Importance of cardiac biomarkers in risk stratification in acute pulmonary embolism

Małgorzata Mikulewicz and Jerzy Lewczuk
Cardiology Department, County Hospital, Wrocław, Poland

Abstract
At present there is consent that patients with acute pulmonary embolism (APE) and hemodynamic instability have poor prognosis and benefit from thrombolytic therapy or embolectomy, whereas hemodynamically stable patients without echocardiographic signs of right ventricular overload/dysfunction (RVO) have good prognosis and should be treated with anticoagulation alone. The optimal treatment for stable APE patients with RVO remains a challenge, and cardiac biomarkers can probably add to risk stratification and therapeutic decision making. Troponins are indicators of irreversible cardiac cell injury, and in patients with APE even a moderate rise of the blood troponin level correlates with RVO, hemodynamic instability and cardiogenic shock. However, the positive predictive value of cardiac troponins is relatively low. It can be increased when the results of troponins and echocardiography are combined. The clinical benefits of cardiac troponins result foremost from the high negative predictive value of in-hospital events, including death. Likewise, elevated levels of natriuretic peptides such as BNP and NT-proBNP, caused by increased right ventricular stress, show close association with RVO and with increased in-hospital risk. Instead, the low level of natriuretic biomarkers indicates an uncomplicated outcome of APE.

There are some proposals of algorithms that combine both biomarkers and echocardiography for risk stratification. The principal aim of ongoing studies is to find patients with hemodynamically stable APE who can be candidates for thrombolytic therapy. The usefulness of biomarkers in long-term prognosis and their value to identify APE patients in whom chronic thromboembolic pulmonary hypertension can develop should also be confirmed.

Key words: cardiac biomarkers, acute pulmonary embolism, risk stratification

Introduction
At present, the assessment of patient hemodynamic status, and echocardiography in stable patients, have been the most important prognostic factors of acute pulmonary embolism (APE). However, risk stratification based on echocardiography has proved to be unsatisfactory. Right ventricular dilation, hypokinesis, flattening, paradoxical movement of interventricular septum, as well as increased end-diastolic dimension and tricuspid insufficiency are considered the most typical echocardiographic features of right ventricular overload/dysfunction (RVO). Demonstrating RVO in hemodynamically stable APE patients classifies them into the submassive APE category, which has a worse prognosis than non-massive APE, i.e. without RVO features; however, the presence of RVO does not
have enough discriminative force for the decision process of thrombolysis initiation.

Recently cardiac biomarkers were suggested for risk determination and therapeutic method selection in APE patients. Two biomarker groups have been extensively studied: myocardial damage (necrosis) indicators and neurohormonal activation indicators.

**Prognostic role of myocardial necrosis indicators in patients with acute pulmonary embolism**

Myocardial damage markers, which allow diagnosis of even minor myocardial injury such as cardiac troponin T and I, mioglobin, CPK-MB (MB fraction of phosphocreatine kinase), have already been used for ischemic heart disease, left ventricular failure and myocarditis diagnosis and prognosis. Their usefulness in new indications is based on their capability of indication of myocardial necrosis regardless of causative mechanism. In APE, myocardial necrosis may be due to right ventricular infarction, which may be secondary to APE or may accompany this condition [1, 2] even if coronary arteries show no pathology [3]. During an APE incident, CPK-MB serum activity and cardiac troponins I and T level increase were demonstrated; an increase of mioglobin level was reported to occur even before CPK-MB and troponins [4]. Recent reports indicate that the new myocardial necrosis marker, h-FABP (heart fatty acid binding protein), may also be a promising indicator of early cardiac injury and a marker of early risk in APE superior to troponins and mioglobin [5, 6].

Troponins, widely used biomarkers of irreversible myocardial damage, are highly sensitive and specific. They are released into the bloodstream in large amounts during myocardial infarction, and elevated levels of these can be found in serum over seven days even in non-ST elevation acute coronary syndromes [7]. However, in APE, troponin level increase is mild, may occur from 6 to 12 hours after acute embolic incident and is transient, usually lasting no longer than 2–3 days [8]. Troponin increase is known to occur in hemodynamically unstable, massive acute pulmonary embolism and has prognostic relevance [9, 10]. However, from a clinical point of view, the determination of troponin levels in massive APE has no therapeutic implications because all patients with this condition require fibrinolysis or embolectomy anyway. Nevertheless, troponin level determination may be relevant in hemodynamically stable APE. A good correlation between troponin levels and echocardiographical features of RVO has been repeatedly demonstrated in this disease [11]. Pruszczyk et al. [12] reported an elevated troponin T level > 0.01 ng/mL to be the only parameter to predict adverse events in a 15-day in-hospital period, and all eight deaths occurred in patients with positive troponin tests. What is even more clinically relevant, the negative result of troponin test was demonstrated to predict uncomplicated disease course [13]. This was shown in the largest study yet (Mappet 3) comparing anticoagulation and fibrinolysis in 106 patients with stable, submassive APE [14]. In acute coronary syndrome, serum troponin level increase is a recognized risk factor which necessitates invasive therapy.

