

CLINICAL STUDY

The ratio of brain natriuretic peptide level and computed tomography pulmonary angiography parameters in pulmonary embolism in relation to sex

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ABSTRACT

OBJECTIVES: The objective of this study was to investigate whether there are differences between brain natriuretic peptide (BNP) levels and computed tomography pulmonary angiography (CTPA) parameters, in patients with acute PE, with respect of sex.

BACKGROUND: Acute pulmonary embolism (PE) may provoke sudden right ventricle overload and stretching of their thin walls, causing significant raise of BNP blood levels, which correlates to acute PE severity. The properties of RV are different between sexes.

METHODS: This retrospective analysis was gained from the data of 1612 PE patients from the regional PE register. The patients have had CTPA verification of PE, with described localization of thrombus masses, as well as the ratio between RV and left ventricle (RV/LV), and BNP as biomarker, measured during the first 24 hours upon admission.

RESULTS: Out of 96 male patients with detected central thrombus, 75.0% patients had an increase in BNP level compared to 25.0% patients with normal BNP value ($p < 0.001$). Of the 94 female patients with central thrombus, 85.1% patients had an elevated BNP level, compared to 14.9% patients, with BNP normal values ($p < 0.001$). Of the 135 male patients with RV/LV > 1, 79.3% of them, had elevated BNP, compared to 20.7% patients whose BNP level was normal ($p < 0.001$). Out of 123 female patients with RV/LV > 1, 91.1% patients had elevated BNP compared to 8.9%, whose BNP was normal ($p < 0.001$).

CONCLUSION: Elevated BNP blood level correlates with CTPA parameters, such as the presence of central thrombus and the ratio between right and left ventricles greater than 1, in patients with acute PE, regardless of sex (Tab. 2, Fig. 2, Ref. 23). Text in PDF www.elis.sk

KEY WORDS: acute pulmonary embolism, computed tomography pulmonary angiography, brain natriuretic peptide, right ventricle.

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Introduction

Severe acute pulmonary embolism causes acute right ventricle (RV) overload and dysfunction, which is the marker of dismal prognosis. During the diagnostic stage, all patients with acute pulmonary embolism (PE) should have computed tomography pulmonary angiography (CTPA) because this imaging represents the golden standard for diagnosis, but it is also important for the patient's risk stratification. The ratio between RV and left ventricle (RV/LV) more than 1 and the presence of central thrombus on CTPA are associate with increased hospital mortality in acute PE. However, the relationship between these signs and blood biomarkers has not been thoroughly investigated.

Increased production of brain natriuretic peptide (BNP) occurs in conditions of excessive stretching of the ventricles. BNP binds to natriuretic receptors, thus leading to an increase in natriuresis, and consequently to a decrease in peripheral vascular resistance, thereby reducing the so-called preload chamber loading, accord-

ing to the principle of negative feedback. BNP stands for Brain natriuretic peptide, since it was first isolated from brain tissue. Due to the direct correlation of BNP level (as well as its precursor NT pro-BNP) with the degree of RV distension, it is recommended that in patients with dyspnea, these peptides are also determined in ambulatory conditions, together with other biomarkers of oxidative stress (1–3).

Myocytes secrete NT pro-BNP, the precursor of BNP, which is an inactive form and is composed of 108 amino acids. Upon reaching the circulation, NT pro-BNP is broken down into the NT (N-terminal) part, which contains 76 amino acids, and into the active part – BNP, which is composed of 36 amino acids (4).

Acute distension of the RV, caused as a result of pulmonary embolism (PE), i.e. pulmonary hypertension, is associated with an increase in the level of BNP (5–10).

In our study, we wanted to compare the values of BNP and individual CTPA parameters (presence of central thrombus and RV/LV ratio), in patients with CTPA verified PE, in relation to the sex. The study was conducted as a retrospective analysis of the regional PE register, established in 2015.

Methodology

Patients of both sexes aged >18 years with confirmed acute PE diagnosis using multidetector CTPA were included. During the study period, spanning from January 2015 to May 2022, a total of 1,612 patients were enrolled. They were recruited from five university cardiology or pulmonology clinics: the Military Medical Academy in Belgrade, the Institute of Pulmonary Dis-

eases of Vojvodina in Sremska Kamenica, the Clinical Center in Niš, the University Clinic Zemun in Belgrade, and the Clinical Center in Kragujevac. Additionally, patients were enrolled from one general hospital in Pancevo and three centers outside of Serbia, specifically the Clinic of Cardiology at the University Hospital Banja Luka in Bosnia and Herzegovina, the Clinic of Cardiology at the University Hospital Podgorica in Montenegro, and the Clinic of Cardiology at the University Hospital Skoplje, North Macedonia.

