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Usefulness of NT-proBNP serum level in the diagnosis of dyspnea in COPD patients

Przydatność oznaczania NT-proBNP w diagnostyce duszności u chorych na POChP

Results of this study are the part of NCBR project "Chronic obstructive pulmonary disease (COPD) — systemic disease, the biggest threat of XXI century". All the study subjects signed an informed consent. The study was approved by the Bioethical Committee of the Medical University of Warsaw.

Abstract

Introduction. Cardiovascular diseases often coexist with chronic obstructive pulmonary disease (COPD), and in some cases it is difficult to differentiate between cardiac and pulmonary cause of dyspnoea. It is well known that the serum concentration of NT-proBNP in patients with cardiovascular diseases, especially with congestive heart failure, is elevated. The aim of this study was to estimate the usefulness of NT-proBNP serum level measurement in patients with COPD complaining of chronic dyspnoea.

Material and methods. The study group consisted of 81 stable COPD patients in the mean age, 65 ± 7 years, (57 of them with concomitant cardiovascular disease). Serum concentration of NT-proBNP was measured using VITROS laboratory test.

Results. There were no statistical differences in serum NT-proBNP between patients stratified according to the GOLD staging system for COPD severity or BODE index and mMRC breathlessness scale. The concentration of NT-proBNP was statistically significantly higher in the patients with coexisting cardiovascular diseases (220.8 ± 258.1 vs. 95.4±56.1 pg/ml). The group of patients with NT-proBNP concentration > 125 pg/ml (n = 36) was statistically significantly older (67.5 ± 6 years old vs. 63.2 ± 7.1 years old; p = 0.009) and had statistically significantly lower PaO2 (67.4 ± 11.8 mm Hg vs. 73.0 ± 11.6 mm Hg; p = 0.04).

Conclusions. 1. In the group of stable COPD patients there were no differences between NT-proBNP serum concentration according to GOLD staging, BODE index, and mMRC breathlessness scale. 2. The NT-proBNP serum concentration was statistically significantly higher in the group of COPD patients with the concomitant cardiovascular disease. 3. In patients with chronic dyspnoea testing of serum NT-proBNP may be useful in the detection of patients with cardiovascular problems, who require more intensive therapy.

Key words: NT-proBNP, COPD, cardiovascular diseases

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Introduction

According to the *Global Initiative for Chronic Obstructive Lung Disease* (GOLD), patients with chronic obstructive lung disease (COPD) are at higher risk for cardiovascular diseases, which is a result of general inflammatory process [1]. Establishing the cause of breathlessness in patients with COPD may be challenging as symptoms of COPD and heart failure are similar. Some tests, such as: spirometry, chest X-ray, and echocardiogram may be useful, but they require specialistic equipment, that is not always available. A laboratory test that may be helpful in the process of investigating the

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cause of breathlessness is the measurement of N-terminal fragment of natriuretic peptide (NT-proBNP) serum level.

The natriuretic peptides (*atrial natriuretic peptide* — ANP and *brain natriuretic peptide* — BNP) are neurohormones. They play a role in the regulation of the water and sodium balance, and in the homeostasis of the cardiovascular system [2]. Natriuretic peptides are released by cardiomyocytes as a response to stretching. They reduce the secretion of rennin and aldosterone, inhibit the activity of the adrenergic nervous system, augment urine volume and sodium excretion, and have a direct vasodilating effect. An increase in NT-proBNP blood level is a result of activation of compensatory mechanisms before clinical features of heart failure develop [3]. High levels of NT-proBNP have also been observed in atrial fibrillation [4], left ventricle hypertrophy [5], and pulmonary hypertension [6]. Many authors have reported on the usefulness of NT-proBNP in acute dyspnoea [7]. The aim of our study was the evaluation of the usefulness of NT-proBNP in patients with stable COPD complaining of chronic breathlessness.

Materials and methods

Subsequent COPD patients from the Chest Outpatient Clinic in the Public Central Teaching Hospital of the Medical University in Warsaw were recruited in the study. The diagnosis of COPD was established on the basis of typical symptoms and spirometry, in accordance with the Polish Society of Lung Diseases (PTChP) guidelines [8]. The exclusion criteria were: respiratory tract infection or symptoms suggesting COPD exacerbation in the preceding month. Due to these criteria around 5% of the initially recruited patients were ultimately excluded from the study.

