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Risk-adapted management of pulmonary embolism

Stefano Barco [a], Stavros V. Konstantinides [a,b,*]

[a] Center for Thrombosis and Hemostasis, University Medical Center of the Johannes Gutenberg University, Mainz, Germany
[b] Department of Cardiology, Democritus University of Thrace, Alexandroupolis, Greece

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ABSTRACT

The presence and severity of right ventricular (RV) dysfunction is a key determinant of prognosis in the acute phase of pulmonary embolism (PE). Risk-adapted treatment strategies continue to evolve, tailoring initial management to the clinical presentation and the functional status of the RV. Beyond pharmacological and, if necessary, mechanical circulatory support, systemic thrombolysis remains the mainstay of treatment for hemodynamically unstable patients; in contrast, it is not routinely recommended for intermediate-risk PE. Catheter-directed pharmacomechanical reperfusion treatment represents a promising option for minimizing bleeding risk; for reduced-dose intravenous thrombolysis, the data are still preliminary. Non-vitamin K-dependent oral anticoagulants, directly inhibiting factor Xa (rivaroxaban, apixaban, edoxaban) or thrombin (dabigatran), have simplified initial and long-term anticoagulation for PE while reducing major bleeding risk. Use of vena cava filters should be restricted to selected patients with absolute contraindications to anticoagulation, or PE recurrence despite adequately dosed anticoagulants.

1. Introduction

Acute pulmonary embolism (PE), a clinical manifestation of venous thromboembolism (VTE), is the third most frequent acute cardiovascular syndrome behind acute myocardial infarction and stroke. In Europe, the annual number of PE-related deaths may exceed 500,000 in the population according to a frequently cited epidemiological model [1]. Depending on clinical severity and the presence of hemodynamic instability at presentation, more than 30% of the patients suffering acute PE may die within the first 30 days [2], and as many as 30% of survivors may present with VTE recurrence or some sort of chronic disabling symptoms within months or years after the index event [3]. These facts highlight the importance of effective management strategies for acute PE and its sequelae.

2. Contemporary risk stratification of PE

The optimal management of patients following the diagnosis of acute PE requires the stratification of patients into classes of disease severity in order to adjust the initial treatment to the individual's early death risk [4]. The key determinants of prognosis in the acute phase of PE are, (i) the patient's clinical presentation, history and comorbidities; and, (ii) the presence and severity of RV dysfunction as assessed clinically, by echocardiography or computed tomographic pulmonary angiography (CTPA), and/or with the help of laboratory markers such as cardiac troponins and natriuretic peptides [4]. At the "high" end of the risk spectrum are patients with overt, non-compensated RV failure resulting in reduced cardiac output and clinically manifesting as persistent arterial hypotension accompanied by signs of end-organ hypoperfusion. The patients with high-risk (or "massive") PE are those expected to benefit most from immediate reperfusion treatment combined, if necessary, with circulatory and respiratory support.

High-risk PE patients represent only 5% or even less of the entire PE patient population [2,5]. The large remaining group of (apparently) stable, not-high-risk PE patients can be further stratified by employing two categories of tools: the Pulmonary Embolism Severity Index (PESI), or its simplified form (sPESI); and imaging as well as laboratory tests detecting manifest or subclinical RV dysfunction [4]. Interestingly, male sex adds 10 points to the patient's early death risk as calculated by the original PESI, suggesting that women with acute PE may have a (slightly) more favorable early outcome than men; however, sex-specific differences of risk are not consistent and disappeared when the simplified version of the score was developed. An updated overview (Barco S and Konstantinides S. Pulmonary Embolism. ERS Monographs 2016; in press) of the imaging and laboratory findings for prediction of intermediate-high or intermediate-low risk PE, with the corresponding cutoff values, is provided in Table 1.

The PESI and sPESI primarily serve to identify "low-risk" patients who may not require further testing and may be eligible for early discharge and home treatment. For the remaining patients at intermediate risk, echocardiographic (or computed tomographic) or

* Corresponding author: Stavros V. Konstantinides, MD, Center for Thrombosis and Hemostasis, University Medical Center Mainz, Langenbeckstrasse 1, Building 403, 55131 Mainz, Germany. Tel.: +49 6131 17 8382; Fax: +49 6131 17 3456.
E-mail address: stavros.konstantinides@unimedizin-mainz.de (S.V. Konstantinides).

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Table 1
Update on imaging and laboratory tests for prediction of intermediate-high or intermediate-low risk PE.

