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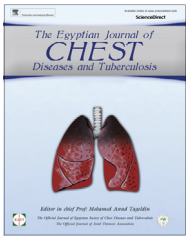

ORIGINAL ARTICLE

Role of N-terminal pro B-type natriuretic peptide in acute exacerbation of chronic obstructive pulmonary disease

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Abstract *Objectives:* Acute exacerbation of chronic obstructive pulmonary disease (AECOPD) is a major public health problem. Recognition of comorbid heart dysfunction in such patients is often difficult. The aim of this work is to evaluate the role of N-terminal pro B-type natriuretic peptide (Nt-pro BNP) in AECOPD with respiratory failure.

Patients and methods: This study was conducted on 20 patients with AECOPD and respiratory failure. All patients were subjected to history taking, clinical examination, routine laboratory investigations, arterial blood gases analysis, echocardiography and estimation of plasma level of NT-pro BNP.

Results: Patients were classified into 3 groups: Group I: those without heart dysfunction (40%), Group II: those with diastolic heart failure (40%), and Group III: those with systolic heart failure (20%). NT-pro BNP mean ± SD in group I was 673.38 ± 416.02, in group II 1962 ± 847.88, and in group III 6776.75 ± 1433.59 pg/ml. There was a statistically significant difference between the three groups ($p = 0.001$). NT-pro BNP showed a statistically significant inverse correlation with pH ($p = 0.005$), ejection fraction ($p = 0.007$) and a direct one with both left ventricular systolic

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($p = 0.008$) and diastolic ($p = 0.016$) dimensions and E/A ($p = 0.016$). The NT-pro BNP significantly decreased after recovery from AECOPD ($p = 0.030$). The receiver operating characteristic curve demonstrated a ruling out of LV dysfunction in AECOPD of a sensitivity of 100% and a specificity of 60%; and a ruling in of a sensitivity of 48% and a specificity of 67%.

Conclusion: Plasma BNP is usually elevated in AECOPD and is related to right or left ventricular systolic or diastolic dysfunction.

Introduction

Chronic obstructive pulmonary disease (COPD) remains a major public health problem. It has some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases. The chronic airflow limitation characteristic of COPD is caused by a mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema), the relative contributions of which vary from person to person [1].

An exacerbation of COPD is defined as "an event in the natural course of the disease characterized by a change in the patient's baseline dyspnea, cough, and/or sputum that is beyond normal day-to-day variations, is acute in onset, and may warrant a change in regular medication in a patient with underlying COPD" [2]. The most common causes of an exacerbation are the infection of the tracheobronchial tree and air pollution, but the cause of approximately one-third of severe exacerbations cannot be identified [3]. In COPD there is a background of mild inflammation. There is a general belief that exacerbations are episodes where the inflammatory process is enhanced. There are varying degrees of inflammation affecting the large and small airways as well as the alveoli, resulting in mucus hypersecretion, airway narrowing and alveolar destruction. The main mediators directly responsible for this damage are proteinases released by inflammatory cells, particularly neutrophils, that are found in abundance in the bronchial secretions of patients with COPD [4].

Pulmonary arterial hypertension (PAH) develops late in the course of the natural history of patients with COPD and is associated with the development of severe hypoxemia. It is a major cardiovascular complication of COPD and is associated with the development of right ventricular hypertrophy (namely, "cor pulmonale") and has a poor prognosis [5]. In patients with COPD, without severe hypoxemia or hypercapnia, the pulmonary artery pressure (PAP) is usually normal or only slightly elevated when measured at rest, but may rise abnormally during exercise. Despite slow progression, the presence of pulmonary hypertension implies a poor prognosis in patients with COPD [6].

Echocardiography is a useful tool to diagnose pulmonary hypertension and cor pulmonale. However, measurement cannot be achieved in all patients since hyperinflation of the chest will alter sound-wave transmission through the chest. Invasive measurements of pulmonary arterial pressure by right heart catheterization remain the "gold standard" measurement of the pulmonary arterial pressure [7].

It has become clear that cardiac events are the major cause of death for patients with COPD in all stages of disease. These associations could be from shared risk factors, most notably cigarette smoking. Increases in C-reactive protein, for example, represent a major risk factor for cardiovascular disease. In this context, COPD is also an inflammatory disease and increases in C-reactive protein are present in patients with COPD [8]. However, there are mechanical and physiologic relationships that could account for these associations. Clinically, it is often difficult to distinguish between cardiac and pulmonary disease as a cause for dyspnea. The assessment of brain natriuretic peptide (BNP) may prove useful in this regard.

It has been almost 50 years since the first anatomical clues to an endocrine function of the heart were reported. Electron microscopy revealed secretory granules in atrial myocytes, which structurally resembled storage granules in peptide-hormone-producing cells [9]. It was only in 1981, however, that Adolfo de Bold and his coworkers put the endocrine heart to the test and infused extracts of atrial tissue into anesthetized rats. The infusion elicited prompt renal excretion of sodium and water, decreased the blood pressure, and increased the hematocrit. The substance was logically named atrial natriuretic factor [10]. Soon after, this factor was purified and identified as a peptide of 28 amino acid residues and was named atrial natriuretic peptide (ANP) [11]. This discovery of a new peptide paved the way for the later identification of the different but structurally related peptide in porcine brain: brain natriuretic peptide (BNP) [12]. However, BNP was found to be produced mainly in the heart, and the name "brain natriuretic peptide" now is often replaced with "B-type natriuretic peptide" [13].