A medical history, with special attention paid to concomitant cardiovascular conditions, was taken from all patients and a physical examination was performed. The results of additional tests (chest X-ray) and discharge letters from the past were also analysed. The following tests were performed: spirometry and plethysmography with reversibility test (LungTest 1000Spirometer, MES, Poland; Vmax 6200 Sensormedics Plethysmograph, Yorba Linda, USA) according to PTChP guidelines [9], and the assessment of diffusing capacity of the lungs for carbon monoxide (DLCO) (n = 30). Six-minute walk test (6MWT) was performed in 77 patients; guidelines of the American Thoracic Society (ATS) were applied [10]. The degree of dyspnoea was assessed using the Medical Research Council (MRC) scale [11].

For the purposes of statistical analyses the studied population was divided in 2 groups: group A — without concomitant cardiovascular diseases, and group B — with concomitant circulatory system diseases. In addition, 4 stages of COPD severity according to GOLD 2010 guidelines were distinguished. Based on BODE (body mass index, airflow obstruction, dyspnoea, exercise capacity) index [12] patients were allocated to one of four quartiles: 1 — BODE index ≤ 2, 2 — BODE index 3–4, 3 — BODE index 5–6, and 4 — BODE index ≥ 7.

VITROS NT-proBNP Reagent Pack and VITROS NT-proBNP calibrators were used to measure serum levels of NT-proBNP. A sample of peripheral venous blood (5 ml) was taken from the patients. The upper limit of normal for NT-proBNP level in patients younger than 75 years of age was established following the manufacturer's recommendations at 125 pg/ml. According to information provided by the manufacturer of the reagent, the sensitivity and specificity of the test were, respectively: 89.5% and 84.1% for men, and 94.9% and 75% for women. Depending on the NT-proBNP blood level, two groups in the studied population were distinguished: with normal (≤ 125 pg/ml) and with elevated (> 125 pg/ml) NT-proBNP levels.

Arterial blood gases analysis, in room air, was also performed.

Statistical analyses

All analyses were performed using STATISTICA v.10 (StatSoft, Inc, 2011; www.statsoft.com) computer software. Results were expressed as the mean values ± standard deviation, the number of patients in a sample, and the percentage of studied populations it constitutes, as shown in the tables. Most of the variables did not have a normal distribution; therefore, U Mann-Whitney test and ANOVA Kruskal-Wallis test were used for comparisons between the groups. Correlations between parameters were checked with Spearman's correlation coefficient. $P<0.05$ was considered statistically significant.

Results

Eighty-one COPD patients were enrolled into the study (35 women, 46 men), all of them younger than 75 years of age (mean age 65 ± 7 years). At the time of recruitment 55 patients were treated for arterial hypertension, ischaemic heart disease, or chronic heart insufficiency; 16 patients had oxygen concentrators at home. The following groups of medications were used in the group of patients with cardiovascular diseases: angiotensin-converting enzyme inhibitors (n = 36), beta-adrenocep-

tor blockers (n = 29), diuretics (n = 21), statins (n = 26), calcium channel blockers (n = 18), and digitalis (n = 2). The full characteristics of the studied group are presented in Table 1. All degrees of COPD severity (according to GOLD 2010) and whole BODE index range were represented in the studied group (Tab. 2).

