Current Controversies in Caring for the Critically Ill Pulmonary Embolism Patient

Samuel Francis, MD[a,*], Christopher Kabrhel, MD, MPH[b]

KEYWORDS

- Pulmonary embolism • Thrombolysis • Deep venous thrombosis
- Venous thromboembolism

KEY POINTS

- Appropriate classification of the patient with pulmonary embolism (PE) into high-risk, intermediate-risk, or low-risk allows physicians to start proper resuscitative strategies.
- Due to the pathophysiology of PE, intravenous (IV) fluids and positive pressure ventilation can lead to deterioration of hemodynamic status, and physicians need to recognize if and when that occurs.
- Timely thrombolytic administration in the correct cohort of patients saves lives and can improve hemodynamic status of those with high-risk PE.

INTRODUCTION

Five percent of patients with pulmonary embolism (PE) present with hemodynamic instability, and death from PE usually occurs within the first hour.[1–4] Typical approaches to resuscitation, however, can be detrimental to patients with acute right ventricular (RV) overload due to PE. Emergency resuscitation, therefore, must be targeted to the unique pathophysiology of PE.

PULMONARY EMBOLISM PATHOPHYSIOLOGY

Acute pulmonary thromboembolism increases pulmonary vascular resistance and RV pressure, which leads to increased RV distention, septal bowing, and decreased left ventricular (LV) preload. Because RV distention asymmetrically compresses the intraventricular septum, LV volume can be compromised in the setting of severe RV

[a] Division of Emergency Medicine, Department of Surgery, Duke University Hospital, DUH Box 3096, 2301 Erwin Road, Durham, NC 27710, USA; [b] Department of Emergency Medicine, Center for Vascular Emergencies, Massachusetts General Hospital, Zero Emerson Place, Suite 3B, Boston, MA 02114, USA
* Corresponding author.
E-mail address: Samuel.francis@duke.edu
Twitter: @edmullet (S.F.); @chriskabrhel (C.K.)

Emerg Med Clin N Am 38 (2020) 931–944
https://doi.org/10.1016/j.emc.2020.06.012
emed.theclinics.com

overload, decreasing cardiac output (Fig. 1).[5] Individuals with preexisting heart disease or congestive heart failure are particularly prone to shock from PE.[6]

PE also can cause ventilation/perfusion (V/Q) mismatch, increased alveolar dead space, and a low mixed venous O_2 level.[5,7,8] Although hypoxia from V/Q mismatch usually is reversible with supplemental oxygen, hypoxic pulmonary vasoconstriction can worsen pulmonary hypertension, and myocardial ischemia can decrease cardiac output.

PULMONARY EMBOLISM CLASSIFICATION

Current terminology classifies PE as (1) high-risk, or massive; (2) intermediate-risk, or submassive; or (3) low-risk[1] (Table 1). Treatment, management, and disposition of patients depend on risk class, although the classification of PE can change over the course of a patient's care as new data become available or circumstances change[9]; 5% to 8% of patients clinically deteriorate or die from their PE after hospital admission.[10,11]

High-Risk or Massive Pulmonary Embolism

Patients with massive PE present with hypotension or shock. These patients are critically ill, so prompt recognition and resuscitation are required. Patients qualify as high-risk PE with either (1) systemic hypotension with systolic arterial pressure less than 90 mm Hg or a drop in systolic arterial pressure of at least 40 mm Hg for 15 minutes, not caused by a dysrhythmia or other etiology, or (2) shock manifested by tissue hypoperfusion or hypoxia. Shock can include altered level of consciousness, oliguria, or cool clammy extremities.[2,12] PE patients with arterial hypotension have greater than 25% mortality. PE is a common cause of cardiac arrest. One decision instrument found that greater than 50% of individuals less than 65 years old with pulseless electrical activity (PEA) as the initial rhythm had PE as the cause of cardiac arrest.[13] Patients with PE who present in cardiac arrest have mortality of greater than 90%.[5]

Intermediate-Risk or Submassive Pulmonary Embolism

Normotensive patients with RV dysfunction do not qualify as high-risk PE but have a higher all-cause mortality, 4% to 21%, compared with patients with normal RV function.[1,2,14,15] **Box 1** outlines criteria that define an intermediate-risk PE.[16] Approximately 35% to 40% of PE patients manifest at least 1 of these findings.[1,17] The 2019 European Society of Cardiology guidelines incorporate the Pulmonary Embolism Severity Index (Table 2) or its simplified version (Table 3)[18,19] and further delineate

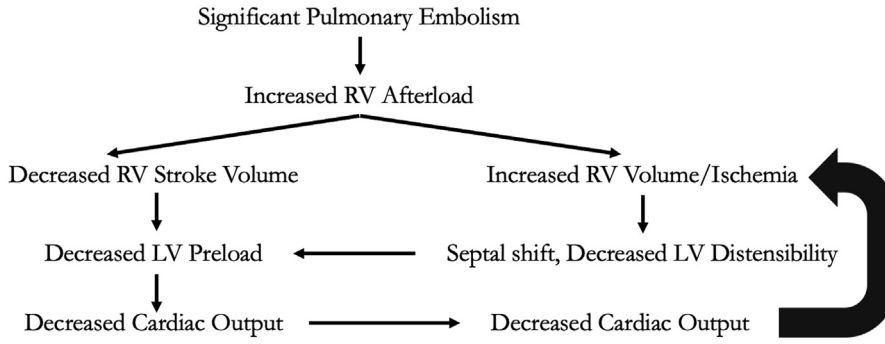

Fig. 1. Pathophysiology of PE.

