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UNIVERSITATEA DE MEDICINĂ, FARMACIE, ȘTIINȚE ȘI TEHNOLOGIE „GEORGE EMIL PALADE" DIN TÂRGU MUREȘ

I.O.S.U.D.

***GEORGE EMIL PALADE* UNIVERSITY OF MEDICINE, PHARMACY, SCIENCE AND TECHNOLOGY OF TÂRGU-MUREȘ- DOCTORAL SCHOOL OF MEDICINE AND PHARMACY**

Clinical and echocardiographic factors for vital risk stratification in patients with acute pulmonary thromboembolism

PhD Student: **Dan Octavian Nistor**

Scientific Coordinator: **Prof. Dr. Klara Brînzaniuc**

Acute pulmonary thromboembolism (APT) is the most severe manifestation of venous thromboembolic disease, the third most common acute cardiovascular disease and the most common preventable cause of death in hospitalized patients. The natural evolution of the disease most often leads to death, but prompt and effective treatment produces complete recovery in most patients. Vital risk assessment is an important part of disease management, guiding important treatment choices. Patients who present without hemodynamic instability, the so-called normotensives, have a lower risk of early mortality and constitute the absolute majority of patients, thus most deaths come from these risk classes, where current risk stratification algorithms remain lacking. They rely on identifying features associated with increased risk from clinical examination, cardiac imaging and laboratory markers of myocardial injury. While the use of clinical judgement has now been aided by the development and validation of risk scores with proven prognostic value, the use of laboratory markers and cardiac imaging, particularly echocardiography, remains a subject of controversy, because no clear definition of right ventricular dysfunction exists, nor does a consensus on which cardiac biomarker has the highest prognostic value.

Risk stratification in normotensive patients with APT can be improved by identifying all clinical, echocardiographical and laboratory parameters that are associated with early mortality. In this regard, we conducted a series of prospective, observational studies on normotensive patients with APT consecutively admitted to the Adult Cardiology Clinic of the Emergency Institute for Cardiovascular Diseases and Transplant of Târgu Mureș during different time periods. All patients had a confirmed diagnosis of APT using the gold standard, contrast enhanced computed tomographic pulmonary angiography. Patients considered at high risk of death during the initial evaluation were excluded from the studies. The research goals included conducting an initial clinical, echocardiographic and laboratory assessment of patients with APT, monitoring patient outcomes for 30 days while recording death and other prespecified adverse events and identifying parameters significantly associated with poor prognosis.

The objective of the first study was to determine right ventricular outflow tract fractional shortening (RVOT-FS), a 2D echocardiography parameter that evaluates the systolic function of this anatomical region of the heart, in normotensive patients with APT and to assess the predictive value of this parameter for early mortality or severe complications. From a total of 70 consecutive patients considered eligible, 12 were excluded due to a high risk of death or late presentation, thus 58 patients were included in the study. The composite endpoint of death caused by APT, disease recurrence, ischemic stroke or acute myocardial infarction within the first 30 days was observed in 6 patients (10.3%). RVOT-FS showed abnormal values in most of the patients enrolled with lower values in the composite endpoint group vs. the non-endpoint group, group means 19 vs. 24%, but with no statistical significance, p=0.148. ROC analysis showed an area under the curve for RVOT-FS in predicting the endpoint of 0.670, but of no significance, p=0.176. The correlation analysis between RVOT-FS and the other echocardiographic parameters of right ventricular function revealed a strong significant correlation between TAPSE and RVOT-FS, with a coefficient r=0.91. In conclusion, while RVOT-FS showed usefulness in identifying right ventricular dysfunction in normotensive patients with APT and is correlated with other parameters of right ventricular function, it did not demonstrate a predictive value for the composite endpoint.

