>Male 30 (100%)</td>
</tr>
<tr>
<td>Age in years</td>
<td>Range 41–69</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 47.9± 6.48</td>
</tr>
<tr>
<td>BMI</td>
<td>Range 20–34.2</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 25.05 ± 3.9</td>
</tr>
<tr>
<td>FVC%</td>
<td>Range 39–98</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 77.5 ± 17.3</td>
</tr>
<tr>
<td>FEV1%</td>
<td>Range 25–81</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 59.5 ± 19.8</td>
</tr>
<tr>
<td>FEV1/FVC%</td>
<td>Range 38–69</td>
</tr>
<tr>
<td></td>
<td>Mean ± SD 60.03 ± 10</td>
</tr>
</tbody>
</table>
Discussion

This study was created on 50 subjects, 30 COPD male patients (BNP hormone WAS measured during exacerbation and after remission) their age ranging from (41 to 69) years plus 20 age matched apparently healthy control group (10) of them are healthy smokers and (10) are non smokers and their age ranging from (42 to 63) years and that both FEV1%, FVC% were significantly higher in control group than case group (Table 1).

In the current study, Plasma level of BNP was found to be higher in COPD patient with mean (60.52 ± 30.98) pg/mL compared to controls (smokers and non smokers) with mean (21.13 ± 4.61) pg/mL and the difference between them was statistically highly significant.(p < 0.005) in (Table 2, Fig. 1).

These results agree with [8] 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.

Table 2
Comparison of plasma BNP level (pg/mL) in COPD patients as a whole (group A) and control (group B).

<table>
<thead>
<tr>
<th>BNP</th>
<th>COPD patients (30)</th>
<th>Control group (20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD</td>
<td>60.52 ± 30.98</td>
<td>21.13 ± 4.61</td>
</tr>
<tr>
<td>Range</td>
<td>45.3–161.5</td>
<td>19.6–35.5</td>
</tr>
<tr>
<td>St t test</td>
<td>5.63</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>P &lt; 0.005</td>
<td></td>
</tr>
</tbody>
</table>

Figure 1. Comparison of plasma BNP level (pg/mL) in COPD patients as a whole (group A) and control (group B).

Table 3
Comparison of BNP level (pg/mL) in COPD patients as a whole during exacerbation and after stability.

<table>
<thead>
<tr>
<th>BNP pg/mL</th>
<th>Mean</th>
<th>Range</th>
<th>Paired t test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During exacerbation</td>
<td>60.52 ± 30.98</td>
<td>45.3–161.5</td>
<td>6.06</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>After stability</td>
<td>35.65 ± 16.54</td>
<td>21.9–115</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Comparison of BNP level (pg/mL) in COPD patients as a whole during exacerbation and after stability.

Table 4
Comparison of BNP level (pg/mL) between Group A1, A2 and A3 COPD patients during exacerbation and after stability.

<table>
<thead>
<tr>
<th>Group A COPD Patients</th>
<th>Group A1</th>
<th>Group A2</th>
<th>Group A3</th>
<th>ANOVA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP during exacerbation</td>
<td>37.86 ± 8.81</td>
<td>56.76 ± 6.2</td>
<td>86.94 ± 40.19</td>
<td>10.62</td>
<td>P &lt; 0.005</td>
</tr>
<tr>
<td>BNP after stability</td>
<td>28.15 ± 7.27</td>
<td>33.81 ± 6.38</td>
<td>44.98 ± 25.9</td>
<td>3.06</td>
<td>P &gt; 0.05</td>
</tr>
</tbody>
</table>

Also it was found that BNP level was significantly higher in COPD patients during exacerbation (60.52 ± 30.98 pg/mL) than after stability (35.65 ± 16.54 pg/mL). (Table 3 and Fig. 2) and the difference between them was statistically highly significant (p < 0.005), And BNP level was significantly higher in Group A3 COPD patients than Group A2 and higher in Group A2 than Group A1 (Table 4 and Fig. 3).

This result agrees with [9] who measured plasma BNP level and found that it was 55.4 (26.9–129.3) pg/mL at the first hospitalization with AECOPD during the study period, and in the stable patients, it was 18.3 (10–45.3) pg/mL. This difference was statistically highly significant at (p < 0.005).

It has been reported that the elevated levels of NT-pro BNP are one of the mortality predictors among patients admitted to the hospital with AECOPD.

There are at least two possible mechanisms for BNP rise. First, pulmonary hyperinflation has the potential for significant adverse effects on cardiovascular function in COPD and AECOPD is characterized by worsening lung hyperinflation.

It is possible that BNP was released from the heart as a result of this, rather than as a direct effect of intrinsic myocardial function.

Second, BNP may reflect systemic or lung inflammation during AECOPD 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.