There were no significant differences in NT-proBNP levels depending on the COPD severity, BODE index quartile, or scores in MRC scale. Statistically significant differences in NT-proBNP levels were, however, found between groups A and B (95.4 ± 56.1 vs. 220.8 ± 258.1 pg/ml, p = 0.03) (Tab. 2). There were no differences between groups A and B in respect to pulmonary function tests, but there was a difference in 6MWT distance 486.9 ± 129.1 m vs. 394.7 m ± 119.0, respectively; p = 0.003) — Table 3. There were no significant relationships between NT-proBNP levels and degree of oxygen desaturation during 6MWT, either. Mean DLCO for 30 patients (13 patients with normal NT-proBNP levels and 17 patients with elevated NT-proBNP levels) was 63.5 ± 28.3% of predicted value. Groups A and B, as well as patients with normal and elevated levels of NT-proBNP, did not differ in regard to DLCO. There was no correlation between DLCO (expressed in actual values, percentage of predicted value, or corrected for the alveolar volume) and NT-proBNP levels, either. Patients with NT-proBNP > 125 pg/ml (n = 36) were significantly older (67.5 ± 6.0 vs. 63.2 ±7.1 years; p = 0.009) and had significantly lower PaO_2 (67.4 ±11.8 vs. 73.0 ± 11.6 mmHg; p = 0.04) in comparison to patients with normal NT-proBNP levels. Both groups had similar smoking history and body mass index (BMI). There were no significant differences in cardio-vascular medications (angiotensin-converting enzyme inhibitors, beta-adrenoceptor blockers, diuretics, statins, calcium channel blockers, digitalis) or respiratory medications (short- and long-acting beta agonists, anticholinergic agents, methylxantines, inhaled corticosteroids) between these two groups.

Table 1. Characteristics of study group

	All patients	Patients without cardiovascular disease (A)	Patients with cardiovascular disease (B)	p
N	81	26	55	
Age (years)	65 ± 7	62,7 ± 7,3	65,8 ± 6,6	0,009
Number of smoke pack/years	41 ± 20,1	44,9 ± 24,5	40,0 ± 18,7	NS
BMI [kg/m^2]	27,3 ± 5,3	26,0 ± 5,0	28 ± 5,4	NS
Home oxygen therapy n (%)	16 (20)	3 (13)	16 (29,1)	NS

Table 2. NT-proBNP concentration according to sex. concomitant cardiovascular disease. GOLD 2010 staging system for COPD severity and BODE index

	N	NT-proBNP [pg/ml]	p
All study group	81	189.8 ± 234.1	
Men	46	194.2 ± 257.6	
Women	35	169.4 ± 134.2	NS
Patients without cardiovascular disease (A)	26	95.4 ± 56.1	
Patients with cardiovascular disease (B)	55	220.8 ± 258.1	0.03
GOLD 1	14	113.6 ± 123.6	
GOLD 2	25	232.2 ± 307.8	
GOLD 3	20	154.6 ± 152.1	NS
GOLD 4	22	230.8 ± 253.6	
BODE 1 (0–2)	22	198.6 ± 327.2	
BODE 2 (2–3)	29	168.2 ± 144.7	
BODE 3 (4–5)	15	188.5 ± 164.8	NS
BODE 4 (≥ 7)	11	205.5 ± 198.6	

Table 3. Results of the lung function tests and 6MWT

	All patients	Group A	Group B	p
N	81	25	56	
FEV_1 % pred.	52.3 ± 17.1	53.6 ± 20.7	47.6 ± 16.5	NS
FVC % pred.	83.2 ± 19.01	84.7 ± 23.1	80.2 ± 21.05	NS
TLC % pred.	124.5 ± 21.2	129.5 ± 17	127.9 ± 19.4	NS
RV % pred.	194.1 ± 56.1	203.5 ± 61.7	207.8 ± 54.1	NS
RV% TLC	60.6 ± 9.6	57.4 ± 12.6	62.7 ± 8.9	NS
Salbutamol 400 μg				
FEV_1 % pred.	58.8 ± 18.6	59.9 ± 23.1	53.4 ± 18.8	NS
FVC % pred.	92.8 ± 19.2	95.4 ± 21.7	88.3 ± 21.8	NS
FEV_1%FVC	49.7 ± 11.4	49.6 ± 11.9	48.3 ± 11.3	NS
TLC % pred.	121.8 ± 21.7	128.5 ± 17.8	124.4 ± 20.7	NS
RV % pred.	173.5 ± 52.28	185.3 ± 54.3	187.2 ± 56.3	NS
RV %TLC	55.7 ± 9.6	53.3 ± 12.1	58.3 ± 9.9	NS
6MWT (N)	77	22	55	
Distance [m]	433.5 ± 114.2	486.9 ± 129.1	394.7 ± 119.0	0.003