The second study investigated the comparative prognostic value of laboratory biomarkers, specifically D-dimers, troponin I, NT pro-BNP, creatinine and glucose, and evaluated their correlation with death or haemodynamic instability occurring within the first 30 days after APT diagnosis. We enrolled 75 consecutive normotensive patients and during follow-up the composite endpoint of death or the need for inotropic drug support was recorded in 7 patients (9.3%). The composite endpoint group presented on

average higher values of troponin I, NT pro-BNP, creatinine and glucose, but with no statistical significance. ROC analysis for predicting the endpoint showed an area under the curve for NT pro-BNP of 0.782, with a p value of 0.019 and a cut-off value of 5300 pg/mL was determined, which could identify patients with an increased risk of death or hemodynamic decompensation. Univariate and multivariate logistic regression did not identify any significant correlations of the biomarkers analysed with the composite endpoint. Thus, elevated NT pro-BNP levels greater than 5300 ng/mL showed an increased risk for death or the need for inotropic drug support during the first 30 days in normotensive patients with APT, unlike the other biomarkers studied, which did not.

The third study analysed the prognostic value of heart-type fatty acid-binding protein (H-FABP), a peptide resulting from myocardial injury, and other biomarkers, for predicting mortality or the need for inotropic drug support during the first 30 days in normotensive patients with APT. In all, 61 patients were included and during follow-up 9 patients (14.8%) recorded endpoint events. Higher mean values were recorded for all cardiac biomarkers in the composite endpoint group, with a mean H-FABP of 9.3 vs. 4.8 ng/mL, p=0.046. ROC analysis of the biomarkers for endpoint prediction showed the H-FABP assay as a good predictor, with an area under the curve of 0.709, likewise for Troponin I, with an area under the curve of 0.752, and a NT-proBNP level as a very good predictor, with an area under the curve of 0.814, all statistically significant. Also, cut-off values for each biomarker useful for identifying patients at increased risk were determined. Univariable logistic regression showed a significant correlation between the H-FABP and NT-proBNP levels and the composite endpoint, unlike the multivariable logistic regression, which did not identify any significant correlations. In conclusion, elevated biomarker levels like a H-FABP greater than 5.4 ng/ml, a NT-proBNP greater than 10174 pg/ml or a troponin I above 0.105 ng/mL are markers of an increased risk of mortality or haemodynamic instability during the first 30 days in normotensive patients with APT.

The fourth study was aimed at determining the prognostic value of right ventricular longitudinal strain (RVLS), measured by speckle-tracking echocardiography, and of other echocardiographic parameters of right ventricular function for the occurrence of death or the need for inotropic drug support during the first 30 days in normotensive patients with APT. We analysed 52 patients, and during follow-up composite endpoint events were recorded in 9 patients (17.3%). Myocardial deformation analysis revealed a significantly higher free-wall RVLS in the composite endpoint group, mean value -10.3% vs. -14.9%, p=0.004, and a higher global RVLS in the same group, mean value -13.7% vs. -15.8%, but with no statistical significance, p=0.131. The ROC analysis showed a very good predictive power for the composite endpoint for free-wall RVLS, with an area under the curve of 0.805, p=0.004, and a cut-off value with ideal sensitivity and specificity of -10.6 % was determined. Multivariate logistic regression identified a significant correlation between free wall RVLS and the composite endpoint with an adjusted OR of 1.79, and a p value of 0.035. Thus, a value of free wall RVLS greater than -10.6% can be used to stratify patients into having a low or high risk of death or hemodinamic instability, but the result is specific to the equipment used in this study. No other echocardiographic parameter of right ventricular function, including global RVLS, showed any predictive value for the composite endpoint in our patients.

An analysis of the combined populations included in our studies showed that in 135 normotensive patients with APT, 6 deaths were reported during the first 30 days, representing 4.4% of patients, a much lower death rate than previously reported. In our individual studies, myocardial injury biomarkers have proven their prognostic value, but non-cardiac markers did not show any such value. However, a ROC analysis of the entire population monitored during research, comprised of 166 normotensive patients with APT, showed that both serum creatinine and eGFR, calculated through the CKD-EPI formula, demonstrated significant predictive values for death or the need for inotropic support during the first 30 days, with areas under the curve of 0.653 for creatinine, p=0.017, respectively 0.703 for eGFR, p=0.001, identifying renal injury as a significant predictor of adverse events in these patients.

Laboratory biomarkers together with echocardiographic parameters and clinical factors have a higher combined predictive power than their individual ones and should be used together for improving risk stratification in normotensive patients with APT, ideally by using a risk score comprised of all significant predictors.