Test or biomarker	Cut-off value	Sensitivity, % (95% CI)	Specificity, % (95% CI)	NPV, % (95% CI)	PPV, % (95% CI)	OR or HR (95% CI)	Number of patients	Studies providing the evidence
Echocardiography	Various criteria of RV dysfunction	74 (61–84)	54 (51–56)	98 (96–99)	8 (6–10)	2.4 (1.3–4.3)	1,249	Meta-analysis
CT angiography	RV/LV ≥1.0	46 (27–66)	59 (54–64)	93 (89–96)	8 (5–14)	1.5 (0.7–3.4)	383	Meta-analysis
	RV/LV ≥0.9	84 (65–94)	35 (30–39)	97 (94–99)	7 (5–10)	2.8 (0.9–8.2)	457	Prospective cohort
	LA volume ≤62 mL	NR	NR	NR	NR	2.4 (1.5–3.9)	636	Retrospective cohort
	RA/LA ratio >1.2	NR	NR	NR	NR	2.1 (1.3–3.4)		
	LV ≤67 mL	NR	NR	NR	NR	1.8 (1.1–3.0)		
BNP	75–100 pg/mL	85 (64–95)	56 (50–62)	98 (94–99)	14 (9–21)	6.5 (2.0–21)	261	Meta-analysis
NT-proBNP	600 pg/mL	86 (69–95)	50 (46–54)	99 (97–100)	7 (5–19)	6.3 (2.2–18.3)	688	Prospective cohort
	Various assays/cut-off values	NR	NR	NR	NR	8.6 (4.1–18.0)	1,664	Meta-analysis
Troponin I	Various assays/cut-off values	NR	NR	NR	NR	4.0 (2.2–7.2)	1 303	Meta-analysis
Troponin T	Various assays/cut-off values	NR	NR	NR	NR	8.0 (3.8–16.7)	682	Meta-analysis [a]
	14 pg/mL [b]	87 (71–95)	42 (38–47)	98 (95–99)	9 (6–12)	5.0 (1.7–14.4)	526	Prospective cohort
	Age-adjusted	88 (70–96)	54 (50–58)	99 (98–100)	7 (5–10)	8.7 (2.6–29.3)	682	Prospective cohort
H-FABP	6 ng/mL	89 (52–99)	82 (74–89)	99 (94–99)	28 (13–47)	36.6 (4.3–304)	126	Prospective cohort
		95 (76–99)	59 (52–64)	99 (96–100)	15 (10–23)	26.9 (3.5–203.8)	271	Prospective cohort
	Various assays/cut-off values	88 (75–95)	70 (65–70)	NR	NR	26.0 (6.6–101.7)	749	Meta-analysis
Copeptin + hsTnT + NT-proBNP	24 pmol/L, 14 pg/mL, 600 pg/mL	73 (48–89)	83 (77–87)	98 (95–99)	20 (12–32)	13.0 (3.9–42.7)	268	Prospective cohort

From the 2014 European Society of Cardiology Guidelines on the Diagnosis and Management of Pulmonary Embolism [4], updated and modified (Barco S, Konstantinides S. ERS Monographs 2016; in press).
In most studies, "early" refers to the in-hospital period or the first 30 days after the index event.
Abbreviations: BNP, brain natriuretic peptide; CT, computed tomographic; H-FABP, heart-type fatty acid-binding protein; HR, hazard ratio; LV, left ventricular; NPV, negative predictive value; NR, not reported in the reference cited; NT-proBNP, N-terminal pro-brain natriuretic peptide; OR, odds ratio; PE, pulmonary embolism; PPV, positive predictive value; RV, right ventricular.
[a] In the studies considered in this meta-analysis, cut-off values for the cardiac troponin tests used corresponded to the 99th percentile of healthy subjects with a coefficient variation of <10%.
[b] High-sensitivity assay.

Table 2
Evolving (2014–2016) risk stratification of patients with acute pulmonary embolism.

Early mortality risk		Risk parameters and scores			
		Shock or hypotension	PESI class III-V or sPESI ≥1	Signs of RV dysfunction on an imaging test	Cardiac laboratory biomarkers
High		+	(+)	+	(+)
Intermediate	Intermediate-high	–	(+)[a]	Both positive	
	Intermediate-low	–	(+)[a]	Either one (or none) positive	
Low		–	–	Assessment optional; if assessed, both negative	

From the 2014 European Society of Cardiology Guidelines on the Diagnosis and Management of Pulmonary Embolism, updated and modified [4].
[a] Current guidelines do not routinely recommend further risk assessment in patients belonging to the PESI class I-II, or with a sPESI of 0, who are considered to be at "low risk" based on large cohort studies. Nevertheless, some of these patients have been reported to exhibit RV dysfunction on imaging tests and/or elevated biomarker (cardiac troponin or natriuretic peptide) levels in the blood. If any doubts persist regarding the severity of PE upon clinical evaluation of the patient, even in the presence of a formally low PESI or a sPESI of 0, the functional status of the RV should be assessed. If RV dysfunction is then detected, the patients' risk should be classified based on the results of imaging and biochemical tests.

biochemical markers of RV dysfunction are the next tool for defining the groups of "intermediate-low risk" (with *either* evidence of RV dysfunction *or* elevated biochemical markers) or "intermediate-high risk" (with RV dysfunction *combined* with elevated biochemical markers) (Table 2). This advanced classification on the basis of the functional status of the RV helps to determine the duration of hemodynamic monitoring, the need for reperfusion treatment, and the choice of the anticoagulant drug and regimen [4].

3. Management of acute right heart failure

The principles of acute right heart failure management have been reviewed in a statement from the Heart Failure Association and the Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology [6]; an overview of the current treatment options for acute RV failure is provided in Table 3.

Acute RV failure principally responds to changes in preload, but excessive volume loading may overdistend the RV, and consequently further impair left ventricular filling and systemic cardiac output. Cautious volume loading aimed at maintaining normal central venous pressure (CVP) is the appropriate approach. Beyond volume management, vasopressors and/or inotropes are indicated in acute high-risk PE with hemodynamic instability. Vasopressors, particularly noradrenaline, restore blood pressure and improve cerebral, coronary, and other organ perfusion; contrary to widespread belief,