N-terminal fragments from the cardiac precursor peptides proANP and proBNP were also found to circulate in plasma and provided new molecular markers for biochemical detection of heart failure. Atrial and ventricular myocytes differ in their endocrine apparatus. It is a well established fact that atrial myocytes contain secretory granules for proBNP, in contrast, ventricular myocytes in the healthy heart do not seem to produce these granules, and do not contain proBNP derived peptides [14].

The aim of this work is to evaluate the role of N-terminal pro B-type natiuretic peptide (NT-pro BNP) in acute exacerbation of chronic obstructive pulmonary disease with respiratory failure.

Patients and methods

This study was conducted in the intensive care unit of the chest disease department in main Alexandria University Hospital. It

was carried out on 20 patients suffering from acute exacerbation of chronic obstructive pulmonary disease with respiratory failure.

All patients were subjected to full history taking, thorough clinical examination emphasizing on signs of COPD, respiratory failure, cor pulmonale and heart failure. Electrocardiogram was carried out to all patients. Venous blood sample was taken and analyzed for complete blood picture, renal and liver function tests, fasting blood glucose level, prothrombin activity, total serum protein, albumin, lactate dehydrogenase content and C-reactive protein. Arterial blood sample was drawn from the radial artery and analyzed for hydrogen ion concentration (pH), partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), oxygen saturation and bicarbonate (HCO_3) level.

Echocardiography was performed (HP screen, 100 CF Hewlett Packard) for the assessment of pulmonary artery hemodynamics by doppler analysis of pulmonary flow measuring the acceleration time (AT) (time from onset to the peak of the ejection flow velocity), left ventricular end systolic dimension (LVES), left ventricular end diastolic dimension (LVED), right ventricular dimension (RVD), left ventricular ejection fraction (LVEF), peak velocities of blood flow during early diastolic filling (E wave) and atrial contraction filling (A wave) then the ratio (E/A) is calculated.

Peripheral blood sample was taken and examined for N-terminal pro B-type natiuretic peptide (NT-pro BNP) level. N-terminal brain natriuretic peptide was measured with a Roche Diagnostics proBNP assay on an Elecsys 2010 analyser. In this two-site assay 20 µl of sample is incubated with biotinylated polyclonal antibody plus a different polyclonal antibody labeled with a ruthenium complex. Both antibodies are directed to the proBNP (amino acids 1-76 of proBNP) region. Following incubation the bound fraction is separated with streptavidin-coated microparticles and quantitated by chemiluminescence. Data provided by Roche Diagnostics show that total assay precision ranges from 1.8% at 800 pmol/l to 2.7% at 20.7 pmol/l and the detection limit is 0.6 pmol/l. Crossreactivity with other peptides including amino-terminal proANP peptides, C-type natriuretic peptide, and components of the renin-angiotensin system was all $< 0.001\%$.

Results

We classified the patients according to history, clinical examination and echocardiographic finding into 3 groups: Group I: COPD exacerbation with no heart failure (8 patients: 40%), GroupII: COPD exacerbation with diastolic heart failure (8 patients: 40%), and Group III: COPD exacerbation with systolic heart failure (4 patients: 20%).

The patients' characteristics of all 20 patients showed a mean ± SD age of 57.85 ± 9.37 years ranging from 47 to 76 years. Sixteen (80%) patients were males and four (20%) were females. Fifteen (75%) patients were smokers and five (25%) were non smokers. The mean ± SD duration of smoking was 32 ± 8.71 years ranging from 15 to 43 years. The duration of COPD had a mean ± SD of 9.9 ± 5.34 years ranging from 4 to 20 years. Twelve (60%) patients were hypertensive and four (20%) were diabetic. Fifteen (75%) patients were previously hospitalized for acute exacerbation of COPD (AECOPD).