CTPA examination was performed at the time of admission of patients with suspected PE if their hemodynamic status permitted it; otherwise, it was performed as soon as the patient was hemodynamically stabilized. A positive CTPA finding and diagnosis of acute PE were established if the patient had at least one segmental artery thrombus.

CTPA was conducted with a 35 cm field of view, 1 mm section thickness, 70 ml contrast material volume, and a 4 ml/s contrast material injection rate. The radiologist described a central PE if there are thrombotic masses in the main, left or right pulmonary artery (PA), or lobar branches and peripheral PE with thrombotic masses at the segmental or subsegmental PA level.

In addition, the ratio of right ventricular diameter and left ventricular diameter (RV/LV) was measured, just below the tricuspid annulus.

Peripheral venous blood specimens from the antecubital vein were collected, centrifuged, and immediately analyzed using standard laboratory techniques, and BNP was analyzed within 24 hours of the hospital admission (which minimizes the influence of administered therapy). EDTA-plasma was utilized for BNP measurements,

Tab. 1. Basic characteristics of patients.

	Male 750 (46.5%)	Female 862 (53.5%)	p	Missing data
Age (years)	60.37±15.77	66.49±15.08	<0.001 ^{1*}	0
Age >75 years	133 (17.7%)	275 (31.9%)	<0.001 ^{2*}	0
Body mass index (kg/m ²)	27.28±4.35	27.50±5.14	<0.001 ^{1*}	491 (30.5%)
COPD	84 (11.2%)	86 (10.0%)	=0.474 ²	0
Malignancy	95 (12.7%)	122 (14.2%)	=0.424 ²	0
Deep vein thrombosis	285 (38.7%)	307 (36.8%)	=0.455 ²	41 (2.5%)
Type 2 diabetes	132 (17.6%)	190 (22.0%)	=0.032 ^{2*}	1 (0.1%)
Coronary disease	91 (12.2%)	94 (11.0%)	=0.485 ²	8 (0.5%)
Stroke	50 (6.7%)	65 (7.5%)	=0.570 ²	2 (0.1%)
Chronic heart failure	115 (15.3%)	122 (14.2%)	=0.551 ²	0
Creatinine clearance: <60 ml/min	222 (29.8%)	343 (40.1%)	<0.001 ^{2*}	12 (0.7%)
Creatinine clearance: <30 ml/min	43 (5.8%)	94 (11.0%)	<0.001 ^{2*}	15 (0.9%)
Arterial hypertension	402 (53.9%)	572 (66.6%)	<0.001 ^{2*}	7 (0.4%)
Smoking	176 (25.3%)	103 (12.8%)	<0.001 ^{2*}	111 (6.9%)
Anemia	157 (21.1%)	281 (33.0%)	<0.001 ^{2*}	
Systolic blood pressure (mmHg)	122.91±24.37	122.71±26.21	=0.023 ^{1*}	1 (0.1%)
Diastolic blood pressure (mmHg)	75.70±14.86	74.08±14.86	=0.253 ¹	17 (1.1%)
Heart rate	98.90±22.56	99.16±23.01	=0.482 ¹	0
PESI: >0 / 0	499 (66.6%) / 250 (33.4%)	610 (70.8%) / 252 (29.2%)	=0.082 ²	1 (0.1%)
spO ₂ <90% or paO ₂ <55mmHg	189 (27.6%)	211 (28.1%)	=0.879 ²	178 (11%)
RVSP	47.25±18.21	48.17±17.18	=0.649 ¹	207 (12.8%)

¹Independent Samples Test; ²Chi-square test; * p<0.05, COPD: chronic obstructive pulmonary disease; SpO₂: oxygen saturation; paO₂: partial pressure of oxygen; RVSP: right ventricular systolic pressure

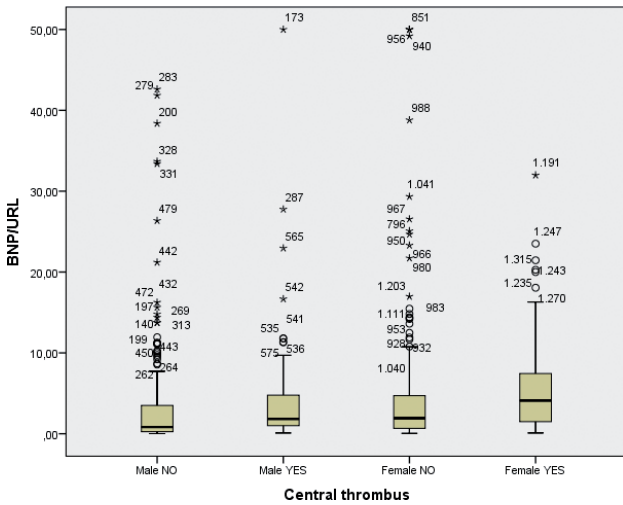


Fig. 1. The relationship between ratio of BNP and central thrombus in male and female patients.

