



Have we found how to identify candidates for thrombolysis among normotensive patients with acute pulmonary embolism?

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If prospectively validated, modified FAST could identify normotensive patients with PE for primary thrombolysis <http://ow.ly/WTZIs>

Acute pulmonary embolism (PE) results in a wide spectrum of haemodynamic compromise and in hospital PE-related mortality. It is generally accepted that haemodynamically unstable patients with systolic blood pressure <90 mmHg at presentation form a high-risk group (~5% of all PE patients), with short-term mortality exceeding 15%. They require urgent primary revascularisation performed mostly with systemic thrombolysis. In contrast, only a few patients without shock or hypotension are at risk of an adverse early outcome [1]. Thus, clinically stable, non-high risk patients require further risk stratification in order to optimise their management, including selection of the therapeutic strategy and the duration of the hospitalisation. Current European Society of Cardiology (ESC) guidelines introduced the simplified Pulmonary Embolism Severity Index (sPESI) [2], used for identification of the low-risk group [1]. Patients with sPESI of 0 are at the “benign” end of the risk spectrum; mostly, they have uncomplicated clinical courses and are candidates for very short hospitalisation or can even be managed as outpatients without any further risk stratification.

However, there is ongoing debate on the optimal risk stratification of so-called intermediate-risk patients and a potential role of thrombolysis in this group. Right ventricular dysfunction (RVD) is observed in ~25% patients with PE. Importantly, a progressive dilatation of the right ventricle with increasing wall strain and oxygen myocardial demand can result in ongoing myocardial injury, leading to rapidly deteriorating right ventricular (RV) failure with potentially fatal haemodynamic collapse. Such a scenario can be expected in approximately 5–6% of anticoagulated patients with intermediate–high-risk PE; this is a group of normotensive patients with RVD and biochemical signs of myocardial injury [3].

Therefore, since RV failure is the main cause of early PE-related deaths, it seems attractive to use direct imaging parameters of RVD or biomarker indicators of myocardial injury for prognostic assessment of PE patients. Non-elevated high-sensitivity plasma troponins alone or, especially, in combination with a sPESI of 0 showed excellent performance in the identification of low-risk patients with benign clinical course [4], and elevated plasma troponins levels indicate an increased risk of PE-related mortality. However, no defined plasma troponin cut-off values have been proposed that could be used for selection of normotensive candidates for thrombolysis [5]. Several studies have shown that RV/left ventricular (LV) ratio is associated with clinical outcome. In a meta-analysis covering >13 000 patients, an abnormally increased RV/LV ratio (>1.0 in most studies) on computed tomography (CT) was associated with an ~2.5-fold risk of all-cause mortality [6]. Increased RV/LV ratio on echocardiography is also predictive of increased mortality risk [7]. Up till now, there is no consensus on the definition of RVD, especially for echocardiography, and there are still studies trying to detect echocardiographic parameters optimal for

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selection patients at risk of early deterioration among initially stable subjects [8, 9]. Importantly, despite these efforts, no individual clinical, imaging or laboratory parameter has been identified to predict risk of an adverse in-hospital outcome with sufficient positive predictive value that could justify primary reperfusion.

Combinations of various clinical parameters with laboratory and or imaging findings were tested in order to improve risk stratification in non-high risk PE patients [10–12]. According to recent ESC guidelines, further risk stratification of subjects with a sPESI of at least 1 should be considered and it should include assessment of RVD by CT or echocardiography and detection of myocardial injury assessed by an elevation of plasma cardiac troponins [1]. However, there are still some areas of uncertainty for this stepwise ESC prognostic approach. As mentioned above, no decision-making troponin plasma levels have been indicated by the ESC guidelines and there is no validated imaging RVD definition. Moreover, this risk stratification strategy has never been tested in management outcome trials. The PEITHO (Pulmonary Embolism Thrombolysis) study showed that intermediate–high-risk patients benefit from thrombolytic therapy with tenecteplase (OR 0.44, 95% CI 0.23–0.87) [3]. However, this benefit was counterbalanced by significantly increased intracranial bleeding in the thrombolysed group. Therefore, further studies on risk stratification especially re-defining intermediate–high risk as candidates for more aggressive therapy are warranted.