The patients' characteristics of the three groups are shown in Table 1. In group I the mean ± SD age was 59.38 ± 9.05 years ranging from 51 to 76 years, in group II it was 58.13 ± 7.74 years ranging from 47 to 68 years, in group III it was 54.25 ± 15.2 years ranging from 42 to 76 years; there was no statistical significant difference between the 3 groups. In group I there were seven male patients (87.5%) and 1 female (12.5%); in group II there were five male patients (62.5%) and 3 females (37.5%); and in group III all patients (100%) were males. In group I six patients were smokers (75%) and 2 were non smokers (25%); in group II five patients were smokers (62.5%) and 3 were non smokers (37.5%); and in group III all patients were smokers (100%). In group I the mean ± SD duration of smoking was 30 ± 10.49 years ranging from 15 to 40 years, in group II it was 35.6 ± 5.86 years ranging from 30 to 43 years, and in group III it was 30 ± 10 years ranging from 20 to 40 years; there was no statistical significant difference between the 3 groups. The mean ± SD duration of COPD in group I was 10 ± 4.63 years ranging from 5 to 15 years, in group II it was 9.13 ± 5.51 years ranging from 4 to 20 years, in group III it was 11.25 ± 7.5 years ranging from 5 to 20 years; there was no statistical difference between the three groups. Hypertension was present in 4 (50%) patients in group I, in 5 (62.5%) patients in group II and in 3 (75%) patients in group III. Diabetes mellitus was present in 1 (12.5%) patient in group I and in 3 (37.5%) patients in group II. History of previous cardiac disease, notably ischemic heart disease was given by 3 (37.5%) patients in group II and by all 4 (100%) patients in group III. Regarding previous hospitalization for AECOPD, it was recorded in 5 (62.50%) patients in group I, in 6 (75.00%) patients in group II and in all 4 (100%) patients

Table 1 Patients' characteristics of the three groups.

	Age years	Gender		Smoking history	DOS years	Duration of COPD years	PH for AECOPD
		M	F				
Group I	59.38 ± 9.05	7 (87.5%)	1 (12.5%)	6 (75.0%)	30 ± 10.49	10 ± 4.63	5 (62.50%)
Group II	58.13 ± 7.74	5 (62.5%)	3 (37.5%)	5 (62.5%)	35.6 ± 5.86	9.13 ± 5.51	6 (75.00%)
Group III	54.25 ± 15.2	4 (100%)	0 (0.0%)	4 (100%)	30 ± 10	11.25 ± 7.5	4 (100%)
t-Value	0.358				0.625	0.195	
p	0.704				0.553	0.825	
x^2		2.813		2			2
p		0.245		0.368			0.368

M: male; F: female; DOS: duration of smoking; PH: previous hospitalization; COPD: chronic obstructive pulmonary disease; AECOPD: acute exacerbation of COPD.

in group III. There was no statistical significant difference between the three groups.

The clinical examination of all the twenty patients showed a mean ± SD heart rate of 107.4 ± 12.6 beats per minute ranging from 90 to 140 beats per minute; a mean ± SD systolic blood pressure of 139 ± 17.4 mmHg ranging from 120 to 190 mmHg; a mean ± SD diastolic blood pressure of 89 ± 8.52 mmHg ranging from 80 to 110 mmHg. The mean ± SD respiratory rate was 25.95 ± 4.21 breaths per minute ranging from 20 to 40 breaths per minute. The mean ± SD temperature was 37.47 ± 0.82 °C ranging from 37 to 40 °C. Wheezes and diminished air entry were found in all patients. Bilateral basal crackles were heard in 9 (45%) patients; congested neck veins were seen in 9 (45%) patients; hepatic enlargement was found in 4 (20%) patients and bilateral lower limb edema was found in 12 (60%) patients.

On comparing the three groups, the mean ± SD heart rate in group I was 108.75 ± 11.88 beats per minute, in group II 100.88 ± 6.58 beats per minute, and in group III 117.75 ± 18.08 beats per minute. There were no significant differences between the three groups ($p = 0.08$). The mean ± SD systolic blood pressure in group I was 145 ± 21.38 mmHg, in group II 137.5 ± 15.81 mmHg, and in group III 130 ± 8.16 mmHg. There were no significant differences between the three groups ($p = 0.375$). The mean ± SD diastolic blood pressure in group I was 93.75 ± 10.61 mmHg, in group II 87.5 ± 4.63 mmHg, and in group III 82.5 ± 5 mmHg. There were no significant differences between the three groups ($p = 0.072$). The mean ± SD respiratory rate in group I was 25.63 ± 3.74 breaths per minute, in group II 24.63 ± 0.92 breaths per minute, and in group III 29.25 ± 7.63 breaths per minute. There were no significant differences between the three groups ($p = 0.198$).

The arterial gasometric studies of all 20 patients showed a mean ± SD pH of 7.29 ± 0.09 ranging from 7.05 to 7.42; a mean ± SD $PaCO_2$ of 68 ± 21.63 mmHg ranging from 34.9 to 103.8 mmHg; a mean ± SD PaO_2 of 87.65 ± 89.45 mmHg ranging from 38.4 to 213 mmHg; a mean ± SD oxygen saturation of 86.74 ± 9.47% ranging from 65.8% to 99.3%; a mean ± SD bicarbonate level of 33.095 ± 8.08 mEq/l ranging from 23 to 51.2 mEq/l and a mean ± SD PaO_2/FIO_2 of 109.73 ± 51.3 ranging from 96 to 236. Most patients were already put on oxygen and some of them intubated when the arterial blood gases sample was taken.

