EDITORIAL COMMENT

The potential of new and old biomarkers for risk stratification in pulmonary embolism

Potencialidades de novos e velhos biomarcadores na estratificação de risco no tromboembolismo pulmonar

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Pulmonary embolism (PE) is a common cardiovascular emergency that has a non-specific clinical presentation and is difficult to diagnose. Its severity must be promptly assessed by stratifying the risk of in-hospital and short-term (30-day) mortality on an individual basis using risk markers.

Rapid and accurate risk stratification in PE has tended to focus on thrombus size and location, as well as its effects on systemic blood pressure and heart rate, and evidence of right ventricular (RV) dilatation and/or dysfunction on imaging studies. However, PE induces a wide range of biochemical changes, including the release of neurohormonal factors such as serotonin, which may partly explain increased pulmonary artery pressures. The same cardiac biomarkers used to assess myocardial necrosis in acute coronary syndromes can be useful for risk stratification of patients with PE. Measurement of serum troponins is included in the stratification algorithm to quantify RV microvascular lesion and microinfarction. Assessment of brain natriuretic peptide (BNP) or its N-terminal fraction (NT-proBNP) levels may also be important to quantify acute RV overload, although clinical decisions based on these results have yet to be standardized.

Obviously, no biomarker can be used without taking account of the clinical context. While the cost of assessing biomarkers may not be great, we cannot allow ourselves to standardize their use in a rational manner to obtain clear benefits in the management of patients.

PE risk can be stratified on the basis of clinical criteria (shock and systemic hypotension), evidence of RV dysfunction, and markers of myocardial injury (positive cardiac troponin T or I).

High-risk PE is an emergency with early mortality of over 15%, and thus requires prompt diagnosis and aggressive treatment. A classification of non-high-risk PE is based on the presence of markers of RV dysfunction and/or myocardial injury: in intermediate-risk patients there is at least one positive risk marker (RV dysfunction and/or laboratory evidence of myocardial injury), while patients in whom both are negative are classified as low-risk.

Prognostic assessment is primarily based on hemodynamic status, hypotension or shock being indicative of high risk for mortality, with obvious therapeutic implications.

Echocardiography shows evidence of RV dysfunction in at least a quarter of patients with PE, which in itself doubles the risk of death. Various studies have demonstrated good prognosis for patients with normal echocardiogram, with short-term mortality of <1%. However, the criteria used for RV dysfunction vary between studies and can include RV dilatation or hypokinesia, increased ratio between right and left ventricular (LV) dimensions and increased tricuspid regurgitant jet velocity. Thus, since there is no generally accepted definition of RV dysfunction on echocardiographic criteria, only a completely normal exam can be considered indicative of low-risk PE.

RV dysfunction associated with overload and myocardial stretch leads to heightened production of BNP and NT-proBNP. There has been increasing evidence in recent
years of the value of these biomarkers as indicators of the severity of RV dysfunction, hemodynamic compromise and prognosis, providing additional information to that obtained by echocardiography.\textsuperscript{10-12} Although high levels of BNP or NT-proBNP are associated with worse prognosis, their positive predictive value is reported as low (12–26%); their importance resides in the fact that low BNP or NT-proBNP levels in the context of PE can be taken as a reliable marker of good prognosis, with a negative predictive value of over 94%.\textsuperscript{13}

Troponins T and I are also important laboratory markers in PE, although RV myocardium may not be their only source; nevertheless, several studies have consistently reported an association between elevated troponin levels and increased mortality.\textsuperscript{14}

Simultaneous assessment of troponins and NT-proBNP can be used to stratify normotensive patients with PE. In patients in whom both are elevated, 40-day mortality can exceed 30%, and those with elevated NT-proBNP alone have an intermediate mortality rate of 3.7%, while those with low levels of both markers present a good prognosis.\textsuperscript{15}

An alternative approach is troponin measurement combined with echocardiographic assessment. Troponin I \textgreater{}0.1 ng/l associated with RV/LV ratio \textgreater{}0.9 identified a subgroup of patients with overall 30-day mortality of 38%, while the absence of echocardiographic evidence of RV dysfunction and markers of myocardial injury was indicative of excellent prognosis.\textsuperscript{16}

Some studies have reported the prognostic value of new biomarkers in PE such as heart-type fatty acid-binding protein (H-FABP), which have been shown to be highly sensitive in detecting myocardial necrosis. Following ischemic myocardial injury, H-FABP is released from damaged myocytes within 1–3 hours and normalizes after 12–24 hours.\textsuperscript{17}