and studied in Siemens ADVIA Centaur System (ADVIA Centaur BNP assay, Bulletin 10629823-EN Rev.U, 2017–07, Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). BNP upper reference level was 100 ng/L. But since in some institutions from the PE register, NT pro BNP was determined, instead of BNP, so as different essays, we expressed the BNP value through: How many times the BNP is higher than the upper range limit (URL) of the normal value (which for our lab is 100 pg/ml) – BNP/URL.

This retrospective study was approved by the Ethics Committee.

Statistical analysis

Data analyzes were performed with SPSS, version 26.0 (SPSS, Inc., Chicago, IL). Results are expressed as mean

Tab. 2. Relationship between the CTPA parameters and BNP levels.

men	BNP/URL>1 YES	BNP/URL>1 NO	p
central thrombus YES	72(75.0%)	24(25.0%)	*<0.001
central thrombus NO	92(45.1%)	112(54.9%)	
women	BNP/URL>1 YES	BNP/URL>1 NO	
central thrombus YES	80(85.1%)	14(14.9%)	*<0.001
central thrombus NO	130(61.0%)	83(39.0%)	
men	BNP/URL>1 YES	BNP/URL>1 NO	
RV/LV >1 YES	127(55.0%)	104(45.0%)	*<0.001
RV/LV >1 NO	28(20.7%)	107(79.3%)	
women	BNP/URL>1 YES	BNP/URL>1 NO	
RV/LV >1 YES	165(62.5%)	99(37.5%)	*<0.001
RV/LV >1 NO	112(91.1%)	11(8.9%)	

*Chi square test; BNP/URL – the ratio between brain natriuretic peptide level and upper range limit (100 pg/ml); RV/LV – the ratio between right ventricle and left ventricle; missing values – central thrombus: men 562(65.2%), women 443(59.1%); RV/LV: men 496(57.5%), women 363(48.4%)

with standard deviation (SD), or median with interquartile range (25th–75th percentile) according to data distribution. The Kolmogorov-Smirnov test was used to test the normality of the data distribution. Categorical variables were presented as frequency, and sex differences were analyzed using the Chi-square test. For parametric continuous variables, means were compared using independent samples Student’s t-test. For non-parametric continuous variables, the Mann-Whitney U test was used. Statistical significance was defined as $p<0.05$ for all comparisons.

Results

In total, 1,612 patients were enrolled in the study (750 men and 862 women) (Tab. 1), and the average age was 64 ± 16 years. Female patients were significantly older than male patients (66 ± 15 vs 60 ± 16 years) ($p<0.001$). In addition, most patients aged >75 years were women (31.9% vs 17.7%). Various comorbidities presented differently in women and men. Women were more likely to have diabetes mellitus (22.0% vs 17.6%), a glomerular filtration rate <30 mL/min (11.0% vs 5.8%), arterial hypertension (66.6% vs 53.9%), and anemia (33.0 vs 21.1%) compared to men. In contrast, men were more likely to smoke than women.

Out of 300 male patients, 96 patients (32.0%) had a central thrombus on CTPA, compared to 204 patients (68.0%), with a thrombus in one of the segmental or subsegmental branches. In 204 male patients, without central thrombus, 92 of them (45.1%) had $BNP/URL>1$, while 112 patients (54.9%), had $BNP/URL\leq 1$. Out of 96 patients with detected central thrombus, 72 patients (75.0%) had $BNP/URL>1$, while 24 patients (25.0%) had $BNP/URL\leq 1$, which is a significant difference ($p<0.001$) (Tab. 2).

Out of 307 female patients, 94 patients (30.6%) were found to have a central thrombus on CTPA, compared to 213 patients (69.4%), with a thrombus in one of the segmental or subsegmental branches. Out of 213 patients without central thrombus, 130 patients (61.0%) had an elevated BNP level ($BNP/URL>1$) versus 83 patients (39.0%) with $BNP/URL\leq 1$. Out of 94 patients with central thrombus, 80 patients (85.1%) had an elevated BNP level, which is a significant difference ($p<0.001$), compared to 14 patients (14.9%), with BNP normal values (Fig. 1).

