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“Prognostic biochemical markers in patients with post thromboembolic pulmonary hypertension”

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In the recent years, significant progress has been observed in understanding the pathophysiology of pulmonary hypertension (PH). There is growing interest in the use of various biochemical markers both for screening and diagnosis, and for monitoring the effect of the treatment. The test for determining the ideal biomarker should be fast, cheap and easy to measure. Its levels should be highly reproducible and widely applicable to different classes of diseases. Comorbidity, age, gender, the presence of kidney disease should not affect the results obtained. The biomarker should be sensitive, specific and the change in its value should reflect the clinical condition of the patient. No such universal marker has been found yet, but recently, increasing evidence has been accumulating to support their use in clinical practice. Some of these markers, such as BNP, NT pro BNP, and troponin T, may soon become part of routine practice for monitoring different groups of patients with PH.

Chronic postthromboembolic pulmonary hypertension (CTEPH) is the only potentially curable form of pulmonary hypertension. Rapid and accurate diagnosis is essential for successful treatment. Clinical signs and symptoms may be nonspecific. Risk factors such as venous or pulmonary thromboembolism are not always present. Routine screening for CTEPH after pulmonary embolism is not supported by current evidence. Traditional methods for diagnosing CTEPH include echocardiography, ventilation-perfusion scintigraphy, computed tomographic pulmonary angiography, and right heart catheterization, in addition to the above, functional class assessment and 6-minute walk test. Biochemical markers have emerged in the last decade as a noninvasive method for the evaluation and monitoring of patients with right ventricular dysfunction. Natriuretic peptides are a marker of cardiac dysfunction, but they are not specific for cardiovascular disease alone. They are a group of proteins with a common structure. These include atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP). NT pro BNP represents the terminal region of BNP. It is considered a prognostic marker with clinical significance for the assessment of hemodynamic stress in conditions associated with volume overload of the heart. It can be used to evaluate patients with PE, PH, and chronic cor pulmonale. The physiological role of natriuretic peptides is related to the maintenance of water and electrolyte balance, peripheral vascular resistance, which assigns them a place as the main antagonists of the renin angiotensin aldosterone and sympathetic systems. In contrast to the numerous studies on the role of BNP and NT pro BNP in left-sided heart failure, the diagnostic and prognostic significance in right ventricular dysfunction resulting from chronic lung diseases remains unclear. An increased level of NT pro BNP can be a biochemical marker for patients with clinically unmanifested

right-sided heart failure. NT pro BNP correlates with the degree of right ventricular dysfunction and provides information both in making a diagnosis and in monitoring patients to assess the effect of the treatment or after PEA. NT pro BNP is considered a strong predictor for predicting survival.

CTEPH is a serious complication in patients after acute or recurrent pulmonary embolism. Follow-up and monitoring of symptomatic patients predetermines early diagnosis and modern treatment, with a view to increasing patient survival. NT pro BNP is a reliable indicator for selecting appropriate patients for further investigations in the search for CTEPH, but it does not have the accuracy to represent a good independent screening test. BNP and NT pro BNP levels increase proportionally to the degree of right ventricular dysfunction in patients with PH. High plasma NT pro BNP levels and their increase during follow-up may have a strong independent association with increased mortality in patients with PH. NT pro BNP correlates with measurements of systolic pulmonary artery pressure on echocardiography and can be used to exclude preclinical or symptomatic CTEPH in patients with previous PE. NT pro BNP identifies patients at increased risk of complications and assesses short-term and long-term survival. Determination of its plasma levels allows monitoring of treatment effects in terms of their prognostic significance. A low plasma level or a stable decrease in NT pro BNP can be a valuable marker for successful disease control and therapeutic regimen. The level of NT pro BNP correlates positively with increased pulmonary artery pressure, increased mean right ventricular pressure and increased pulmonary vascular resistance, a negative correlation is observed with right ventricular ejection fraction.

Chronic post-thromboembolic pulmonary hypertension (STEP) is often a difficult-to-diagnose condition. It is thought to result from an incident of acute or recurrent pulmonary thromboembolism, arising from or in association with venous thromboembolism. For reasons that are still unclear, thrombi do not resorb in survivors of acute PE, but rather organize and form an obstruction in the pulmonary artery lumen. According to recent prospective studies, the incidence of the disease is between 1.0-3.8% in patients after acute PE. The main recommendation for monitoring patients after acute PE with manifestations of right-sided heart failure in order to exclude STEP is to perform an echocardiographic examination and NT pro BNP level, followed by right heart catheterization if there is any doubt about this diagnosis. A prospective study of 62 patients with acute or recurrent pulmonary embolism was performed. Plasma NT pro BNP levels were determined with an automatic chemiluminescent immunoanalyzer Immulite 2000 in the Central Clinical Laboratory of “St. Marina” University Hospital. The studies were carried out under project № 16030/2016 financed by “Nauka” Fund at the Medical University “Prof. Dr. Paraskev Stoyanov” – Varna. In addition to NT pro BNP, echocardiographic parameters, blood gas analysis and a 6-minute walk test (6MWT) were assessed in these patients.