The comparison of the arterial gasometric study of the three groups is shown in Table 2. The mean ± SD pH in group I was 7.25 ± 0.1, in group II 7.27 ± 0.09, and in group III 6.59 ± 1.45. There were no significant differences between the three groups ($p = 0.175$). The mean ± SD $PaCO_2$ in group I was 67.21 ± 20.46 mmHg, in group II 79.59 ± 17.98 mmHg, and in group III 46.4 ± 15.89 mmHg. There was a significant statistical difference between group II and group III ($p = 0.033$). The mean ± SD PaO_2 in group I was 91.78 ± 73.22 mmHg, in group II 63.51 ± 16.42 mmHg, and in group III 97.68 ± 27.18 mmHg. There were no significant differences between the three groups ($p = 0.237$). The mean ± SD oxygen saturation in group I was 85.59 ± 11.89%, in group II 85.56 ± 7.35%, and in group III 91.43 ± 8.75%. There were no significant differences between the three groups ($p = 0.569$). The mean ± SD bicarbonate level in group I was 30.6 ± 7.85 mEq/l, in group II 35.93 ± 8.47 mEq/l, and in group III 32.2 ± 7.92 mEq/l. There were no significant differences between the three groups ($p = 0.435$). The mean ± SD PaO_2/FIO_2 in group I was 110.44 ± 40.74, in group II 97.38 ± 41.56, and in group III 134 ± 75.61. There were no significant differences between the three groups ($p = 0.505$).

Regarding the laboratory investigations of all 20 patients, the hemoglobin level ranged from 11.5 to 16.5 g/dl with a mean ± SD of 13.93 ± 1.8 g/dl; the hematocrit level ranged from 34.2% to 57.5% with a mean ± SD of 45.86 ± 6.84%; the white blood cells ranged from 3.95 to 30.2 cell/mm^3 with a mean ± SD of 10.68 ± 6.36 cell/mm^3; the creatinine level ranged from 0.5 to 2.2 mg/dL with a mean ± SD of 1.11 ± 0.505 mg/dL; the C-reactive protein (CRP) level ranged from 9.2 to 202 mg/l with a mean ± SD of 35.38 ± 42.51 mg/l; the erythrocyte sedimentation rate (ESR) in the first hour ranged from 4 to 80 mm/hr with a mean ± SD of 34.63 ± 24.36 mm/hr; the ESR in the second hour ranged from 15 to 110 mm/hr with a mean ± SD of 61.73 ± 32.09 mm/hr and the NT-pro BNP ranged from 54 to 8852 pg/ml with a mean ± SD of 2409.50 ± 2453.95 pg/ml.

The comparison of the laboratory results of the three groups is shown in Table 3. The hemoglobin level mean ± SD in group I was 14.51 ± 1.69 g/dl, in group II 13.91 ± 2.04 g/dl, and in group III 12.43 ± 0.4 g/dl. There were no significant differences between the three groups ($p = 0.247$). The hematocrit level mean ± SD in group I was 47.23 ± 7.57%, in group II 46.59 ± 6.78%, and in group III 40.33 ± 2.08%. There were no significant differences between the three groups ($p = 0.324$). The white blood cells mean ± SD in group I was 9.03 ± 4.88 cell/mm^3, in group II 10.26 ± 4.62 cell/mm^3, and in group III 16.27 ± 12.19 cell/mm^3. There were no significant differences between the three groups ($p = 0.248$). The erythrocyte sedimentation rate (ESR) in the first hour in group I was 18.75 ± 15.71 mm/hr, in group II 43.86 ± 24.31 mm/hr, and in group III 50.25 ± 24.66 mm/hr. There was a statistical significant difference between group I and groups II and III

Table 2 Arterial gasometric study in the three groups.

	pH	$PaCO_2$ (mmHg)	PaO_2 (mmHg)	O_2 sat (%)	HCO_3 (mEq/l)	PaO_2/FIO_2
Group I	7.25 ± 0.1	67.21 ± 20.46	91.78 ± 73.22	85.59 ± 11.89	30.6 ± 7.85	110.44 ± 40.74
Group II	7.27 ± 0.09	79.59 ± 17.98	63.51 ± 16.42	85.56 ± 7.35	35.93 ± 8.47	97.38 ± 41.56
Group III	6.59 ± 1.45	46.4 ± 15.89	97.68 ± 27.18	91.43 ± 8.75	32.2 ± 7.92	134 ± 75.61
t-Value	1.934	4.207	1.569	0.583	0.878	0.712
p	0.175	0.033*	0.237	0.569	0.435	0.505

pH: hydrogen ion concentration; $PaCO_2$: arterial partial pressure of carbon dioxide; PaO_2: arterial partial pressure of oxygen; O_2 sat: oxygen saturation in arterial blood; HCO_3: bicarbonate level; FIO_2: fraction of inspired oxygen.
* Statistical significance at $p < 0.05$.

Table 3 Laboratory investigations in the three groups.

