

The role of NT-proBNP as a diagnostic marker in patients with COPD

Улогата на Nt-proBNP во евалуација на пациентите со ХОББ

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Абстракт :

Вовед:

BNP и Nt-proBNP се добро познати биомаркери за срцева слабост и примарно се користат за дијагноза и ризик стратификација. Зголемените вредности на Nt-proBNP се најдени и кај пациенти со ХОББ без знаци за срцева слабост, најчесто заради услови на десно вентрикуларно оптеретување.

Материјал и методи:

Нашата студија вклучи 38 пациенти кои беа со потврдена хронична белодробна болест(ХОББ) во изразена/многу изразена форма на болеста. Пациентите беа поделени во две подгрупи- пациенти со акутно влошување и клинички стабилни пациенти. Сите пациенти беа клинички евалуирани (анамнеза, статус на пациентот, ЕКГ) и им беше направена ехокардиографска проценка. Кај сите пациенти беше направена анализа на Nt-proBNP серолошки. Демографска анализа и анализа на ризик фактори беше направена кај сите 38 пациенти. Ехокардиографија беше направена кај сите пациенти со посебен осврт на десно срцевите параметри во корелација со натриуретски пептид.

Резултати:

Во нашата студија доминантен беше машкиот пол, а просечна возраст на пациентите беше 67 години. Три ризик фактори беа анализирани(ХТА, ДМ, ХЛП) и тоа : ХТА со 57.9%, ДМ со 18,4%, дислипидемија 42,2%. Во однос на БМИ, најголем дел од пациенти беа обезни (42,2%). Во двете групи на пациенти вредностите на Nt-proBNP беа покачени посебно во групата со акутно влошување на болеста. Во однос на параметрите кои укажуваат на десно вентрикуларната функција најдовме дека TAPSE, S' од тивниот доплер на десната комора и FAC беа со редуцирани вредности особено во групата со акутно влошување.

Заклучок:

Ехокардиографијата како неинвазивна метода успешно се користи во евалуација на десносрцевите параметри посебно кај пациентите со ХОББ. Достапноста на Nt-proBNP како серолошки маркер и зголемените апликабилни можности помагаат во рана дијагноза и мониторинг на пациентите со ХОББ и десно срцева слабост.

Клучни зборови: ХОББ, десно срцева слабост, Nt-proBNP, ехокардиографија

Abstract:

Introduction: BNP and Nt-proBNP are well known biomarkers of heart failure and are primarily used for diagnosis and risk stratification. Increased values of NT-proBNP are found in patients with COPD without any signs of heart failure mostly as a result of right ventricular overload.

Material and methods:

Our study included 38 patients with established COPD with severe/very severe form of the disease. Patients were divided into two subgroups - patients with acute exacerbation and clinically stable patients. All patients were clinically evaluated (anamnesis, status of the patient, ECG) and underwent echocardiography. All patients had NT-proBNP serological examination. Demographic background and correlation of risk factors was done in all 38 patients. Echocardiography analysis included several parameters with emphasis to right chamber echo parameters in correlation to natriuretic peptide.

Results: In our study male gender was predominant, and the average age was 67.

Three risk factors (HTA, HLP, DM) were taken for analysis: HTA was 57.9%, DM 18.4%, dyslipidemia 42.2%. According to BMI, most of the patients were obese (42.2%)

In both group of patients NT-proBNP was with increased values, especially in the group of patients with acute exacerbation. In relation to parameters that indicates right ventricular function, we found that TAPSE, S' wave from the tissue doppler of the right ventricle and FAC were with reduced values, especially in the group of patients with acute exacerbation.

Conclusion: Echocardiography is a noninvasive method and successful strategy for evaluation of right chamber parameters and function, especially in patients with COPD.

The availability of NT-proBNP as a serological marker and its increasing applicability assist in early diagnosis and monitoring of patients with right heart failure.