Table 1
Pulmonary embolism classification

Type	Percentage of Total Pulmonary Embolism	Mortality at 3 Months
High-risk/massive	5%	58%
Systolic blood pressure <90		
Systolic blood pressure drop >90 mm Hg for ≥15 min		
Shock with tissue hypoperfusion or hypoxia		
Intermediate-risk/submassive	40%	21%
RV dilation on echocardiogram or CTPA		
Elevation of BNP or NT-proBNP		
Elevation of troponin		
ECG changes		
Low-risk	55%	<1%

Data from Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol. 1997;30(5):1165-1171.

intermediate-risk PE into intermediate-high and intermediate-low categories based on positive biomarkers. Intermediate-high patients have both RV dysfunction on transthoracic echocardiogram or computed tomography pulmonary angiography (CTPA) and elevated cardiac troponin levels. Intermediate-low patients can have 1 of RV dysfunction or elevated troponin, or neither.[12]

Low-Risk Pulmonary Embolism

Hemodynamically stable patients without RV dysfunction are considered low risk.

Box 1
Criteria for intermediate-risk pulmonary embolism

1. RV dilation by RV diameter/LV diameter >0.9 or RV systolic dysfunction as noted on echocardiography
2. RV dilation by RV diameter/LV diameter greater than 0.9 on CTPA
3. Elevation of BNP (>90 pg/mL)
4. Elevation of NT-proBNP (>500 pg/mL)
5. ECG changes (new incomplete or complete right bundle branch block, anteroseptal ST segment changes, or anteroseptal T-wave inversion)
6. Myocardial necrosis by troponin testing (troponin I >0.4 ng/mL; troponin T >0.1 ng/mL)

Data from Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation. 2011;123(16):1788-1830.

Table 2
The Pulmonary Embolism Severity Index score

Age	___ years	
Sex	Female, 0 points	Male, +10 points
History of cancer	No, 0 points	Yes, +30 points
History of heart failure	No, 0 points	Yes, +10 points
History of chronic lung disease	No, 0 points	Yes, +10 points
Heart rate ≥110 beats per minute	No, 0 points	Yes, +20 points
Systolic BP <100 mm Hg	No, 0 points	Yes, +30 points
Respiratory rate ≥ 30/minute	No, 0 points	Yes, +20 points
Temperature <36C°	No, 0 points	Yes, +20 points
Altered mental status	No, 0 points	Yes, +60 points
O_2 saturation <90%	No, 0 points	Yes, +20 points

Total Score	Risk Category	30-day Mortality
0–65	I: very low	0%–1.6%
66–85	II: low	1.7%–3.5%
86–105	III: intermediate	3.2%–7.1%
106–125	IV: high	4%–11.4%
>125	V: very high	10%–24.5%

Data from Drahomir Aujesky, D. Scott Obrosky, Roslyn A. Stone, Derivation and Validation of a Prognostic Model for Pulmonary Embolism. Am J Respir Crit Care Med. 2005 Oct 15; 172(8): 1041–1046. Published online 2005 Jul 14. https://doi.org/10.1164/rccm.200506-862OC.

INITIAL EVALUATION AND TESTING

Bedside tests cannot confirm a diagnosis of PE but can increase suspicion and help risk-stratify patients.

Point-of-care echocardiography

In the critically ill patient too unstable to obtain confirmatory chest imaging (eg, CTPA), point-of-care echocardiography showing new RV dilatation (a ratio of the RV to LV internal diameter in diastole [RV:LV ratio] >1:1 [**Fig. 2**]) should increase physician suspicion of PE.[20] RV dilatation also can risk-stratify a patient with confirmed PE to the intermediate-risk category.[21] Visualization of a thrombus in the right-sided chambers of the heart, clot-in-transit, is associated with higher mortality (21% vs 11%) and can be an indication for surgical thromboembolectomy or thrombolysis.[22]

Electrocardiogram

Electrocardiogram (ECG) findings in PE typically are associated with new-onset RV dysfunction. Studies have demonstrated that patients with isolated T-wave inversions in either the precordial or inferior leads (**Fig. 3**) are more likely to have PE than acute coronary syndrome.[23,24] PE can be associated ST segment elevation in aVR with diffuse ST depression, a finding that can be confused with primary cardiac etiologies.[25,26] The ECG findings most predictive of cardiovascular collapse in patients with PE were new precordial T-wave inversions, new heart block, and atrial fibrillation.[27]

Table 3
The simplified Pulmonary Embolism Severity Index score

Age in years	≤80, 0 points	>80, +1 point
History of cancer	No, 0 points	Yes, +1 point
History of heart or lung disease	No, 0 points	Yes, +1 point
Heart rate ≥110 beats per minute	No, 0 points	Yes, +1 point
Systolic blood pressure <100 mm Hg	No, 0 points	Yes, +1 point
O_2 saturation <90%	No, 0 points	Yes, +1 point

Total Score	Risk Category	30-day Mortality
0	Low	1.1%
≥1	High	8.9%

Data from Jiménez 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(15):1383-1389. https://doi.org/10.1001/archinternmed.2010.199.