	HB	HCT	WBC	ESR1	CRP	NT-pro BNP
Group I	14.51 ± 1.69	47.23 ± 7.57	9.03 ± 4.88	18.75 ± 15.71	23.68 ± 12.79	673.38 ± 416.02
Group II	13.91 ± 2.04	46.59 ± 6.78	10.26 ± 4.62	43.86 ± 24.31	49.53 ± 63.65	1962 ± 847.88
Group III	12.43 ± 0.4	40.33 ± 2.08	16.27 ± 12.19	50.25 ± 24.66	28.9 ± 10.31	6776.75 ± 1433.59
t-Value	1.529	1.211	1.524	4.046	0.76	69.871
p	0.247	0.324	0.248	0.038*	0.484	0.001*

HB: hemoglobin; HCT: hematocrite; WBC: white blood cell; ESR1: erythrocyte sedimentation rate in 1st hour; CRP: C reactive protein; NT-pro BNP: N-terminal pro B-type natiuretic peptide.
* Statistical significance at $p < 0.05$.

($p = 0.038$). The ESR in the second hour in group I was 38.63 ± 25.46 mm/hr, in group II 74.86 ± 27.73 mm/hr, and in group III 85 ± 24.14 mm/hr. There was a statistical significant difference between group I and groups II and III ($p = 0.014$). The CRP level in group I was 23.68 ± 12.79 mg/l, in group II 49.53 ± 63.65 mg/l, and in group III 28.9 ± 10.31 mg/l. There were no significant differences between the three groups ($p = 0.484$). The NT-pro BNP mean ± SD in group I was 673.38 ± 416.02 pg/ml ranging from 54 to 1541 pg/ml, in group II 1962 ± 847.88 pg/ml ranging from 1050 to 3588 pg/ml, and in group III 6776.75 ± 1433.59 pg/ml ranging from 5620 to 8852 pg/ml (Fig. 1). There was a statistically significant difference between the three groups regarding NT-pro BNP ($p = 0.001$).

The echocardiographic parameters of all 20 patients showed a mean ± SD LVES of 3.5375 ± 1.09 cm ranging from 2.03 to 6.25 cm; a mean ± SD LVED of 4.955 ± 0.99 cm ranging from 3.65 to 7.92 cm; a mean ± SD LVEF of 60.22 ± 11.65% ranging from 38% to 80%; a mean ± SD RVD of 3.33 ± 0.86 cm ranging from 2.1 to 5.32 cm; a mean ± SD pulmonary flow acceleration time of 75.9 ± 15.344 ms ranging from 55 to 120 ms and a mean ± SD E/A ratio of 1.44 ± 0.2 ranging from 0.8 to 2.1.

The comparison of the echocardiographic findings of the three groups is shown in Table 4. The mean ± SD LVES in group I was 3.02 ± 0.61 cm, in group II 3.25 ± 0.67 cm, and in group III 5.14 ± 1.13 cm. There was a statistical significant difference between group III and the other two groups ($p = 0.001$). The mean ± SD LVED in group I was 4.51 ± 0.58 cm, in group II 4.74 ± 0.63 cm, and in group III 6.28 ± 1.25 cm. There was a statistical significant difference between group III and the other two groups ($p = 0.004$). The mean ± SD LVEF in group I was 68.63 ± 8.7%, in group II 59.75 ± 6.43%, and in group III 44.38 ± 7.97%. There was a statistical significant difference between group III and the other two groups ($p = 0.001$). The mean ± SD RVD in group I was 3.20 ± 1.06 cm, in group II 3.51 ± 0.89 cm, and in group III 3.22 ± 0.17 cm. There was no significant differences between the three groups ($p = 0.762$). The mean ± SD E/A in group I was 1.2 ± 0.4, in group II 1.98 ± 0.3, and in group III 0.87 ± 0.2. There was a statistical significant difference between group II and the other two groups ($p = 0.002$).

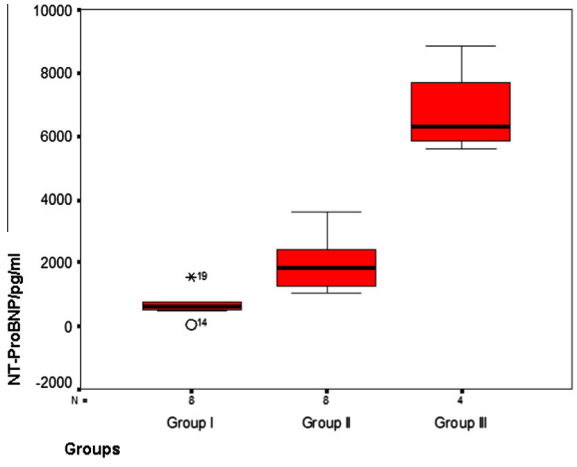

Figure 1 Box plot illustrating N-terminal pro B-type natiuretic peptide (NT-pro BNP) in the 3 studied groups. There was a statistically significant difference between the three groups ($p = 0.001$).