Keywords: COPD, right heart failure, NT-proBNP, echocardiography

Introduction:

B-natriuretic peptide is also known as porcine type of natriuretic peptide and it was first described in 1988 and extracted from a porcine brain. Soon it was established that it derived from the heart and was defined as a cardiac hormone.¹³⁾

BNP belongs to the family of natriuretic peptides along with ANP (atrial natriuretic peptide), C type of natriuretic peptide (CNP) and urodilatin. The natriuretic peptides have in common a characteristic biochemical structure which consists of a 17 amino-acid ring and disulfide bridge between two cysteine molecules. Synthesis and secretion of BNP is mainly done from the heart chambers. BNP and Nt-proBNP are well known biomarkers for heart failure and are primarily used for diagnosis and risk stratification. Increased values of NT-proBNP are found in patients with COPD without any signs of heart failure mostly as a result of right ventricular overload. Cor pulmonale, secondary pulmonary hypertension and hypoxemia are important stimuli for natriuretic peptide release and increased BNP expression from the right side of the heart.

B-natriuretic peptide is a product of the prohormone pro-BNP, which is composed of 108 amino acids and divided into two fragment and secreted from the myocytes. The final product is BNP and NT-proBNP composed of 76 amino acids. Its pathophysiological role is in maintaining homeostasis of plasma volume and blood pressure as well as in prevention of salt and fluid retention in the body. There are several mechanisms of action: regulation of the sympathetic nerve system and the system of renin-angiotensin-aldosterone, improvement of diuresis and natriuresis, acting on afferent and efferent blood vessels and distal tubules on kidney level, reduction of peripheral vascular resistance and improvement of muscular relaxation [1].

BNP and Nt-proBNP are substances that are released from the heart muscle as a result of increased stretching and ventricular dilatation.

Recent studies suggest that ventricular “end-diastolic” stress of the myocardial wall as well as its rigidity may be a predominant factor for Nt-proBNP release. These markers are suitable for diagnosis and evaluation of the degree of the heart failure. They play a big role in patients with COPD due to existence of pulmonary hypertension and right ventricular dysfunction which are a result of pulmonary pressure overload. COPD by itself can cause stretching of the myocardial wall and right ventricular dilatation, increased vascular pressure that promotes secretion of NT-proBNP.

BNP is a biomarker used for prognostic purposes in patients with pulmonary hypertension. In patients with COPD who have advanced parenchymal changes, there may be increased values of NT-proBNP and prognostic significance.

NT-proBNP is not a standard test in itself that is conclusive. Its role comes to the fore together with the overall clinical picture and history of the disease.

Aim:

The aim of the study was to:

- determine the role of Nt-proBNP as an indicator for the severity of the disease
- the role of Nt-proBNP in patient assessment with severe and very severe stage of the COPD (Gold 3 and 4), in the chronic phase and in conditions of acute exacerbation of the disease.

Material and methods:

The study included 38 patients with confirmed lung disease, that is chronic obstructive lung disease (COPD), and classified by Gold classification into two groups: severe and very severe stage of COPD (Gold 3 and 4)

Standard classification according to Gold covers 4 groups of patients, but in our study only patients with stage 3 and 4 were evaluated.

- severe stage of COPD (FEV1 30-50%) - Gold 3
- very severe stage of COPD (FEV1<30%) - Gold 4

Patients were further classified based on whether they were in acute exacerbation of the disease (hospital patients) or outpatient patients with severe form of the disease, Gold 3 or 4.

Patients with coronary artery disease, congenital heart disease, cardiomyopathies (dilatata hypertrophica), idiopathic pulmonary hypertension, asthma and pulmonary fibrosis were excluded from the study.

In collaboration with the University Clinic for Pulmology and Allergology some of the patients were examined and classified by a pulmonologist (according to spirometric parameters and gas analyzes) and were sent to our Clinic for cardiac evaluation. On admission to the University Clinic for Cardiology, anamnesis and status of the patient were taken, present risk factors, ECG and echocardiographic evaluation was done, with special reference to the right ventricular function.

Other patients who were hospitalized, were sent to our Clinic by prior agreement for reevaluation.

After the examination, venous blood was taken in a test tube together with KEDTA (serum blood, 5 ml) for the analysis of natriuretic peptide hormone NT-proBNP. Processing was done with

commercially available tests by immunoassay fluorescent method.²⁾ The results after their processing were issued in a printed form.

Echocardiographically, a couple of parameters were analyzed which gave special reference to right ventricular function in correlation with Nt-proBNP.