The advantage of measuring H-FABP compared to troponin is the fact that the former is released earlier and that levels are elevated in myocardial ischemia irrespective of the presence of necrosis. In prognostic terms, H-FABP is similar to troponin in the context of acute coronary syndrome. Studies have suggested that H-FABP may even be superior to troponin for risk stratification of PE at admission, a value of \textgreater{}6 ng/ml having a positive predictive value of 23–37% and a negative predictive value of 96–100%.\textsuperscript{18,19}

At present, there are no consistent data from sufficiently large patient populations to justify therapeutic options such as thrombolysis in patients with non-high-risk PE, since many variables affect prognosis in PE.

Against this background, the article entitled “NT-proBNP for risk stratification of pulmonary embolism” in this issue of the \textit{Journal} constitutes a pertinent reflection on and analysis of risk stratification in PE.\textsuperscript{20}

The aim was to characterize a sample of patients hospitalized with PE according to serum NT-proBNP level at hospital admission and to assess the impact of this biomarker on short-term evolution. It was a retrospective analysis of consecutive patients admitted with PE over a period of 3.5 years. Based on the median NT-proBNP at hospital admission, the patients were divided into two groups (Group 1: NT-proBNP < median and Group 2: NT-proBNP \textgreater{} median). The two groups were compared in terms of demographic characteristics, personal history, clinical presentation, laboratory, electrocardiographic and echocardiographic data, therapy, in-hospital course (catecholamine support, invasive ventilation and in-hospital death and the combined endpoint of these events) and 30-day all-cause mortality.

A receiver operating characteristic (ROC) curve was constructed to determine the discriminatory power and cut-off value of NT-proBNP for all-cause mortality at 30 days.

In this study, 91 patients, mean age 69±16.4 years (51.6% aged \textgreater{}75 years), 53.8% male, were analyzed. Of the total sample, 41.8% had no etiological or predisposing factors for PE and most (84.6%) were stratified as intermediate risk for PE. Median NT-proBNP was 2440 pg/ml. Patients in Group 2 were significantly older (74.8±13.2 vs. 62.8±17.2 years, p=0.003) and more had a history of heart failure (35.5% vs. 3.3%, p=0.002) and chronic kidney disease (32.3% vs. 6.7%, p=0.012). They had more tachypnea on initial clinical evaluation (74.2% vs. 44.8%, p=0.02), less chest pain (16.1% vs. 46.7%, p=0.01) and higher creatininemia (1.7±0.9 vs. 1.1±0.5 mg/dl, p=0.004). Group 2 also more frequently had right chamber dilatation (85.7% vs. 56.7%, p=0.015) and lower left ventricular ejection fraction (56.4±17.6% vs. 66.2±13.5%, p=0.036) on echocardiography. Group 2 patients needed more catecholamine support (25.8% vs. 6.7%, p=0.044), had higher in-hospital mortality (16.1% vs. 0.0%, p=0.022) and more frequently had the combined endpoint (32.3% vs. 10.0%, p=0.034). All-cause mortality at 30 days was seen only in Group 2 patients (24.1% vs. 0.0%, p=0.034). By ROC curve analysis, NT-proBNP had excellent discriminatory power for this event, with an area under the curve of 0.848. The best NT-proBNP cut-off value was 4740 pg/ml.

Of the results presented, it is noteworthy that for several clinical variables (dyspnea, syncope, NYHA class, shock, heart rate at admission, and systolic and diastolic blood pressure) there were no differences between the two groups, which raises certain questions. Moreover, laboratory data revealed no differences in troponin levels, a finding that merits further investigation since different results might be obtained in a larger study population.

The authors conclude appropriately that elevated NT-proBNP levels identified PE patients with worse short-term prognosis, and showed excellent power to predict 30-day all-cause mortality. The results of this study may have important clinical implications, since the inclusion of NT-proBNP measurement in the initial evaluation of patients with PE can add valuable prognostic information.

The main limitations of the study as pointed out by the authors are the retrospective nature of the analysis and the small sample size; a further limitation is the fact that it was a single-center study, a common limitation that may perhaps be overcome in the future by encouraging multicenter studies in Portugal.

Conflicts of interest

The authors declare they have no conflicts of interest.

References