The correlations of plasma NT-pro BNP with other parameters are shown in Table 5. Plasma NT-pro BNP did not show any significant correlation with the age ($p = 0.967$), duration of smoking ($p = 0.891$), duration of COPD ($p = 0.235$), heart rate ($p = 0.314$), respiratory rate ($p = 0.219$), systolic blood pressure ($p = 0.133$), PaO_2 ($p = 0.412$), $PaCO_2$ ($p = 0.105$), HCO_3 ($p = 0.843$), PaO_2/FIO_2 ($p = 0.32$), hematocrit ($p = 0.062$), WBC ($p = 0.082$), ESR in the first hour ($p = 0.059$), ESR in the second hour ($p = 0.053$), CRP ($p = 0.714$), RVD ($p = 0.837$) and AT ($p = 0.743$). Plasma NT-pro BNP showed a statistically significant inverse correlation with the diastolic blood pressure ($p = 0.02$), hemoglobin ($p = 0.034$), pH ($p = 0.005$) and LVEF ($p = 0.007$) (Fig. 2). However, the plasma NT-pro BNP showed a statistically significant direct correlation with LVES ($p = 0.008$), LVED ($p = 0.016$) and E/A ($p = 0.016$).

The NT-pro BNP was repeated in 14 patients after recovery from the exacerbation, its mean ± SD value significantly decreased from 1298.4 ± 848.57 pg/ml to 539.48 ± 484.56 pg/ml ($p = 0.030$).

The receiver operating characteristic (ROC) curve demonstrated a cut off value of 900 pg/ml for ruling out the presence of LV dysfunction in AECOPD with a sensitivity of 100% and a specificity of 60%. The cut off value for ruling in the presence of LV dysfunction in AECOPD was 2180 pg/ml with a sensitivity of 48% and a specificity of 67%.

Discussion

Chronic obstructive pulmonary disease is a common disease with a steadily increasing prevalence and mortality. COPD is

Table 4 Echocardiographic parameters in the three groups.

	LVES (cm)	LVED (cm)	LVEF (%)	RVD (cm)	E/A
Group I	3.02 ± 0.61	4.51 ± 0.58	68.63 ± 8.7	3.20 ± 1.06	1.2 ± 0.4
Group II	3.25 ± 0.67	4.74 ± 0.63	59.75 ± 6.43	3.51 ± 0.89	1.98 ± 0.3
Group III	5.14 ± 1.13	6.28 ± 1.25	44.38 ± 7.97	3.22 ± 0.17	0.87 ± 0.2
t-Value	11.534	7.754	13.222	0.277	8.931
p	0.001*	0.004*	0.001*	0.762	0.002*

LVES: left ventricular end systolic dimension; LVED: left ventricular end diastolic dimension; LVEF: left ventricular ejection fraction; RVD: right ventricular dimension; E/A: ratio of peak velocities of blood flow between early diastolic filling (E) and atrial contraction filling (A).
* Statistical significance at $p < 0.05$.

Table 5 Correlations of plasma NT-ProBNP.

		Ph	PaO_2	$PaCO_2$	PaO_2/FIO_2	CRP	AT	RVD	LVEF	E/A
BNP	*r*	−0.602	0.194	−0.373	0.234	0.09	−0.078	−0.049	−0.584	0.531
	p	0.005*	0.412	0.105	0.32	0.71	0.74	0.837	0.007*	0.016*

BNP: N-terminal pro B-type natiuretic peptide; pH: hydrogen ion concentration; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; FIO_2: fraction of inspired oxygen; CRP: C reactive protein; AT: pulmonary flow acceleration time; RVD: right ventricular dimension; LVEF: left ventricular ejection fraction; E/A: ratio of peak velocities of blood flow between early diastolic filling (E) and atrial contraction filling (A).
* Statistical significance at $p < 0.05$.

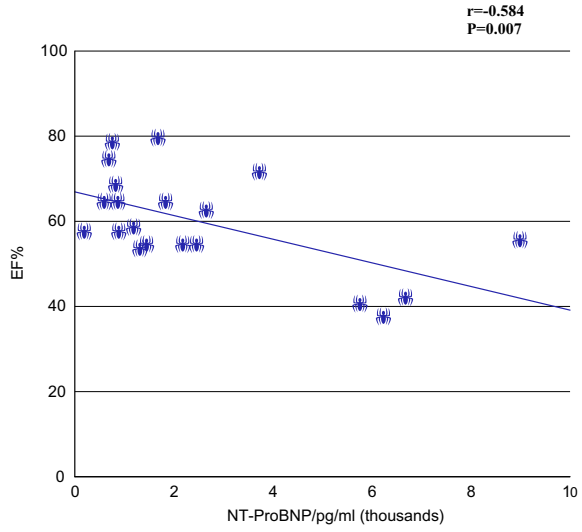

Figure 2 The significant inverse correlation between the N-terminal pro B-type natiuretic peptide (NT-pro BNP) and the left ventricular ejection fraction (EF).

the only major cause of death whose incidence is on the increase [15] and is expected to be the third leading cause of death worldwide by 2020, exceeded only by heart disease and stroke [15,16].