**Neurohormonal activation indicators in risk stratification of acute pulmonary embolism patients**

Indicators of neurohormonal activation, including the most widely known active natriuretic peptide BNP, which is released into peripheral blood by cardiomyocytes and has a short half-life (23 min) and inactive N-terminal pro-brain natriuretic peptide (NT-proBNP) with 5-times longer half-life, seem to have a significant prognostic value in APE. The role of natriuretic peptides in differential diagnosis of cardiac and extracardiac dyspnea has been proved in many trials [15]. Determination of BNP has a high prognostic value, mostly in heart failure [16]. The first report of BNP elevation in serum from a patient with APE was published in 1997 [17]. Four years later, Tulevski et al. [18] demonstrated that elevated BNP levels can be found in APE patients who present echocardiographical RVO features. Kucher et al. [19], who measured BNP concentration in 73 APE patients, showed that most patients who died or required therapy intensification during hospitalization had elevated serum BNP. However, the cutoff value to diagnose 95% patients with mild disease course was not < 90 pg/mL (which is required to exclude left ventricular failure) but was < 50 pg/mL. In studies by Pieralli et al. [20], a BNP level of < 85 pg/mL was shown to exclude echocardiographical findings of RVO in 61 normotensive patients with first APE incident with a high degree of accuracy. However, all patients with BNP over 527 pg/mL revealed RVO features in echocardiography; all acute complications and deaths occurred in this patient group. The role of the BNP precursor, NT-proBNP, in short-term risk prediction in APE patients has also been established.
In studies by Pruszczyk et al. [21], who assessed 79 patients with hemodynamically stable and unstable APE, an increase of NT-proBNP was found in all patients with massive APE, and those who presented RVO in echocardiography and who died or developed other in-hospital adverse effects showed significantly higher concentrations of this marker. NT-proBNP levels also correlated with echocardiographic evidence of RVO.

Suggested risk stratification algorithms in acute pulmonary embolism with use of cardiac biomarkers

Kucher et al. [22], who analyzed pro-BNP in APE patients, demonstrated that low levels, i.e. < 500 ng/mL, are prognostic of an uncomplicated in-hospital course, and troponin and NT-proBNP were complementary in short-term risk assessment in this patient group. Increase of troponin level was diagnostic for patients at risk of death and serious complications, while low proBNP levels were characteristic for low-risk patients who could be managed as outpatients. These were the grounds for a practical risk stratification algorithm, according to which patients with unstable APE do not require biomarker determination (nor echocardiography) since they require thrombolysis irrespectively of the results. Patients with hemodynamically stable APE and normal levels of both biomarkers are classified as low complication risk. On the other hand, hemodynamically stable patients with elevated biomarker levels should have echocardiography performed due to high probability of RVO — if confirmed, these patients are at significant risk, and fibrinolysis should be considered [23]. Kosturbiec et al. [24] also studied risk stratification of APE patients by measuring troponin T and NT-proBNP and performing echocardiography in 100 initially stable APE patients. This procedure allowed the identification patients with high risk of fatal complications in 40-day follow-up (elevated troponin > 0.07 μg/L and elevated NT-proBNP ≥ 600 ng/L). However, the prognosis for patients with NT-proBNP of < 600 ng/mL was good.

Cardiac biomarkers in long-term prognosis in acute pulmonary embolism patients

It has been observed that the determination of biomarkers during acute embolic incident may have some prognostic value in the long-term. In a trial by Wolde et al. [25], baseline BNP < 21.7 pmol/L (75 pg/mL) was related to mortality, not only APE-related, but all-cause. Risk of 3-month death was 17% (95% CI 6–33%) and BNP < 21.7 pmol/L (which equals 75 pg/mL) had a significant negative prognostic value of 99% (95% CI 93–100%). Tulevski et al. [26], who measured BNP and troponin T in 28 normotensive APE patients, confirmed that patients with elevated BNP (204 ± 104 pg/mL), troponin T (0.044 ± 0.025 ng/mL) at baseline and echocardiographical features of RVO were at risk of death. However, from eight patients with elevated BNP at baseline and normal troponin T level, in four cases systolic right ventricular pressure of > 40 mm Hg persisted 90 days after the incident, allowing chronic thromboembolic pulmonary hypertension to be diagnosed. The follow-up BNP of these patients remained elevated, i.e. 162.2 ± 72 pg/mL.

Therefore, biomarker determination in stable APE patients appears to be a valuable diagnostic adjunct, and in some cases may even substitute echocardiography in in-hospital and long-term risk stratification. One should emphasize the work of Polish researchers, namely Piotr Pruszczyk and Adam Torbicki, and their contribution to the understanding of this issue. In future we will probably discover whether the determination of biomarkers will be able to help solve one of the most urgent therapeutic problems of APE — the selection of stable patients for fibrinolysis. Hopefully their role in the prognosis of chronic thromboembolic pulmonary hypertension development following APE will also be established.

Acknowledgements

The authors do not report any conflict of interest regarding this work.

References