- Tricuspid annular systolic excursion (TAPSE) measured by M-mode is an indicator of the longitudinal systolic function of the right ventricle. Cursor in M-mode is placed on the lateral wall of the right ventricle at the level of the tricuspid annulus in 4-chamber view.

Reduction under 16 mm is one of the markers of an impaired longitudinal function of the right ventricle.

- Estimation of the functional area of changes of the right chamber which gives information on the global function of the right ventricle (FAC %). FAC above 35% means a neat right systolic function.

-S' wave of tissue doppler of the right chamber is for evaluation of the longitudinal function. Values below 0.095 met/sec are a marker of an impaired longitudinal function of the right ventricle.

Results:

In our study 38 patients with COPD (chronic obstructive pulmonary disease) were included. All patients were in sinus rhythm. Of all analyzed patients, 71.1% were males, and 28,9% females. The average age of the patients was 67.1 ± 6.3 , in range from 55 to 82 years. The following risk factors were noted: smokers 68.4%, hypertension 57.9%, diabetes mellitus 18.4%, dyslipidemia 7.9%. According to BMI, most of the patients were obese (42.2%), followed by overweight (28.9%) and normal weight (28.9%).

Tab. 1 Demographic features of COPD patients

Variables	Average	Min.	Max.	St.dev
age	67.1	55.0	82.0	6.26518
body weight	82.1	50.0	130.0	20.30017
height	169.6	155.0	186.0	7.85212
gender	No		%	
female	11		28.9	
male	27		71.1	

Yes		
diabetes mellitus	7	18.4
hypertension	22	57.9
hyperlipidemia	3	7.9
smoker		
yes	26	68.4
	12	31.6
BMI kg/m ²		
18,5 – 24.9 normal	11	28.9
25 – 29.9 overweight	11	28.9
>=30 obese	16	42.2

2.)

Of the total number of 38 patients, 31 had elevated values of NT-proBNP above cut-off of 125 pg/ml.

In 81.6% (31) of patients, the reference values of NT-proBNP were above 125 pg/ml, in 18.4% (7) of the patients reference values of NT-proBNP were found; the percentage difference was statistically significant, $p < 0.05$ (difference test).

2a)

Breakdown Table of Descriptive Statistics N=38 (No missing data in dep. var. list)					
Acute pts/ chr. ill	NT-probn-average value	NT-probn - N	NT-probn-st deviation	NT-probn minimum	NT-probn max
Acute patients	786.7350	20	986.9921	291.1000	4570.000

Chronically ill	141.1778	18	74.3675	33.1100	279.000
All patients	480.9447	38	780.6968	33.1100	4570.000

The analysis of the average values of NT-proBNP showed very high values of NT-proBNP in patients with acute exacerbation in correlation with clinically stable patients (Table 2a).

All 20 patients with acute exacerbation (100%) had elevated values of Nt-proBNP above the reference values.

In the group of chronically ill patients, 11 (61%) patients had elevated values of Nt-proBNP. The percentage difference was statistically significant, $p < 0.05$ (difference test, $p = 0.224$) (Table 3).

Table 3. Number of patients with increased values of NT-proBNP in both groups

NT-probBNP	Acute patients	Chronically ill	Total
<125	0	7 (39%)	7
>125	20 (100%)	11 (61%)	31
All Groups	20	18	38

The analysis of the velocity of S' wave and the values of Nt-proBNP showed that values of S' below 0.095 were more common in the group of patients with acute exacerbation as a sign of deterioration of the longitudinal function of the right ventricle *versus* patients with stable form of the disease. In 13 patients with acute exacerbation (65%), S' was below 0.095, and 4 (22.3%) patients were with stable form of the disease (Table 4).

Tbl 4. Speed display of S' wave and NT-probBNP

S wave	Acute pts	Chron. ill	Total
>0.095	7 (35%)	14 (77,7%)	21
<0.095	13 (65%)	4 (22,3%)	17
All Groups	20	18	38

A correlation was registered between the velocity of S' in both groups of patients ($p < 0.05$) (Pearson Chi-square: 7.01220, $df = 1$, $p = .008096$).