The most severe cardiac sequel of chronic lung disease is the load on the right ventricle due to pulmonary hypertension with the development of cor pulmonale; characterized by hypertrophy and/or dilatation of the right ventricle because of a primary impairment of lung function and/or lung structure. Levels of natriuretic peptides can be useful in diagnosing cardiac complications in patients with chronic of lung disease, as they tend to be higher in patients with heart and pulmonary disease rather than in pulmonary disease alone [17]. The ANP and BNP are released primarily from heart but circulate as hormones to act in various tissues in the body. They induce vasodilatation, natriuresis and diuresis. Although ANP is preferentially synthesized and secreted from the atria and BNP from the ventricles both can be synthesized in either chamber under pathologic conditions. Both BNP and NT-proBNP peptides are derived from the 134-amino acid precursor pre pro BNP. They have been shown to be closely correlated to each other and exhibit parallel changes across a broad spectrum of age, renal function, and LVEF. However, they are not interchangeable because the level of NT-pro BNP tends to be about 10-fold higher than that of BNP [18].

The plasma BNP levels in patients with stable COPD who did not have any symptoms or physical findings of pulmonary hypertension or cor pulmonale were previously reported to be significantly higher than those of healthy subjects and patients with severe asthma, and the level increased significantly with disease severity [19]. Another study notified that in patients with chronic hypercapnic respiratory failure NT-proBNP levels were markedly elevated compared to healthy controls and after excluding patients with concomitant heart or renal impairment, levels were still increased. Again the NT-proBNP level correlated with the degree of respiratory impairment [20]. Moreover, plasma BNP level during exacerbations was also reported to be significantly higher than during stable disease [19–21]. We found a significant decrease in the level of NT-pro BNP after recovery from AECOPD. Such observation has been reported formerly [21]. This higher level of BNP was explained by decrease in expiratory flow, leading to air-trapping and hyperinflation of the lung which can impair the cardiac functions [22]. Another hypothesis is that the hypoxia-mediated contraction of the small pulmonary

arterioles results in increased pulmonary arterial pressure and consequently right ventricular dysfunction [21]. In the present study, the NT-pro BNP level was elevated in all patients, those with and those without left heart impairment. However, the level was significantly higher in those with left ventricular systolic or diastolic dysfunction. Also, nineteen of our twenty patients had their pulmonary artery pressure elevated so right cardiac stress could not be excluded.

The absence of significant correlation between BNP level and both PaO_2 and $PaCO_2$ was previously reported in stable COPD patients [19] and those with exacerbation [21]. The former authors explained their findings by the fact that the severity of COPD according to the guidelines is defined by the FEV_1 value alone [19]. The latter authors speculated that BNP levels summarize and integrate the extent of left ventricular systolic dysfunction, left ventricular diastolic dysfunction, valvular dysfunction, and right ventricular dysfunction. Hence, right ventricular dysfunction secondary to hypoxic vasoconstriction reflects only one of four potential BNP triggers. The presence and the extent of the other three factors vary extensively from patient to patient and is to a large extent independent of right ventricular dysfunction [21]. We found no significant correlation between NT-pro BNP level and both PaO_2 and $PaCO_2$. However, most of our patients were already put on oxygen supplementation upon enrollment in the study and it was not possible clinically to stop the oxygen supply; but still, there was no significant correlation between NT-pro BNP level and PaO_2/FIO_2.

Previous reports described a significant correlation between BNP level and both PaO_2 [20,23,24] and $PaCO_2$ [20]. The inverse correlation with PaO_2 was not only reported in the absence of oxygen supplementation but in its presence as well [20]. It was shown also that patients with severe hypoxemia had a higher level of BNP [20,23,25]. Hypoxia causes natriuretic peptides secretion by two mechanisms: the first hypoxia is the most important factor in the development of pulmonary hypertension and right ventricular wall stretch or tension by induction of pulmonary vasoconstriction, the second hypoxia cause direct release of BNP from myocardium [20,23]. The low oxygen tension as such, without increase in the heart mass, causes an increase in natriuretic peptide synthesis [26]. Moreover, it was observed that plasma BNP levels were significantly decreased by long term oxygen therapy [23].

We found significant inverse correlation between pH and N-terminal proBNP level. A previous study found that a small drop in pH slows down the contractile response to stretch but significantly increases the ANP secretion during stretch. These changes are probably due to impaired calcium handling during acidosis, which leads to an increase in diastolic calcium when the muscle is stretched [27]. Also, it was previously reported that various systolic Doppler indices and pulmonary arteries' dimensions were significantly correlated with the arterial pH, indicating that the more the pH becomes acidotic the more the pulmonary hemodynamics become deranged. The correlation was well established in spite of the very narrow range of pH present in this study [28].

In our study we did not find a significant correlation between pulmonary artery flow acceleration time and level of N terminal proBNP. The absence of elevated BNP levels in the presence of pulmonary artery hypertension (PAH) was previously reported [25]. It was speculated that plasma BNP levels did not reflect pulmonary hypertension unless there was left ventricular failure or valvular heart diseases [25]. Some authors reported that BNP levels in patients with steady-state PAH did not differ from the values detected in patients without PAH [21]. Others found BNP to be a predictor of PAP levels in chronic pulmonary embolism and interstitial lung disease groups but not in COPD and chronic respiratory failure. Again, a previous study established no relation between mean PAP and plasma peptide concentrations in patients with terminal parenchymal lung disease and normal left ventricular function; the relation was only recognized when including patients with primary pulmonary hypertension [29].