The mean age of the patients studied was 65.69 ± 11.75 years. 36 men (58.06%) and 26 women (41.94%) were included, no statistically significant difference in mean age by gender was found. The study group included patients with recurrent PE 38.7%, and the remaining 61.3% had acute PE. At the time of the study, 96.8% were receiving anticoagulant treatment, with two having discontinued treatment due to side effects (gastrointestinal

bleeding). Of these, 69.4% of the patients were treated with direct oral anticoagulants, the rest (30.6%) were treated with a combination therapy. In this group of patients, the comorbidities that occupy a leading position are cardiovascular diseases (80.64%) and diabetes mellitus (29%). Most patients have several comorbidities: 93.5% hypertension, 16.1% cancer, 9.7% chronic obstructive pulmonary disease, 17.7% chronic renal failure. The Charlson Index (CCI) is the most widely used index for predicting mortality. A valid and reliable method that can be applied in clinical studies. It has been established that age is also an independent risk factor for death ($p<0.001$), in addition to comorbidity. The average value of this index in prospectively followed patients is 3.26 ± 1.51. Some authors report that if the CCI index is ≥ 3, these are patients with a significant burden of chronic diseases. In the patients we studied, the CCI index ≥ 3 was 62.8%, and patients with an index between 1 - 2 in our group had a relative share of 37.2%. This suggests the presence of significant comorbidities among some of the patients studied in the prospective group.

The main risk factor identified in acute or recurrent PE is deep vein thrombosis (DVT) in 59.7%, absolute arrhythmia in atrial fibrillation in 19.4%, oncological disease in 16.1%, antithrombin III deficiency and genetic defect of factor V Leiden in 3.2%. The study group included patients with massive PE 35.5%, and in 12 of them or 19.4% systemic fibrinolysis was performed. The main symptoms for which prospectively followed patients were questioned in order to search for clinical manifestations of PH or CTEPH were shortness of breath during physical exertion and at rest, syncope, chest pain and dizziness in the last three months. Some of the patients have more than one symptom. The severity of dyspnea was assessed with the mMRC scale. With it, the participants rated shortness of breath with a grade of 0 – 1 in 70.9%, which corresponds to the relative share of the symptom of shortness of breath during exertion and in 11.3% respectively with grade 4, which corresponds to the symptom of shortness of breath at rest. To assess the functional capabilities during physical exertion, 6 MWT was used, and before and after the test, the patients assessed the degree of shortness of breath with the Borg scale. In 48 patients, the test was performed with the average value of the distance traveled in six minutes being 363.21 ± 98.71 meters. A statistically significant difference was found in the distance traveled by men with a 6 MWT, which was on average 100 meters more than that traveled by women ($p=0.002$), a similar statistically significant difference was found when assessing shortness of breath with the Borg scale before and after exercise.

All patients in the prospective group underwent NT pro BNP, echocardiographic examination, and blood gas analysis. The mean values of these indicators during acute PE or recurrent PE and control examinations were compared. A statistically significant difference was found in the main echocardiographic indicators assessing right ventricular function (right ventricular size, TAPSE, systolic pressure in the pulmonary artery) and the CGA indicators ($p<0.0001$). The laboratory study of NT pro BNP found mean values of this biochemical marker in patients with probable CTEPH 6265.38 ± 5947.07 pg/ml. Statistically significant, they were 20 times higher in this group of patients compared to the established levels of NT pro BNP in patients with systolic pressure in the pulmonary artery ≤ 40 mm Hg ($p<0.0001$). In patients with probable CTEPH, a significant positive statistically significant correlation was

found between NT pro BNP levels and pulmonary artery pressure (Pearson Correlation r= 0.751; p=0.032), while for right ventricular size the correlation was significant positive but statistically insignificant (Pearson Correlation r= 0.688; p=0.199); it was a negative significant and also statistically insignificant correlation with TARSE (Pearson Correlation r= -0.709; p=0.115). In patients with probable CTEPH, a significant positive statistically insignificant correlation was found between NT pro BNP levels and 6 MWT (Pearson Correlation r= 0.898; p=0.289), a significant positive statistically insignificant correlation between NT pro BNP levels and the mMRC dyspnea assessment scales (Pearson Correlation r= 0.537; p=0.17) and Borg scale (Pearson Correlation r= 0.537; p=0.17).