As reported in this issue of the *European Respiratory Journal*, HOBÖHM *et al.* [13] compared risk assessment strategies for non-high risk PE performed according to four models: the previous 2008 ESC algorithm, the ESC 2014 model [1], the Bova model [14] and the modified FAST model. The Bova model includes the presence of systolic blood pressure in range of 90–100 mmHg (2 points), elevation of cardiac troponin (2 points), RVD on echocardiography or CT scan (2 points) and heart rate >110 per min (1 point). This model has recently been successfully externally validated in a cohort of 2874 normotensive patients. 30-day PE-related mortality in patients with >4 points reached 10.5% [15]. In the modified FAST model, H-FABP (heart fatty acid binding proteins) was replaced with age-adjusted elevated plasma high-sensitivity troponin T (hsTnT) levels (hsTnT ≥ 14 pg·mL⁻¹ for patients aged <75 years and ≥ 45 pg·mL⁻¹ for patients aged ≥ 75 years [16]). Modified FAST includes age-adjusted elevated plasma hsTnT (1.5 points), syncope (1.5 points) and tachycardia >100 beats per min (1 point). In a group of 388 normotensive PE patients from a single-centre cohort study, 25 (6.4%) patients experienced an adverse 30-day outcome.

All assessed algorithms and scores safely identified low-risk patients, while the modified FAST score appeared to be more suitable than the ESC 2014 or Bova scores for identifying intermediate–high-risk patients. Patients classified as intermediate–high risk by the 2014 ESC algorithm had a 8.9-fold increased risk of an adverse outcome compared to intermediate–low- and low-risk patients, while the highest odds ratio was observed for modified FAST (which could also be named the TroST model (troponin, syncope and tachycardia) score) ≥ 3 points (OR 15.9, 95% CI 5.3–47.6; $p < 0.001$). Almost 30% of all studied patients presented a modified FAST score (TroST score) ≥ 3 points and a complicated clinical course occurred in almost 19% of them. A significant advantage of the modified FAST score is its simplicity, lack of imaging parameters and incorporation of validated high-sensitivity troponin plasma levels. At present, there is no definite answer to the question of if and how we can find subjects at high risk of haemodynamic deterioration requiring treatment escalation among normotensive PE patients. However, it seems that we have a potential clue. If the modified FAST score is externally validated, it could potentially be of value for identification patients that could benefit from primary thrombolysis.

References

- 1 Konstantinides SV, Torbicki A, Agnelli G, *et al.* 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014; 35: 3033–3069.
- 2 Jimenez D, Aujesky D, Moores L, *et al.* Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010; 170: 1383–1389.
- 3 Meyer G, Vicaut E, Danays T, *et al.* Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med* 2014; 370: 1402–1411.
- 4 Lankeit M, Jimenez D, Kostrubiec M, *et al.* Predictive value of the high-sensitivity troponin T assay and the simplified Pulmonary Embolism Severity Index in hemodynamically stable patients with acute pulmonary embolism: a prospective validation study. *Circulation* 2011; 124: 2716–2724.
- 5 Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation* 2007; 116: 427–433.
- 6 Becattini C, Agnelli G, Germini F, *et al.* Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. *Eur Respir J* 2014; 43: 1678–1690.
- 7 Sanchez O, Trinquart L, Colombet I, *et al.* Prognostic value of right ventricular dysfunction in patients with haemodynamically stable pulmonary embolism: a systematic review. *Eur Heart J* 2008; 29: 1569–1577.
- 8 Pruszczyk P, Goliszek S, Lichodziejewska B, *et al.* Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. *JACC Cardiovasc Imaging* 2014; 7: 553–560.
- 9 Lobo JL, Holley A, Tapson V, *et al.* Prognostic significance of tricuspid annular displacement in normotensive patients with acute symptomatic pulmonary embolism. *J Thromb Hemost* 2014; 12: 1020–1027.

- 10 Jimenez D, Kopecna D, Tapson V, *et al.* Derivation and validation of multimarker prognostication for normotensive patients with acute symptomatic pulmonary embolism. *Am J Respir Crit Care Med* 2014; 189: 718–726.
- 11 Jimenez D, Aujesky D, Moores L, *et al.* Combinations of prognostic tools for identification of high-risk normotensive patients with acute symptomatic pulmonary embolism. *Thorax* 2011; 66: 75–81.
- 12 Sanchez O, Trinquart L, Caille V, *et al.* Prognostic factors for pulmonary embolism: the PREP study, a prospective multicenter cohort study. *Am J Respir Crit Care Med* 2010; 181: 168–173.
- 13 Hobohm L, Hellenkamp K, Hasenfuß G, *et al.* Comparison of risk assessment strategies for not-high-risk pulmonary embolism. *Eur Respir J* 2016; 47: 1170–1178.
- 14 Bova C, Sanchez O, Prandoni P, *et al.* Identification of intermediate-risk patients with acute symptomatic pulmonary embolism. *Eur Respir J* 2014; 44: 694–703.
- 15 Fernandez C, Bova C, Sanchez O, *et al.* Validation of a model for identification of patients at intermediate to high risk for complications associated with acute symptomatic pulmonary embolism. *Chest* 2015; 148: 211–218.
- 16 Kaeberich A, Seeber V, Jimenez D, *et al.* Age-adjusted high-sensitivity troponin T cut-off value for risk stratification of pulmonary embolism. *Eur Respir J* 2015; 45: 1323–1331.