Troponin

Elevated troponin in a PE patient indicates myocardial injury from a type II non–ST-elevation myocardial infarction. An elevated troponin is associated with higher mortality after PE and is one of the criteria for intermediate-risk PE.[28] The degree of troponin elevation predicts the degree of RV strain and mortality from PE.[29] The appropriate use of high sensitivity troponin assays are yet to be determined for PE.

B-type natriuretic peptide and N-terminal pro–B-type natriuretic peptide

B-type natriuretic peptide (BNP) and N-terminal pro–B-type BNP are released from cardiac myocytes in the setting of elevated RV pressure. Patients with PE and high BNP/NT-proBNP levels are at increased risk of a complicated in-hospital course and 30-day mortality.[30,31]

Lactate

Normotensive patients with PE and a plasma lactate greater than or equal to 2 mmol/L have higher mortality and are more likely to develop of shock or hypotension and require intubation or CPR.[32]

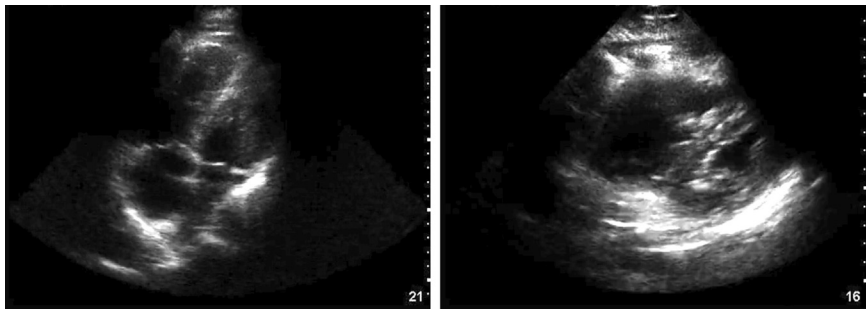

Fig. 2. Echocardiogram demonstrating apical 4 chamber (*left*) and parasternal long (*right*) view of RV dilatation in intermediate-risk PE. (Credit to Drs. Breslin & Gurysh.)

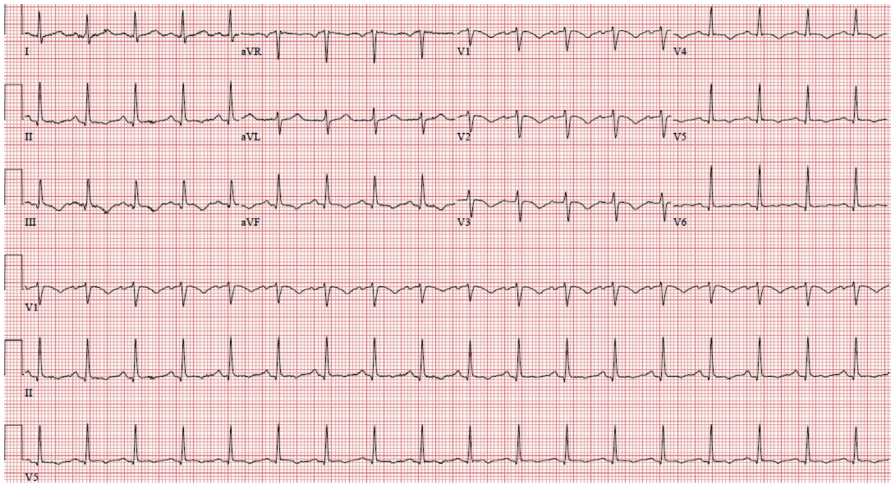

Fig. 3. ECG demonstrating anterior Y-wave inversions (V1–V4) seen in a patient with PE.

ADVANCED IMAGING IN THE PATIENT WITH PULMONARY EMBOLISM

Computed Tomography Pulmonary Angiogram

CTPA (**Fig. 4**) is the most common imaging modality used to confirm a diagnosis of PE. PE clot burden is readily apparent on CTPA. Some studies have shown that clot burden is useful in risk-stratifying patients with acute PE,[33,34] whereas other studies have not.[35] Compared with a gold standard of echocardiography, RV:LV ratio on CT has a lower positive predictive value.[36] Thus, the presence of RV dysfunction on CT should be confirmed with echocardiography. Unless there are data to suggest otherwise, lack of RV dysfunction seen on CTPA likely is correct owing to a sensitivity of 88% for this finding.