Elevated NT pro BNP levels are a biochemical marker for patients with clinically undetected right-sided heart failure. NT pro BNP identifies groups at increased risk of complications and assesses short-term and long-term survival. NT pro BNP has a longer plasma half-life and better stability in circulating blood, so it is considered a more reliable marker. Recently, there is accumulating evidence that its plasma level increases proportionally to the degree of pulmonary hypertension and right ventricular dysfunction. Some authors have proposed noninvasive markers for excluding CTEPH, which they claim are highly sensitive (100%, 95% CI 56-100%) and highly reproducible. These are the absence of ECG criteria for right ventricular overload and low NT pro BNP levels. Patients with suspected CTEPH with one or more ECG features of pulmonary hypertension and elevated NT pro BNP levels should undergo additional diagnostic tests, including echocardiography and right heart catheterization. These authors consider that echocardiography has 92% sensitivity for proving Sternal hypertension (95% CI 74-99%). A study by Andreassen et al. investigated NT pro BNP levels in various forms of chronic precapillary PH (including Sternal hypertension) and demonstrated that high levels of this biochemical marker are found in symptomatic patients. They are closely related to the hemodynamics and functional capacity of these patients, and multivariate analysis showed that the NT pro BNP level is an independent predictor of mortality and decreases with medical treatment of these patients. Higher baseline plasma levels of NT pro BNP in patients with PH from different groups are associated with higher mortality. According to other studies, NT pro BNP correlates with 6MWT, cardiac index, pulmonary vascular resistance, but does not correlate with mean pulmonary artery pressure (mPAP). A level of this biochemical marker ≥ 1400 pg/ml identifies patients with a poor long-term prognosis. A low plasma level or a stable decrease in NT pro BNP can be a valuable marker of successful disease control and therapeutic regimen.

The values of this biochemical marker of right ventricular dysfunction in patients with probable CTEPH in our group are 20 times higher than those of patients included in the prospective group, in whom the systolic pressure in the AP ≤ 40 mm Hg. According to our results, the level of NT pro BNP correlates with echocardiographic signs of right ventricular dysfunction and systolic pressure in the pulmonary artery, and also correlates with the scales for assessing the severity of dyspnea (mMRC and Borg scale). Survival in this group correlates with the degree of increase in systolic pressure in the pulmonary artery and right ventricular dysfunction at the time of diagnosis. The six-minute test is an independent predictor of survival. If its results are below 250 meters, this is associated with a 50% higher

risk of death in the next 2 years, and with better results the risk is 8%. NT pro BNP > 350 pg/ml is associated with a 25-40% higher risk of death in the next 2 years, while lower values are associated with a 10% risk.

Although only a few studies have published data on preoperative assessment of surgical risk in patients with CTEPH using NT pro BNP and 6MWT levels before pulmonary endarterectomy and 3 months postoperatively. The results show that both tests correlate well with hemodynamic parameters and respond to changes in disease severity after surgery. NT pro BNP is a better indicator of persistent postoperative PH. It not only correlates with right ventricular dysfunction, but is also sensitive to changes in pulmonary vascular resistance postoperatively. The authors conclude that NT pro BNP will likely prove useful in long-term follow-up of patients with CTEPH. In conclusion, it is appropriate to state that natriuretic peptides are a marker of cardiac dysfunction, but are not specific only for cardiovascular diseases. NT pro BNP is a reliable criterion in the comprehensive evaluation of patients with probable CTEPH. It is a reliable prognostic marker for this group of patients. For the precise assessment of patients with probable CTEPH, timely and compliant with European standards echocardiographic examination is necessary. The most common comorbidities in patients with CTEPH are cardiovascular diseases, diabetes mellitus, COPD. Patients with probable CTEPH show a statistically significant worse quality of life compared to patients with unincreased systolic pressure in the pulmonary artery and healthy people. The level of NT pro BNP correlates positively with increased systolic pressure in the pulmonary artery, increased mean right ventricular pressure and increased pulmonary vascular resistance, a negative correlation is observed with the ejection fraction of the right ventricle. NT pro BNP is an important prognostic marker with clinical significance in the diagnosis and follow-up of patients with CTEPH.