Risk Stratification in Pulmonary Embolism Based on Biomarkers and Echocardiography

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Since the initial observation that elevated cardiac troponin T levels are closely associated with mortality in acute pulmonary embolism,1 several reports have confirmed the prognostic role of cardiac troponins in this setting.2,3 More recently, yet another group of biomarkers, the natriuretic peptides B-type natriuretic peptide (BNP) and N-terminal-pro-B-type natriuretic peptide (NT-proBNP), emerged to confer additional prognostic information.4–7

The role of cardiac troponins as indicators of irreversible cell injury is well established.8 Although in myocardial infarction circulating troponins result from continuous degradation of the contractile machinery of irreversibly injured cardiomyocytes, the reason for elevated blood levels in pulmonary embolism is less well defined.

In pulmonary embolism the time period of marker elevation is <2 to 3 days in most cases, whereas even in patients with small non–ST-segment–elevation acute myocardial infarction (NSTEMI) cardiac troponins remain elevated for >7 days despite the short half-life of cardiac troponin T of 90 minutes.8 It is highly likely that in pulmonary embolism most of the detectable troponin in circulation corresponds to the unbound cytosolic fraction, which may egress rapidly after membrane damage from injured cells. Because prolonged elevation of troponins in blood is not commonly found in pulmonary embolism, irreversible degradation of the sarcomeric protein complex, which is a surrogate for irreversible cell necrosis, apparently does not often occur in patients who survive pulmonary embolism. Regardless of the exact pathomechanism, at present it is believed that cardiac troponins are being released as the consequence of myocardial damage resulting from the acute increase of right ventricular afterload, which is aggravated in a vicious cycle by decreased cardiac output, reduced coronary blood flow, and diminished oxygen supply.9,10 Consistently, cardiac troponin release in pulmonary embolism has only been encountered together with evidence of severe myocardial distress such as right ventricular dysfunction, hemodynamic instability, or cardiogenic shock.1–3 Likewise in pulmonary embolism, BNP or NT-proBNP is elevated presumably because of increased right ventricular stress,11 explaining the close association of circulating levels with the presence and degree of right ventricular dysfunction and outcome.4,5

At present, there is consent that in pulmonary embolism hemodynamically stable patients without evidence for right ventricular dysfunction should be managed conservatively with anticoagulation alone, whereas patients with prolonged hypotension and shock will benefit from thrombolytic therapy or embolectomy.12 The optimal therapeutic strategy for normotensive patients with evidence of right ventricular dysfunction on cardiac ultrasound is under debate, however.13–15 For this subgroup of patients, biomarkers such as cardiac troponins and natriuretic peptides could be extremely useful for risk stratification and treatment allocation.16

The clinical benefit of cardiac troponins or natriuretic peptides is foremost because of the high negative predictive value, which is in the range of 97% to 99%.1,3–7,17,18 Thus, a patient with a negative biomarker result has an extremely low risk for death or in-hospital complications such as hemodynamic deterioration, mechanical ventilation, or need for inotropic support. This patient obviously will not benefit from any therapy other than anticoagulation. Conversely, the relatively low positive predictive value of a biomarker result, when used alone, does not justify exposing a patient to the risk of intracranial or other major bleeding associated with thrombolytic therapy or the risks associated with embolectomy or vena caval filters.

In the present issue of Circulation, Binder et al propose a new algorithm that combines biomarkers and echocardiography for risk stratification of patients with newly diagnosed acute pulmonary embolism.19 The authors found that combination of biomarkers with echocardiography increased the positive predictive value of cardiac troponin T or NT-proBNP and allowed to distinguish a low-risk group in which biomarkers and echocardiography were both normal, an intermediate-risk group in which either biomarkers or echocardiography were abnormal, and a high-risk group in which biomarkers and echocardiography were both abnormal. There was a gradient of risk with no complications in the low-risk group, a low rate of complications in the intermediate-risk group, and a 10- to 12-fold higher rate of complications in the high-risk group, depending on whether cardiac troponin T or NT-proBNP was used.

It is tempting to speculate that a subgroup of patients with pulmonary embolism characterized by a >10-fold higher risk needs to be treated more aggressively than via mere anticoagulation and watchful waiting. It is therefore obvious that a prospective trial needs to be conducted testing the efficacy of thrombolytic therapy in hemodynamically stable patients.
with indicators of high risk such as cardiac markers and right ventricular dysfunction on echocardiography. The authors must be congratulated on their progress to such a multicenter trial.

What remains to be defined, however, is the relative contribution of natriuretic peptides for risk stratification in clinical practice because there are still some controversies about the use of natriuretic peptides in general and particularly in patients with pulmonary embolism. To date, all studies including the present trial have defined cutoff concentrations for BNP or NT-proBNP retrospectively. The wide variation of cutoff levels across the trials is difficult to explain but may, at least in part, be related to patient selection, different proportions of females or older adults, timing of blood collection, and differences with respect to rates of fibrinolytic therapy. In addition, the results must be adjusted for the presence of left ventricular dysfunction and renal failure. Therefore, before natriuretic peptides can be implemented into a standard risk stratification protocol, these issues need to be clarified. In contrast, several predefined cardiac troponin T or I cutoffs have been tested prospectively and proved reliable for risk stratification in patients with acute pulmonary embolism. Although natriuretic peptides in this trial were associated with an increased risk, at the moment, data for troponins are more robust. Therefore, troponins should be the preferred markers until a common and prospectively validated cutoff for BNP or NT-proBNP has been established and compared head to head with cardiac troponin T or I.

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**References**


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