Ventilation/Perfusion Imaging

V/Q scan results are indeterminate in up to 70% of studies,[37,38] but V/Q imaging can be a useful study for patients with elevated creatinine or iodine dye allergy, those unable to lie flat for a CTPA, or those unable to fit in a CT scanner.[39]

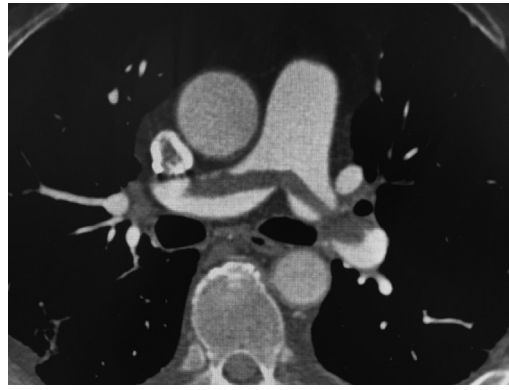

Fig. 4. CTPA demonstrating a saddle embolus.

INITIAL RESUSCITATION

Respiratory Support

Supplemental oxygenation

Hypoxemia from PE, which mostly is due to V/Q mismatch, typically responds to noninvasive supplemental oxygen. To minimize hypoxic pulmonary vasoconstriction and pulmonary hypertension, the emergency physician should aim to maintain oxygenation at or above 90% utilizing nasal cannula, high-flow nasal cannula, or non-rebreather masks.

Noninvasive positive pressure ventilation

Evidence for noninvasive positive pressure ventilation (eg, bilevel positive airway pressure) in patients with PE is limited.[40,41] Noninvasive PPV can open atelectatic lung, overcome pulmonary vascular shunting, and allow time for the physician to begin resuscitation.[42] Positive pressure also has the potential to impair RV function and decrease preload, worsening hemodynamic instability. Because noninvasive positive pressure ventilation can be removed easily in the case of hypotension, it is reasonable to trial for patients who cannot oxygenate or ventilate with supplemental oxygen.

Endotracheal intubation and mechanical ventilation

In patients with impending respiratory failure, intubation sometimes is necessary. Physicians must recognize, however, that intubation of a patient with PE can decrease preload and compress an already compressed LV. In high-risk PE patients who are intubated, 19% have cardiac arrest on induction and another 17% have cardiac arrest shortly afterward.[43,44] Therefore, intubation should be avoided if at all possible. If intubation is necessary, the authors recommend induction with a medication that minimizes hypotension (eg, ketamine) and having a vasopressor (eg, norepinephrine) ready.

Extracorporeal membranous oxygenation

In patients with refractory hypoxia or hypotension, venoarterial extracorporeal membrane oxygenation can provide a bridge to definitive PE therapy like systemic thrombolysis, catheter-directed lysis, or surgical embolectomy. Literature on this subject is limited to case reports and series, but selected patients appear to have good long-term outcomes.[45,46]

Circulatory Support

Intravenous fluids

Intravenous (IV) fluids can be helpful in PE by increasing preload.[47] Excessive IV fluids, however, can increase RV pressures, exacerbate septal bowing, lead to collapse of the LV during systole, and worsen hypotension in patients with severe PE. Expert recommendations recommend careful, not aggressive, fluids in acute PE.[12] A reasonable approach is an IV fluid bolus of 500 mL, if the patient has a history, examination findings, or laboratory findings that suggest hypovolemia, and re-evaluation after the initial bolus. If a patient develops worsening hypotension after IV fluid administration, fluids should be discontinued and vasopressor support started.

Vasopressors

Vasopressor support should be considered early in the resuscitation of patients with hypotension due to PE. Peripheral administration of vasopressors appears safe for the first 24 hours[48] and reduces the risk of large vessel injury that can lead to bleeding when thrombolytics are used. Norepinephrine, titrated to systolic blood pressure greater than 90 mm Hg,[49] is recommended as first-line vasopressor for patients

with PE. Epinephrine and dopamine increase chronotropy, which can exacerbate hypotension.[50–52] Dobutamine can increase cardiac index and decrease vascular resistance in patients with PE,[53] but it also is associated with systemic vasodilation, which can worsen hypotension. The authors recommend adding dobutamine if additional inotropic support is required in addition to norepinephrine.

Nitric oxide

Inhaled nitric oxide's ability to decrease pulmonary vascular resistance without affecting systemic blood pressure makes it a tantalizing potential therapy in patients with PE.[54] A clinical trial examining inhaled nitric oxide in patients with intermediate-risk PE, however, showed improvement in RV hypokinesis and dilation but no benefit in the primary study outcome.[55]

ANTICOAGULATION, THROMBOLYSIS, AND THROMBOEMBOLECTOMY

Anticoagulation

All patients without absolute contraindications should receive prompt anticoagulation after a diagnosis of PE. In patients with a high probability of PE, empiric treatment with anticoagulation is recommended, especially if diagnosis is expected to be delayed. For patients in whom an advanced intervention (thrombolysis or thromboembolectomy) is being considered, intravenous unfractionated heparin commonly is recommended because it can be discontinued easily. Direct-acting oral anticoagulants (DOACs), such as apixaban or rivaroxaban, and low-molecular-weight heparin (LMWH), all are reasonable first-line treatments for most stable patients with PE. For pregnant patients with confirmed PE, both the American College of Chest Physicians and American College of Obstetricians and Gynecologists recommend LMWH or heparin for the treatment of PE.[56,57] In pregnant patients with stable PE, LMWH is preferred over heparin. DOACs have not been widely studied in pregnant women.