The result also agrees with [8] who found that Plasma BNP levels during exacerbation was (79.9 ± 16.2 pg/mL) and it was significantly higher than in patients with stable COPD (41.2 ± 8.7 pg/mL) (p < 0.005).

In addition, plasma BNP levels were elevated when exacerbations occurred in some subjects. Exacerbation is associated with a transient decrease in expiratory flow. Radical decreases in expiratory flow may lead to increased air-trapping and hyperinflation.

**Table 5**

<table>
<thead>
<tr>
<th>BNP (pg/mL)</th>
<th>Mean ± SD</th>
<th>Range</th>
<th>ANOVA</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild COPD (Group A1)</td>
<td>37.86 ± 8.81</td>
<td>28.5–59.4</td>
<td>21.97</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Moderate COPD (Group A2)</td>
<td>56.76 ± 6.2</td>
<td>47.55–67.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe COPD (Group A3)</td>
<td>86.94 ± 40.19</td>
<td>45.3–161.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control smokers (Group B)</td>
<td>23.54 ± 2.8</td>
<td>19.8–29.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control non smokers (Group B)</td>
<td>18.72 ± 4.92</td>
<td>11.55–25.95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6**

<table>
<thead>
<tr>
<th>BNP (pg/mL)</th>
<th>Pearson correlation</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking index (SI)</td>
<td>0.817</td>
<td>&lt;0.005</td>
<td>Highly significant</td>
</tr>
</tbody>
</table>

Figure 3. Comparison of BNP level (pg/mL) between Group A1, A2 and A3 COPD patients during exacerbation and after stability.

Figure 4. Comparison of plasma BNP level (pg/mL) in COPD patients (Group A1, 2, 3) and healthy smokers and non smokers (Group B).
of the lung. It is possible that such hyperinflation is associated with decreased cardiac function and may lead to an increase of plasma BNP level during exacerbation.

Setu patolia et al. [10] who found that BNP levels were significantly elevated during the acute exacerbation (86.96 pg/mL). These results of elevation of BNP levels suggest higher severity of COPD patients and associated with increase mortality and hospital length of stay.

In this work (Table 5 and Fig. 4) show that Group (A) COPD patients have significantly higher level of BNP level than group (B) control smokers and non smokers. And also those control healthy smokers have higher level of BNP level than control non smoker. Table 6 and Fig. 5 show Significant and direct correlation between smoking index and BNP level in COPD patients.

This agrees with [11] who found that NT-pro-BNP levels were significantly higher in current smokers (21.7 ± 2.3) pg/ml than in never smokers (17.9 ± 2.1) pg/ml (p < 0.005). And Current smokers had an increased odds ratio (3.04, 95% for elevated NT-pro-BNP >54.5) pg/ml compared to never smokers.

Cigarette smoking impairs arterial function and promotes atherosclerosis. These results suggest that cigarette smoking increases cardiac overload, whereas smoking cessation ameliorates these conditions.

The result also in a agreement with [12] who included in the study 75 healthy habitual smokers (40 females, 35 males, with mean age of (36.5 ± 8.5 years), and 73 nonsmokers (45 females, 28 males, with mean age of (34.6 ± 7.2 years), and found that smoking result 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 and these results explained by that cigarette smoking increase the risk of acute cardiac event related with endothelial dysfunction and increase sympathetic activity and coronary vasoconstriction and platelet aggregation.

The mechanisms of the effects of nicotine involve both stimulation and blocking of the autonomic ganglia, liberation of adrenomedullary epinephrine, stimulation of carotid body chemoreceptors and aortic baroreceptors, and direct action in the central nervous system.

Table 7 and Fig. 6a and b show Significant and direct correlation between BNP and blood gases in COPD patients.

![Figure 5. Correlation between BNP level and smoking index in COPD patients.](image)

![Figure 6. (a), (b): Correlation between BNP and blood gases in COPD patients.](image)

**Table 7**

<table>
<thead>
<tr>
<th>Blood gases</th>
<th>Pearson correlation</th>
<th>P value</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNP level pg/mL</td>
<td>Po2</td>
<td>-0.156</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td></td>
<td>Pco2</td>
<td>0.454</td>
<td>P &lt; 0.05</td>
</tr>
</tbody>
</table>

This result agrees with [13] who found that were a Significant and direct correlation between BNP and PaCO2 with the p value was (p < 0.005).
The result also agrees with [14] as there were correlation between BNP and arterial blood gas parameters PaCO2 (r = 0.476) with the (p < 0.005).

The result disagrees with [8] who found regarding PaCO2 there was no correlation between plasma BNP level and PaCO2.

Stolz [15] hypothesize that the elevation of BNP may be due to hypoxia-mediated contraction of the small pulmonary arterioles, resulting in increased pulmonary arterial pressure and consequently cardiac stress.

Conclusions

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) 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.

References