In contrast, significant correlation between plasma BNP level and PAP was reported [19,20,24,30], and higher BNP levels were reported in the presence of PAH [30]. It was even stated that BNP level determination has a role in the diagnosis of cor pulmonal in COPD patients [24]. Increased BNP values have been found to be correlated with pulmonary hypertension in chronic lung disease of different etiologies and to serve as a risk factor for mortality [31]. Moreover, exercise-induced BNP levels elevation may be a useful alternative to pulmonary artery catheterization in identifying COPD patients without right ventricular dysfunction at rest who are likely to benefit from long-term oxygen therapy [32]. The inability of our study to demonstrate a direct correlation between N terminal pro BNP level and acceleration time may be related to small sample population and the presence of other factors affecting NT-pro BNP level in plasma.

We found statistically significant difference in NT-pro BNP level between AECOPD with and without left ventricular dysfunction. The BNP measurements are helpful in the diagnosis of left heart dysfunction in COPD patients either in stable condition or during acute exacerbation of COPD [20,33]. It is also able to uncover new onset of left heart failure associated with weaning difficulties from mechanical ventilation in COPD patients [33]. Different BNP assays are helpful diagnostic indicators for selecting patients who should undergo echocardiographic screening to detect previously unknown heart failure, in a population of stable elderly patients with a primary care diagnosis of COPD [34].

We found also a direct significant correlation between NT-pro BNP level and both LVES and LVED and a significant inverse correlation between NT-pro BNP level and LVEF. Such direct [35] and inverse [19,35] correlations were previously reported in COPD patients.

Heart failure is a clinical syndrome that can result from any structural or functional cardiac disorder that impairs ventricular filling or ejection [36]. The signs and symptoms of heart failure are nonspecific (dyspnea, exercise intolerance, fatigue, weakness) and often can be attributed to other conditions, such as pulmonary disease, anemia, hypothyroidism, depression, and obesity [37]. When the syndrome is associated with a reduced ejection fraction, it is often called "systolic heart failure." When the ejection fraction is normal or near normal (preserved), terms such as "diastolic heart failure," "heart failure with preserved systolic function," "heart failure with normal ejection fraction," and "heart failure with a preserved ejection fraction" have all been advocated [36]. Cardiac catheterization remains the gold standard for demonstrating impaired relaxation and filling, because it provides direct measurement of ventricular diastolic pressure. However, the balance of benefit, harm, and cost argues against its routine use in diagnosing diastolic dysfunction [37]. Doppler

echocardiography has assumed the primary role in the noninvasive assessment of cardiac diastolic function and is used to confirm the diagnosis of diastolic heart failure [37,38].

BNP blood levels were reported to be significantly and markedly higher in patients with diastolic heart failure than those without in COPD patients [39]. We found a significant direct correlation between plasma NT-pro BNP and E/A. On echocardiography, the peak velocity of blood flow across the mitral valve during early diastolic filling corresponds to the E wave. Similarly, atrial contraction corresponds to the A wave. Under normal conditions, E is greater than A and the E/A ratio is approximately 1.5. In early diastolic dysfunction, relaxation is impaired and, with vigorous atrial contraction, the E/A ratio decreases to less than 1.0. As the disease progresses, left ventricular compliance is reduced, which increases left atrial pressure and, in turn, increases early left ventricular filling despite impaired relaxation. This paradoxical normalization of the E/A ratio is called pseudonormalization. In patients with severe diastolic dysfunction, left ventricular filling occurs primarily in early diastole, creating an E/A ratio greater than 2.0 [38].

It was speculated that the most appropriate use of BNP assays in routine practice would be as an exclusion test of left ventricular dysfunction, where positive values would result in further cardiac investigation, including echocardiography [40]. In the present study the ROC curve for plasma NT-pro BNP showed a cut off value for ruling out LV dysfunction in AECOPD more specific and more sensitive than the cut off value for ruling in. Our cut off values for ruling out and ruling in LV dysfunction in AECOPD were not that different from those reported by previous studies [41]. However, those latters demonstrated better sensitivity and specificity, being higher for values of ruling out [41]. In COPD patients, those cut off values were found to be greater than those usually recommended for suspecting LV dysfunction [41]. This could be explained by a supraphysiologic secretion of natriuretic peptides in AECOPD patients because of the presence of hypoxemia, pulmonary hypertension, and RV dysfunction [41–43].

Plasma BNP is usually elevated in AECOPD. After recovery, its level significantly decreases. The elevation of plasma NT-pro BNP level is related to overt left ventricular systolic or diastolic dysfunction or right ventricular stress from elevated pulmonary artery pressure. Even in the absence of apparent cardiac dysfunction, elevated NT-pro BNP levels in AECOPD could not be dissociated from heart stress which increases from the pulmonary physiological changes in such condition. However, plasma NT-pro BNP can help in follow up patients with AECOPD.

Conflict of interest

The authors declare that there are no conflict of interests.

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