Systemic Thrombolysis

Systemic thrombolysis can be lifesaving but also is associated with an increased risk of major intracranial and fatal hemorrhages. Thrombolysis is indicated for high-risk, hemodynamically unstable PE and may be considered for some intermediate-risk PE. Thrombolysis is not indicated for low-risk PE (**Table 4**).

Table 4
Contraindications to thrombolysis administration in pulmonary embolism

Absolute Contraindications	Relative Contraindications
Prior intracranial hemorrhage	Age >75 y
Known intracranial vascular malformation	Currently on anticoagulation
Known intracranial malignancy	Pregnancy
Recent significant facial or closed head injury	>10 min of cardiopulmonary resuscitation
Recent spinal or intracranial surgery	Noncompressible vascular punctures
Active bleeding or bleeding diathesis	Internal bleeding within the past month
Aortic dissection suspected	History of uncontrolled or severe hypertension
Ischemic stroke within 3 mo	Hypertension >180 mm Hg systolic or >110 mm Hg diastolic on presentation
	Dementia
	Ischemic stroke >3 mo old
	Major surgery within 3 wk

Absent contraindications, patients with high-risk PE should be treated with thrombolytics. When thrombolytics are indicated, delay in administration is associated with increased mortality.[58,59] The typical dose is 100 mg of tissue plasminogen activator (tPA) over 2 hours.[60] Weight-based tenecteplase also can be used. Compared with anticoagulation alone, meta-analyses demonstrate a 55% reduction in death or recurrent PE in high-risk PE patients treated with systemic thrombolytics,[61] with intracranial hemorrhage occurring in up to 2% and major extracranial bleeding occurring in 6% of patients.[11] For patients who present in cardiac arrest, societal guidelines suggest thrombolysis when a physician suspects PE.[16,56,62] Empiric thrombolysis in undifferentiated cardiac arrest, however, does not improve mortality benefit.[63]

For pregnant women in developed countries, PE causes 11% to 20% of maternal deaths.[64,65] As with nonpregnant patients, the mortality of high-risk PE in pregnant women is high, and delayed treatment increases mortality.[58,66] Thrombolysis should not be withheld in a pregnant woman with high-risk PE.[67,68] Neither tPA nor streptokinase crosses the placenta.[69] A recent systematic review of 127 pregnant high-risk PE patients treated with systemic thrombolysis found 6% maternal mortality and 12% fetal mortality. This same review found major bleeding complications of 18% and 58%, respectively, in the prepartum and postpartum periods.[70]

Thrombolytics therapy for patients with intermediate-risk PE is controversial. Full-dose thrombolysis appears to decrease the rate of hemodynamic compensation but does not reduce mortality, long-term morbidity, or chronic thromboembolic pulmonary hypertension.[61,71,72] Thrombolysis is associated with an increased risk of intracranial hemorrhage and major bleeding, particularly in patients over 65 years old.[73] Half-dose (ie, 50 mg) thrombolysis has been suggested as an approach to reduce major bleeding.[74,75] Similarly, this approach has been associated with improvement in RV function but not mortality.

Catheter-Directed Interventions

Catheter-directed intervention techniques include catheter-directed thrombolysis, clot maceration, and rheolytic and suction thrombectomy. In patients with high-risk or intermediate-risk PE, catheter-directed intervention may be beneficial, although data are sparse. To date, only 1 randomized controlled trial has compared catheter-directed thrombolysis to anticoagulation alone. This study, and several registries, have demonstrated short-term improvement in RV function, but no difference in mortality.[76]

Surgical Thromboembolectomy

Surgical thromboembolectomy should be considered in patients with high-risk PE in whom there are contraindications to systemic thrombolytic administration or after thrombolysis has failed.[77] Early patient identification and appropriate patient selection are associated with better mortality. Case series have demonstrated immediate improvement in RV function and high 1-month survival after successful embolectomy.[78,79]

Pulmonary Embolism Response Teams

PE response teams (PERTs) comprise multidisciplinary specialists who provide clinical expertise and expedite the care and disposition of patients with life-threatening PE. These teams are now in place across the United States and in many other countries. PERTs have been shown to improve disposition times, access to advanced therapies, and improve overall care.[80,81]

SUMMARY

Emergency physicians must be prepared to diagnose and resuscitate patients with PE rapidly. Certain aspects of PE resuscitation, however, run counter to typical approaches to resuscitation, so specific understanding of the pathophysiology of PE is required to guide resuscitation and avoid cardiovascular collapse. Once PE is diagnosed, treatment is guided by a patient's risk class. Although anticoagulation remains the mainstay of PE treatment, emergency physicians also must understand the indications and contraindications for thrombolysis and also should be aware of new therapies and models of care that may improve outcomes.