We also monitored the ratio of the diameters of the right and left ventricles (RV/LV). Of the total number of male patients (366), in 135 patients (36.9%), RV/LV was greater than 1 ($RV/LV>1$). $RV/LV\leq 1$ was found in 231 patients (63.1%). When we look at patients with $RV/LV>1$, out of 135 patients in 107 (79.3%) BNP was elevated ($BNP/URL>1$), which is significantly higher compared to 28 patients (20.7%), whose BNP was normal ($p<0.001$). Out of 231 patients with $RV/LV\leq 1$, in 127 of them (55.0%) BNP was not elevated, while 104 patients (45.0%) had $BNP/URL>1$.

Out of 387 female patients, in 123 of them (31.8%), we noted $RV/LV>1$. In 112 patients (91.1%) BNP/URL was >1 , which is significantly higher compared to 12 patients (8.9%), whose BNP was normal ($p<0.001$). Out of 264 patients with $RV/LV\leq 1$, BNP

was normal in 99 patients (37.5%), and 165 patients (62.5%) had BNP/URL>1 (Fig. 2).

Discussion

In our study, which was conducted as a retrospective analysis of the regional PE registry, in patients with CTPA verified PE, we compared values in the blood and the presence of certain CTPA parameters, in relation to the sex of the patients.

The current modality of choice for PE imaging is CTPA (11). The first CTPA parameter we observed, was the presence of thrombus masses in the pulmonary arterial network. Localization of thrombus masses in the main trunk of the pulmonary artery, main and lobar branches, was described as central thrombus (central PE). The finding of a central thrombus on CTPA is associated with a higher frequency of hemodynamic decompensation, and therefore an increased mortality rate, and more often requires reperfusion therapy (12–14). The level of BNP in the blood, in a patient with acute PE, corresponds to the degree of RV load and hemodynamic compromise (15, 16).

Therefore, we wanted to determine the association between the finding of a central thrombus on CTPA and the level of BNP in the blood, in patients with acute PE. We observed male and female patients separately. Significantly higher number of male patients (75.0%), with CTPA findings of central thrombus, had an elevated level of BNP in the blood, compared to 25.0% of patients, in whom BNP was within the reference values. A significant difference was also found in female patients, since 85.1% of patients with central thrombus had an elevated level of BNP, compared to 14.9% of patients, whose BNP was normal.

So, we found in our study a correlation between BNP level and the finding of a central thrombus on CTPA, in both, men and women, with acute PE, confirmed on CTPA.

Another CTPA parameter, which we observed, is the ratio of the diameters of the right and left ventricles (RV/LV). RV/LV is usually less than 1 ($RV/LV \leq 1$), and in case of RV distension, RV/LV is higher than 1 ($RV/LV > 1$). The increase in RV/LV occurs as a consequence of the afterload of RV, in the case of obstruction of different degrees of the pulmonary arterial network. The sensitivity of this parameter is 92–100%, the specificity is 97–100%, and the prognostic factor is 100% (17–21). According to the European Society of Cardiology (ESC), $RV/LV > 1$ is the main prognostic factor for RV dysfunction (22, 23).

In male patients, with $RV/LV > 1$, in 79.3% of them, an elevated value of BNP was registered, which is significantly higher compared to 20.7%, in whom BNP was not elevated. In women, this difference is even more significant. In 91.1% of patients with $RV/LV > 1$, BNP was above the reference values, compared to 8.9% of patients, whose BNP was normal.

Conclusion

Elevated brain natriuretic peptide blood level correlates with computed tomography pulmonary angiography parameters, such as the presence of central thrombus and the ratio between right

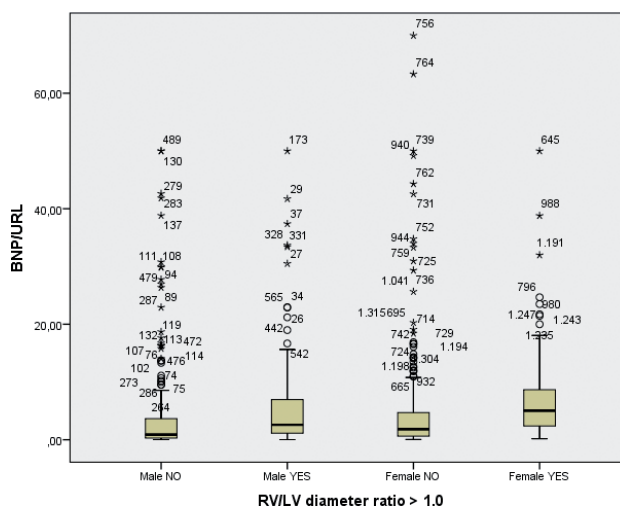


Fig. 2. The relationship between ratio of BNP and RV/LV in male and female patients.

and left ventricles greater than 1, in patients with acute pulmonary embolism, regardless of sex.

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