Discussion

The coexistence of COPD and cardiovascular system diseases has been confirmed by studies and recommendations of scientific societies [1, 8]. The results of our research also indicate such a relationship [13]. Cigarette smoking — the main cause of COPD — carries a 50% increase of heart insufficiency risk [14]. Between 10 and 33% of patients with heart failure report coexistence of COPD [15, 16]. The prevalence of COPD in the population with heart failure is higher than in the general population (20% vs. 13%) [17]. Ivernes et al. showed the coexistence of these two conditions by performing spirometry in 532 patients with heart insufficiency. COPD and heart failure coexisted in 35% of the studied patients, and only 43% of patients with COPD diagnosed on that occasion knew about it before. On the other hand, 1/3 of patients who had claimed to have COPD did not fulfil spirometric criteria for such a diagnosis [18].

The necessity of differentiation between possible causes of dyspnoea, in the situation when such a large proportion of patients give incorrect information about their medical history, prompts the search for new, simple diagnostic tools. In the study of Morrison et al., among 321 patients admitted to the emergency department due to acute breathlessness, 42 had COPD and 134 had chronic heart failure. Mean BNP level in COPD patients was 54 ± 71 pg/ml, whereas in cardiac patients it was significantly higher — 758 ± 798 pg/ml [19]. Other authors assessed NT-proBNP levels in patients hospitalised due to COPD exacerbation. They found that factors associated with elevation of NT-proBNP included atrial fibrillation and age. No influence of sex and renal function were observed [20]. Fabbian et al. found elevated levels of NT-proBNP in 68.7% of elderly patients admitted to a hospital due to breathlessness (in 49.2% of patients with heart failure and in 20.6% of patients with lung diseases). NT-proBNP levels were also elevated in patients with renal insufficiency, low haemoglobin levels and — similarly as in the study of Sanches-Marteles et al. — in patients with atrial fibrillation [20, 21].

The aim of our study was to assess the usefulness of NT-proBNP blood levels in patients with stable COPD complaining of chronic breathlessness. We did not find any significant differences in the levels of this biomarker depending on COPD severity, BODE index, or dyspnoea measured with MRC scale. The presence of circulatory system diseases was the only factor that had a significant influence on NT-proBNP levels, and that was compatible with the findings of other authors. Rutten et al. studied BNP and NT-proBNP in 200 stable COPD patients above 65 years of age in the context of cardiac and respiratory system function. Similarly to the authors of the present study, they found no relationship between the biomarker levels and the severity of COPD (according to GOLD), and the dependence of the biomarker levels on heart failure. What is more, higher levels of both biomarkers were

found in patients with systolic heart failure in comparison to patients with isolated diastolic heart failure [22]. Additionally, the degree of airway obstruction had no effect on NT-proBNP levels in patients with chronic dyspnoea in a study by Wieshammer et al. [23].

Remodelling of skeletal muscles is present in COPD as well as in heart failure. It makes muscles less efficient. The coexistence of both these conditions increases the likelihood of a poor prognosis [24]. Medina et al. investigated the prognostic value of NT-proBNP in patients admitted to a hospital due to exacerbation of COPD, asthma, or acute respiratory tract infections (including pneumonia). NT-proBNP levels > 587.9 pg/ml correlated with the length of hospitalisation and with mortality, whereas NT-proBNP levels > 782.2 pg/ml correlated with the death rate due to cardiopulmonary causes during one year of observation [25]. The other study also showed the usefulness of this biomarker in early death prediction (within 30 days) in patients admitted to hospital due to COPD exacerbation [26].

In summary, measurement of NT-proBNP blood levels in patients with dyspnoea and respiratory system diseases should aim at identification of individuals with coexisting heart failure, which may be relevant for prognosis and further treatment.

Conclusions

1. There were no significant differences in NT-proBNP serum levels between groups depending on the disease severity or on the BODE index in the stable stage of COPD.
2. NT-proBNP levels were significantly higher in patients in whom COPD coexisted with circulatory system diseases in comparison to COPD patients without comorbidities.
3. Measurement of NT-proBNP in patients with chronic dyspnoea may help with the identification of patients in whom therapy for heart insufficiency should be started or intensified and in whom further radiologic diagnostic tests should be carried out.

Conflict of interest

The authors have no conflict of interest to report.

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