DISCLOSURE

Dr C. Kabrhel has received grant funding, paid to his institution, from Diagnostica Stago, Janssen, and Siemens Healthcare Diagnostics. He has consulted for Boston Scientific and EKOS Corporation.

REFERENCES

1. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). Lancet 1999;353(9162):1386–9.
2. Kasper W, Konstantinides S, Geibel A, et al. Management strategies and determinants of outcome in acute major pulmonary embolism: results of a multicenter registry. J Am Coll Cardiol 1997;30(5):1165–71.
3. Goldhaber SZ, Hennekens CH, Evans DA, et al. Factors associated with correct antemortem diagnosis of major pulmonary embolism. Am J Med 1982;73(6):822–6.
4. Laporte S, Mismetti P, Decousus H, et al. Clinical predictors for fatal pulmonary embolism in 15,520 patients with venous thromboembolism: findings from the Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) Registry. Circulation 2008;117(13):1711–6.
5. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest 2002;121(3):877–905.
6. Monreal M, Munoz-Torrero JF, Naraine VS, et al. Pulmonary embolism in patients with chronic obstructive pulmonary disease or congestive heart failure. Am J Med 2006;119(10):851–8.
7. D'Alonzo GE, Dantzker DR. Gas exchange alterations following pulmonary thromboembolism. Clin Chest Med 1984;5(3):411–9.
8. Manier G, Castaing Y, Guenard H. Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. Am Rev Respir Dis 1985;132(2):332–8.
9. Konstantinides S, Geibel A, Olschewski M, et al. Association between thrombolytic treatment and the prognosis of hemodynamically stable patients with major pulmonary embolism: results of a multicenter registry. Circulation 1997;96(3):882–8.
10. Casazza F, Becattini C, Bongarzoni A, et al. Clinical features and short term outcomes of patients with acute pulmonary embolism. The Italian Pulmonary Embolism Registry (IPER). Thromb Res 2012;130(6):847–52.
11. Meyer G, Vicaut E, Konstantinides SV. Fibrinolysis for intermediate-risk pulmonary embolism. N Engl J Med 2014;371(6):581–2.

12. Konstantinides SV, Meyer G, Becattini C, et al, The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS): The Task Force for the diagnosis and management of acute pulmonary embolism of the European Society of Cardiology (ESC). Eur Respir J 2019;54(3):1901647.
13. Courtney DM, Kline JA. Prospective use of a clinical decision rule to identify pulmonary embolism as likely cause of outpatient cardiac arrest. Resuscitation 2005; 65(1):57–64.
14. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. Circulation 2000;101(24):2817–22.
15. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, et al. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. Am Heart J 1997;134(3):479–87.
16. Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. Circulation 2011;123(16):1788–830.
17. Pollack CV, Schreiber D, Goldhaber SZ, et al. Clinical characteristics, management, and outcomes of patients diagnosed with acute pulmonary embolism in the emergency department: initial report of EMPEROR (Multicenter Emergency Medicine Pulmonary Embolism in the Real World Registry). J Am Coll Cardiol 2011;57(6):700–6.
18. 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(15):1383–9.
19. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. Am J Respir Crit Care Med 2005;172(8):1041–6.
20. Dresden S, Mitchell P, Rahimi L, et al. Right ventricular dilatation on bedside echocardiography performed by emergency physicians aids in the diagnosis of pulmonary embolism. Ann Emerg Med 2014;63(1):16–24.
21. Dahhan T, Siddiqui I, Tapson VF, et al. Clinical and echocardiographic predictors of mortality in acute pulmonary embolism. Cardiovasc Ultrasound 2016;14(1):44.
22. Torbicki A, Galie N, Covezzoli A, et al. Right heart thrombi in pulmonary embolism: results from the International Cooperative Pulmonary Embolism Registry. J Am Coll Cardiol 2003;41(12):2245–51.
23. Sinha N, Yalamanchili K, Sukhija R, et al. Role of the 12-lead electrocardiogram in diagnosing pulmonary embolism. Cardiol Rev 2005;13(1):46–9.
24. Sukhija R, Aronow WS, Ahn C, et al. Electrocardiographic abnormalities in patients with right ventricular dilation due to acute pulmonary embolism. Cardiology 2006;105(1):57–60.
25. Harhash AA, Huang JJ, Reddy S, et al. aVR ST segment elevation: Acute STEMI or Not? Incidence of an acute coronary occlusion. Am J Med 2019;132(5): 622–30.
26. Brenes-Salazar JA. ST-segment elevation in lead aVR: a visual reminder of potential catastrophe. JAMA Intern Med 2018;178(6):847–8.
27. Shopp JD, Stewart LK, Emmett TW, et al. Findings from 12-lead electrocardiography that predict circulatory shock from pulmonary embolism: systematic review and meta-analysis. Acad Emerg Med 2015;22(10):1127–37.

28. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. Circulation 2007;116(4):427–33.
29. Andrews J, MacNee W, Murchison J. Measurement of cardiac troponin identifies patients with moderate to large pulmonary emboli and right ventricular strain. Eur Respir J 2014;44(Suppl 58):P2407.
30. Klok FA, Mos IC, Huisman MV. Brain-type natriuretic peptide levels in the prediction of adverse outcome in patients with pulmonary embolism: a systematic review and meta-analysis. Am J Respir Crit Care Med 2008;178(4):425–30.
31. Lega JC, Lacasse Y, Lakhal L, et al. Natriuretic peptides and troponins in pulmonary embolism: a meta-analysis. Thorax 2009;64(10):869–75.
32. Vanni S, Jimenez D, Nazerian P, et al. Short-term clinical outcome of normotensive patients with acute PE and high plasma lactate. Thorax 2015;70(4):333–8.
33. Patel A, Kassar K, Veer M, et al. Clot burden serves as an effective predictor of 30 day mortality in patients with acute pulmonary embolism. J Am Coll Cardiol 2018;71(11 Supplement):A1933.
34. Hariharan P, Dudzinski DM, Rosovsky R, et al. Relation among clot burden, right-sided heart strain, and adverse events after acute pulmonary embolism. Am J Cardiol 2016;118(10):1568–73.
35. Vedovati MC, Becattini C, Agnelli G, et al. Multidetector CT scan for acute pulmonary embolism: embolic burden and clinical outcome. Chest 2012;142(6):1417–24.
36. Dudzinski DM, Hariharan P, Parry BA, et al. Assessment of right ventricular strain by computed tomography versus echocardiography in acute pulmonary embolism. Acad Emerg Med 2017;24(3):337–43.
37. Fennerty T. The diagnosis of pulmonary embolism. BMJ 1997;314(7078):425–9.
38. Investigators P. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). JAMA 1990;263(20):2753–9.
39. Moore AJE, Wachsmann J, Chamarthy MR, et al. Imaging of acute pulmonary embolism: an update. Cardiovasc Diagn Ther 2018;8(3):225–43.
40. Noble WH, Kay JC. Effect of continuous positive-pressure ventilation on oxygenation after pulmonary microemboli in dogs. Crit Care Med 1985;13(5):412–6.
41. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multicenter study. Intensive Care Med 2001;27(11):1718–28.
42. Green RS, Fergusson DA, Turgeon AF, et al. Resuscitation Prior to Emergency Endotracheal Intubation: Results of a National Survey. West J Emerg Med 2016;17(5):542–8.
43. Rosenberger P, Shernan SK, Shekar PS, et al. Acute hemodynamic collapse after induction of general anesthesia for emergent pulmonary embolectomy. Anesth Analg 2006;102(5):1311–5.
44. Bennett JM, Pretorius M, Ahmad RM, et al. Hemodynamic instability in patients undergoing pulmonary embolectomy: institutional experience. J Clin Anesth 2015;27(3):207–13.
45. Al-Bawardy R, Rosenfield K, Borges J, et al. Extracorporeal membrane oxygenation in acute massive pulmonary embolism: a case series and review of the literature. Perfusion 2019;34(1):22–8.
46. Kjaergaard B, Kristensen JH, Sindby JE, et al. Extracorporeal membrane oxygenation in life-threatening massive pulmonary embolism. Perfusion 2019;34(6):467–74.

47. Mercat A, Diehl JL, Meyer G, et al. Hemodynamic effects of fluid loading in acute massive pulmonary embolism. Crit Care Med 1999;27(3):540–4.
48. Cardenas-Garcia J, Schaub KF, Belchikov YG, et al. Safety of peripheral intravenous administration of vasoactive medication. J Hosp Med 2015;10(9):581–5.
49. Ventetuolo CE, Klinger JR. Management of acute right ventricular failure in the intensive care unit. Ann Am Thorac Soc 2014;11(5):811–22.
50. Ghignone M, Girling L, Prewitt RM. Effect of increased pulmonary vascular resistance on right ventricular systolic performance in dogs. Am J Physiol 1984;246(3 Pt 2):H339–43.
51. Vasu MA, O'Keefe DD, Kapellakis GZ, et al. Myocardial oxygen consumption: effects of epinephrine, isoproterenol, dopamine, norepinephrine, and dobutamine. Am J Physiol 1978;235(2):H237–41.
52. Boulain T, Lanotte R, Legras A, et al. Efficacy of epinephrine therapy in shock complicating pulmonary embolism. Chest 1993;104(1):300–2.
53. Jardin F, Genevray B, Brun-Ney D, et al. Dobutamine: a hemodynamic evaluation in pulmonary embolism shock. Crit Care Med 1985;13(12):1009–12.
54. Capellier G, Jacques T, Balvay P, et al. Inhaled nitric oxide in patients with pulmonary embolism. Intensive Care Med 1997;23(10):1089–92.
55. Kline JA, Puskarich MA, Jones AE, et al. Inhaled nitric oxide to treat intermediate risk pulmonary embolism: A multicenter randomized controlled trial. Nitric Oxide 2019;84:60–8.
56. Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl):e419S–96S.
57. ACOG Practice Bulletin No. 196: Thromboembolism in Pregnancy. Obstet Gynecol 2018;132(1):e1–17.
58. Beydilli I, Yilmaz F, Sonmez BM, et al. Thrombolytic therapy delay is independent predictor of mortality in acute pulmonary embolism at emergency service. Kaohsiung J Med Sci 2016;32(11):572–8.
59. Wang Y, Yang Y, Wang C, et al. Delay in thrombolysis of massive and submassive pulmonary embolism. Clin Appl Thromb Hemost 2011;17(4):381–6.
60. Weinberg I, Jaff MR. Treating large pulmonary emboli: do the guidelines guide us? Curr Opin Pulm Med 2013;19(5):413–21.
61. Wan S, Quinlan DJ, Agnelli G, et al. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. Circulation 2004;110(6):744–9.
62. Monsieurs KG, Nolan JP, Bossaert LL, et al. European resuscitation council guidelines for resuscitation 2015: Section 1. Executive summary. Resuscitation 2015;95:1–80.
63. Bottiger BW, Arntz HR, Chamberlain DA, et al. Thrombolysis during resuscitation for out-of-hospital cardiac arrest. N Engl J Med 2008;359(25):2651–62.
64. Benhamou D, Chassard D, Mercier FJ, et al. [The seventh report of the confidential enquiries into maternal deaths in the United Kingdom: comparison with French data]. Ann Fr Anesth Reanim 2009;28(1):38–43.
65. Clark SL, Belfort MA, Dildy GA, et al. Maternal death in the 21st century: causes, prevention, and relationship to cesarean delivery. Am J Obstet Gynecol 2008; 199(1):36.e1-5 [discussion: 91–2.e7-11].
66. Kucher N, Rossi E, De Rosa M, et al. Massive pulmonary embolism. Circulation 2006;113(4):577–82.