The average values of NT-proBNP in patients where TAPSE was below 16 mm were 1045.5 ± 1515.3 , in range from 70.8 to 4570; the average value of Nt-proBNP was above the reference one. The average values of Nt-proBNP in patients where TAPSE was above 16 mm were

330.4±334.7, in range 33.11 to 1881.0; the average value of Nt-proBNP was above the reference one. According to Student test, the difference was statistically significant, $p < 0.05$.

In 7 (22,6) patients where TAPSE was below 16 mm, values above the reference ones for NT-proBNP were registered. In 24 (77.,4%) patients, TAPSE was above 16 mm. There was a statistical significance, $p < 0.05$.

Tbl 5. Correlation between TAPSE and NT-proBNP

TAPSE	NT-proBNP	N	St.deviat ion	min	max
>16 mm	330.4	30	334.664	33.11	1881.0
<16 mm	1045.5	8	1515.297	70.8	4570.0

The average values of NT-proBNP in patients where functional area of shortening of the right chamber was above 35% were 465.6±836.0, in range 10.77 to 4470.0. The average value of NT-proBNP was above the reference values. FAC below 35% was registered in only one patient (345.4 pg/ml), which was above the reference values for NT-proBNP.

Due to the small sample of patients, no further analyses could be performed regarding FAC.

The patient with the reduced right ventricular function, who was assigned in the group of patients with acute exacerbation, had reduced velocity of S' wave from the tissue doppler of the right ventricle, TAPSE 19 mm, and preserved DA area above 18 sm².

The average value of Nt-proBNP in the group of patients with acute exacerbation and FAC above 35% was 810.0±1008.4; the average value of Nt-proBNP was above the reference values. The average value of Nt-proBNP in the group of chronic patients and FAC above 35% was 141.2±74.4; the average value of NT-proBNP was above the reference one. In the group of patients with acute exacerbation, values of NT-proBNP were very high. According to Student t-test, the difference was statistically significant, $p < 0.05$ ($t=2.804457$, $p=0.008170$).

Tbl 6. Correlation between NT-proBNP and FAC%

FAC	NT-proBNP	N	St deviation	min	Max
> 35%	484.6	37	791.1343	33.11	4570.0

Tbl 7. Mean values of NT-proBNP in correlation with acute exacerbated patients and clinically stable patients where FAC was above 35%

average/ acute pts NT- probBN	average/ chr pts NT- probBN	t-value	P	N – acute pts	N – chronic pts	St deviation Acute pts	St deviation Chr pts
810.0	141.2	2.80445 7	0.00817 0	19	18	1008.406	74.36748

Discussion:

Natriuretic peptide is produced and released from the heart as a response to increased pressure and stretching of the wall.

Quantification of NT-proBNP is an increasingly relevant and useful diagnostic tool for heart failure differentiation, especially in patients with COPD and right heart failure. This statement has been confirmed in one study comprising a small series of patients, named: ‘The significance of elevated brain natriuretic peptide levels in chronic obstructive pulmonary disease’. It has been published by a group of authors from the Department of pulmonary medicine in Ankara, Turkey [2].

Several large studies have concluded that a more common cause for death in patient with COPD is cardiac rather than pulmonary cause. Secondary pulmonary hypertension and cor pulmonale are important predictors in this group of patients for poor prognosis and death.

Plasma NT-proBNP is a noninvasive biomarker for diagnosis and monitoring of heart failure. Increased values of Nt-proBNP are an independent risk factor for death in patients with COPD, hence some studies confirm the importance of NT-proBNP in determining the progression of COPD as well as the possibility of developing secondary pulmonary hypertension [3].

In our group of patients, male gender was predominant (71.1%), female gender was represented with 28.9 %. In most studies, male gender dominates, as well as in our study, but one retrospective study from Sweden, published in 2019 found that COPD was more common in females than in males (53.,8%). This trend tended to decrease in later years of the observation period. Another paper published in 2019 in China gives information that prevalence of COPD is larger in male gender [4]

In relation to our study, we found that most of the patients had three dominant risk factors: hypertension was found in 59.7%, diabetes mellitus in 18.4% and hyperlipidemia in 7.9% of patients.

