Heart-type fatty acid-binding proteins (H-FABP): a reliable tool for initial risk stratification of pulmonary embolism?

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This editorial refers to ‘Heart-type fatty acid-binding protein permits early risk stratification of pulmonary embolism’ by M. Puls et al., on page 224

The severity of pulmonary embolism (PE) ranges from asymptomatic to cardiogenic shock with corresponding short-term mortality between 2 and 95%. Whereas the former could be discharged early or managed entirely as outpatients using low-molecular-weight heparin, those with greater severity of PE require rapid echocardiography to evaluate for indications for immediate thrombolysis or embolectomy. However, most patients with PE fall between these two extremes. Patients with PE who do not initially present with life-threatening criteria are usually admitted to a hospital ward where those with intermediate risk might experience a life-threatening recurrent episode requiring emergent thrombolysis and critical care. Therefore, among patients with intermediate clinical severity, it is critical to accurately identify those at risk for adverse medical outcome.

Despite recent advances in risk stratification, it remains difficult to assess the risk of short-term medical outcome and to elicit an appropriate management strategy at the time PE is diagnosed, particularly for patients with intermediate severity criteria. Severe dyspnoea, cyanosis, and syncope indicate life-threatening PE, and accentuated p2, tricuspid regurgitation murmur, or distended neck veins indicates acute right ventricular failure that is consistently associated with adverse short-term outcomes. On the ECG, T-wave inversion or a pseudoinfarction pattern (QR) in the anterior precordial leads indicates right ventricular dilation and dysfunction and are associated with adverse clinical outcome. Echocardiography has emerged as the principal tool for risk stratification in acute PE. Echocardiographic abnormalities (right ventricular hypokinesis, persistent pulmonary hypertension, patent foramen ovale, and free-floating right heart thrombus) rapidly and accurately identify high-risk patients who may benefit from thrombolysis or embolectomy. However, patients without echocardiographic abnormalities can be at high risk of short-term adverse medical outcome. Echocardiography also has limitations, because of its limited round-the-clock availability in the emergency setting, its cost, and technical limitations in patients who are obese or have chronic obstructive pulmonary disease. The Geneva prognostic index, a bedside clinical prediction rule, is limited by its reliance on arterial blood gas and leg vein ultrasound. In contrast, the prognostic model for PE, recently developed by Aujesky et al., is based on variables easily available at initial evaluation that combine medical history, signs, and symptoms and do not require any laboratory tests or radiographic procedures for predicting short-term medical outcome. These rules can assist the physician to accurately identify low-risk patients, i.e. those having an overall 30-day mortality below 2%. However, these clinical prediction rules had low specificity, which indicates a poor ability to discriminate between intermediate- and high-risk patients. As a matter of fact, intermediate-risk patients had predicted mortality ranging from 2.0 to 11.4%. Therefore, physicians attending patients with PE at the initial visit may be able to safely but not accurately identify a proportion of patients at low risk for adverse medical outcomes, and a proportion of patients at high risk of fatal outcome. Therefore, additional tools are needed to refine risk stratification. In this context, accurate prognostic assessment with inexpensive and widely available cardiac biomarkers, including troponins and natriuretic peptides, is an appealing approach and have emerged as the most promising tools for risk assessment of patients with PE. Troponin is a regulatory protein of the contractile molecule constitutive of the striated muscle. The troponin subunits T and I are the most sensitive and specific biomarkers of irreversible myocardial cell damage and as such, troponin level measurements led to profound modifications in the approach to management of acute coronary syndromes. Regarding PE, the increase of plasma troponin T and I levels closely correlate with the extent of right ventricular dysfunction and can occur in patients with PE in the absence of angiographic coronary artery disease. Unlike echocardiography, troponin assays are inexpensive, are well standardized, and could be immediately available round the clock in almost all emergency and acute care departments.
However, Troponin release may be delayed by 6 to 12 h, a fact that might limit its utility for the initial management of patients with PE. Natriuretic peptides are associated with ventricular dysfunction. Plasmatic B-type natriuretic peptide (BNP), the biologically active hormone, and its remaining N-terminal part, NT-pro-BNP, demonstrated advantageous properties for stratifying acute PE episodes. BNP originates from ventricular myocytes, the synthesis mainly stimulated by ventricular stretch, and is closely associated with right ventricular dysfunction in acute PE. However, similar to troponin I and C levels, increased BNP and pro-BNP levels are not specific of acute PE and have been encountered in primary pulmonary hypertension, chronic thromboembolic pulmonary hypertension, and chronic lung disease. Moreover, physicians must keep in mind that the increase in plasma levels of BNP and NT-pro-BNP are delayed in comparison with the time of onset of symptoms. Thus, serial measurements should be performed in patients with symptom duration of less than 6 h.\(^{10}\)

Konstantinides and coworkers, investigators from Gottingen, Germany, a well-known research team in the assessment of PE severity, add new and interesting insight in this clinical research field. They evaluated the characteristics of a test based on the initial measure, in the emergency department (ED) setting, of the heart-type fatty acid-binding proteins (H-FABP) in comparison with other currently available severity biomarkers (i.e. troponin and natriuretic peptides). Since 50–80% of the heart’s energy is provided by lipid oxidation, H-FABP is particularly important for myocardial homeostasis. In as much as H-FABP is a relatively small cytoplasmic protein, it is released in the systemic circulation quicker than troponins are, and is rapidly measurable (90 min) in the circulation after myocardial injury. Thus, H-FABP may potentially help the physician to identify myocardial damages at the very beginning of symptoms. As such it has been demonstrated as a promising biological marker in acute coronary syndrome.

In their observational, prospective study, Konstantinides et al., enrolled 107 consecutive patients with proven PE referred to their ED, and measured H-FABP, troponin T, and NT-proBNP at 4, 8, and 24 h after presentation. Notably, of the 29 patients with H-FABP $>$6 ng/mL on admission, 12 (41%) developed a major PE-related complications, whereas none of those with normal baseline H-FABP experienced PE-related complications. Additionally, they demonstrated almost no overlap of H-FABP levels when comparing patients having a complicated or uncomplicated outcome. Only one patient with a H-FABP level $<$6 ng/mL died during the follow-up, but the cause of his death was unrelated to PE. The ability of H-FABP to discriminate complicated from uncomplicated courses was consistently better than that of troponin T and NT-proBNP throughout the sequential evaluation at 4, 8, and 24 h. The multivariate analysis comparing the three biomarkers resulted in identifying H-FABP as the unique significant predictor of a complicated 30-day outcome. Moreover, H-FABP allowed discrimination within the subgroups of patients defined by echocardiographic findings, a finding that is of critical value for risk stratification.

Although this observational study is single centred and enrolled a limited number of patients with PE, the positive findings call for additional, confirmatory studies, with larger and perhaps more heterogeneous population. Since patients with PE discovered incidentally at diagnostic workup for another suspected disease have been excluded from this study, it would be valuable to assess the characteristics of this test extended to this population. If future studies confirm these characteristics, H-FABP, along with clinical prediction rules and echocardiography, could play an important role in ED algorithms used for the risk stratification of PE, and therefore maybe helpful in guiding medical decision-making, particularly for patients within the intermediate-risk category for adverse short-term medical outcome.

**Conflict of interest:** none declared.

**References cited**