67. Lindquist A, Kurinczuk JJ, Redshaw M, et al. Experiences, utilisation and outcomes of maternity care in England among women from different socioeconomic groups: findings from the 2010 National Maternity Survey. BJOG 2015;122(12):1610–7.
68. Holden EL, Ranu H, Sheth A, et al. Thrombolysis for massive pulmonary embolism in pregnancy–a report of three cases and follow up over a two year period. Thromb Res 2011;127(1):58–9.
69. te Raa GD, Ribbert LS, Snijder RJ, et al. Treatment options in massive pulmonary embolism during pregnancy; a case-report and review of literature. Thromb Res 2009;124(1):1–5.
70. Martillotti G, Boehlen F, Robert-Ebadi H, et al. Treatment options for severe pulmonary embolism during pregnancy and the postpartum period: a systematic review. J Thromb Haemost 2017;15(10):1942–50.
71. Kline JA, Nordenholz KE, Courtney DM, et al. Treatment of submassive pulmonary embolism with tenecteplase or placebo: cardiopulmonary outcomes at 3 months: multicenter double-blind, placebo-controlled randomized trial. J Thromb Haemost 2014;12(4):459–68.
72. Konstantinides SV, Vicaut E, Danays T, et al. Impact of Thrombolytic Therapy on the Long-Term Outcome of Intermediate-Risk Pulmonary Embolism. J Am Coll Cardiol 2017;69(12):1536–44.
73. Chatterjee S, Chakraborty A, Weinberg I, et al. Thrombolysis for pulmonary embolism and risk of all-cause mortality, major bleeding, and intracranial hemorrhage: a meta-analysis. JAMA 2014;311(23):2414–21.
74. Levine M, Hirsh J, Weitz J, et al. A randomized trial of a single bolus dosage regimen of recombinant tissue plasminogen activator in patients with acute pulmonary embolism. Chest 1990;98(6):1473–9.
75. Sharifi M, Bay C, Skrocki L, et al. Moderate pulmonary embolism treated with thrombolysis (from the "MOPETT" Trial). Am J Cardiol 2013;111(2):273–7.
76. Kucher N, Boekstegers P, Muller OJ, et al. Randomized, controlled trial of ultrasound-assisted catheter-directed thrombolysis for acute intermediate-risk pulmonary embolism. Circulation 2014;129(4):479–86.
77. Fukuda I, Daitoku K. Surgical embolectomy for acute pulmonary thromboembolism. Ann Vasc Dis 2017;10(2):107–14.
78. Stein PD, Alnas M, Beemath A, et al. Outcome of pulmonary embolectomy. Am J Cardiol 2007;99(3):421–3.
79. Keeling WB, Sundt T, Leacche M, et al. Outcomes after surgical pulmonary embolectomy for acute pulmonary embolus: a multi-institutional study. Ann Thorac Surg 2016;102(5):1498–502.
80. Kabrhel C, Rosovsky R, Channick R, et al. A multidisciplinary pulmonary embolism response team: initial 30-month experience with a novel approach to delivery of care to patients with submassive and massive pulmonary embolism. Chest 2016;150(2):384–93.
81. Chaudhury P, Gadre S, Schneider E, et al. Impact of multidisciplinary pulmonary embolism response team availability on management and outcomes. Am J Cardiol 2019;124(9):1465–9.