In several studies diabetes was found to be not a rare risk factor in patients with COPD, ranging from 1.6 to 16%. Smoking increases the level of LDL cholesterol, triglycerides and lowers HDL cholesterol [5]

In our study, 16 patients or 28.9% were overweight, with BMI above 30 kg/m². Our results are in agreement with the results presented in one paper where a group of patients with COPD overweight and risk factors was compared with a group of patients with COPD with normal BMI. The

prevalence of obesity was 21.8% and 32.4% of patients were overweight. It was noticed that patients with COPD in class Gold (1 and 2) were more prone to obesity than patients in class Gold (3 and 4). This was not the subject of our current analysis [6]

In our study of 38 patients, 31 patients (81.6%) were found to have significantly higher values of Nt-proBNP above the cut-off values of 125 pg/ml. [7].

In one recent study published in 2019 by a group of authors from Egypt, an analysis of the increased values of NT-proBNP and acute exacerbation of COPD patients in hospital conditions was performed. Their results largely correspond to ours. Our study group of 20 patients (64.5%) with acute exacerbation of COPD had a significantly elevated value of Nt-proBNP [3]7)8)12]

Patients classified in stage 3 and 4 by Gold without signs of acute exacerbation, had elevated values of Nt-proBNP due to the severity of the disease, progression of chronic respiratory failure and development of secondary pulmonary hypertension. This coincides with the results presented in one study from 2012 by a group of authors from the Egyptian society of chest diseases and tuberculosis [3].

In terms of S' wave from the tissue doppler of the right ventricle, in the group of patients with acute exacerbation there was a positive correlation between Nt-proBNP and the values of S' under 0.095m/sec. In 13 patients (65%), S' was below 0.095 in patients with acute exacerbation.

In a recent study entitled "Acute exacerbation impairs right ventricular function in patients with COPD", published by a group of authors in 2015 in Istanbul, Turkey, was noticed that the filling conditions of the right ventricle might affect S' wave from the tissue doppler of the right ventricle. Their results are comparable with ours. This is of great importance because patients that have acute exacerbation of COPD might develop deterioration of the parameters of the right ventricle (TAPSE, S', TDI) as well as negative concordance with the prognosis in this group of patients. Their study as well as other representative papers have not correlated parameters from the right ventricle with Nt-proBNP. In that sense, our study has significant contribution. [9].

In the text from 2015, forementioned in this study, (da se navede referencata i da se izmeni pocetokov na recenicata) was found that their group of patients with acute exacerbation had reduced values for TAPSE, below 16 mm. After recovery, echocardiography was performed and TAPSE values as an indicator of the longitudinal function of the right ventricle was elevated but statistically insignificant.9) In our study, 8 patients had TAPSE below 16 mm and elevated levels of Nt-proBNP. These patients belong to the group of patients with acute exacerbation.

In our study the average value of Nt-proBNP and FAC showed increased values in both groups, especially in the group with acute exacerbation that was statistically significant. In one paper published in 2013 by a group of authors, entitled "NT-proBNP accurately reflects the impact of severe COPD exacerbation on the right ventricle" was found that patients with acute exacerbation of COPD had increased values of Nt-proBNP and a reflection on both morphology and function of the right ventricle.
14)

Conclusion:

Increased values of Nt-proBNP are promising serological markers, which may suggest right ventricular dysfunction in patients with COPD. They can also be a marker for acute deterioration of the condition of the patients with COPD.

Transthoracic echocardiography is probably the best noninvasive method for right heart evaluation in patients with COPD. It can give a quick assessment of the size and thickness of the right ventricle, size and area of the right atrium, as well as other parameters that are used for evaluation of the right ventricular systolic function such as: TAPSE, FAC% and S' from the tissue doppler of the lateral wall of the right ventricle as more subtle parameters.

In patients with COPD, TAPSE, FAC and S' wave (from the tissue doppler of the lateral wall) of the right ventricle can be significant prognostic markers for disease monitoring. Right ventricular remodeling process is often seen in patients with COPD, but without any signs of right ventricular failure even in patients with a long history of the disease.

The possibility to use NT-proBNP as a serological marker in daily routine and the availability of the echocardiography as a noninvasive and repetitive method are crucial for monitoring parameters in this group of patients.

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