Patient Assessment: Clinical Presentation, Imaging Diagnosis, Risk Stratification, and the Role of Pulmonary Embolism Response Team

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Abstract

Keywords

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- pulmonary embolism response team
- interventional radiology

Pulmonary embolism (PE) is currently the third leading cause of death and moreover is likely underdiagnosed. PE remains the most common preventable cause of hospital deaths in the United States, which may be attributable to its diagnostic challenges. Although difficult to diagnose, patient mortality rates are time-dependent, and thus, the suspicion and diagnosis of PE in a timely manner is imperative. Diagnosis based on several criteria which may dictate imaging workup as well as laboratory tests and clinical parameters are discussed. The evolution of treatment guidelines via various clinical trials and recommendations is outlined, setting the stage for the use of fibrinolytics, whether systemic or catheter directed. Treatment, including fibrinolytics, is predicated on patient triage into three large categories—massive, submassive, or low-risk PE. Additionally, a relatively new concept of a multidisciplinary team composed of several subspecialty experts known as the PE response team (PERT) is discussed. PERT's timely and unified recommendations have been shown to optimize care and decrease mortality while tailoring treatment to each individual afflicted by PE.

Objectives: Upon completion of this article, the reader will be able to assess the multiple assessment algorithms that are available which aid in the diagnosis of pulmonary embolism, and the benefits of using such algorithms in clinical practice.

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The diagnosis of stroke or myocardial infarction are commonly discussed and reviewed topics, garnering much interest due to their overwhelming concerns over their morbidity and mortality. Nonetheless, pulmonary embolism (PE) is the third leading cause of death and closely follows these two diagnoses with estimated 200,000 deaths per year.^{1,2} Mortality rates are likely much higher than reported, as many pulmonary thromboemboli are misdiagnosed as acute myocardial infarction or ventricular arrhythmias.³ PE is likely underdiagnosed due to its protean manifestations.

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PE remains the most common preventable cause of hospital death, responsible for 10% of hospital deaths.² Case fatality rates of up to 30% after hospital discharge have been reported.⁴ PE results in cardiovascular collapse largely due to its acute occlusion of the right cardiac outflow tract or various levels of pulmonary arterial system, resulting in right heart failure. These culminate in symptoms such as chest pain, oxygen desaturation, tachypnea, dyspnea, cough, and tachycardia which are commonplace in the emergency room setting.

Pulmonary thromboembolism usually begins as a deep venous thrombus, most commonly of the lower extremities of which the instigating factors were described by Rudolph Virchow in 1884 of blood stasis, endothelial damage, and hypercoagulable state.^{5,6} The DVT usually originates in the calf veins where it propagates centrally before breaking apart to cause a pulmonary thromboembolism; the original calf thrombus or the propagation thereof may all be asymptomatic.^{7,8} Central DVTs have a higher likelihood of resulting in patient symptoms.⁷

PE may masquerade as various disease entities affecting both the cardiovascular and pulmonary systems. It is thus imperative to have thorough knowledge of its clinical presentations, especially specific triggers to acquire additional imaging and risk stratification as well as specific roles of the so-called pulmonary embolism response team (PERT), comprising a multidisciplinary group of experts with one goal—to diagnose and treat life-threatening PE in the most time-efficient and judicious way possible while limiting patient risk of treatment side effects or complications.

Clinical Presentation

PE has been termed “the great mimicker” due to its nonspecific presentation. The spectrum of presenting symptoms range from an incidental imaging finding to sudden death.⁹ The most common symptoms associated with PE are chest pain and cough.¹⁰ The chest pain may be described as pleuritic in nature and may be acute or progressing over days.^{10,11} Other common nonspecific symptoms include dyspnea with exertion or at rest, palpitations, tachycardia, orthopnea, hemoptysis, low-grade fever, or syncope.^{4,12} Lower extremity DVT is evident in up to 79% of patients with PE and may manifest with lower extremity pain and/or swelling.¹⁰ Pleuritic chest pain and hemoptysis are due to pulmonary infarct.¹⁰ It is important to remember that symptom severity does not correlate with the magnitude of thromboembolism, with approximately one-third of patients with DVT having some degree of PE, including large central PE, who may demonstrate mild nonspecific symptoms.^{13,14}

Acute or subacute pulmonary hypertension may result due to thromboembolism with signs including right-sided gallop, parasternal heave, accentuated P2, tricuspid regurgitation murmur, and elevated neck veins.^{3,10} Cardiovascular collapse and sudden cardiac arrest may occur in 8% of patients and appear to be more common in patients younger than 65 years.^{9,15} It is thus imperative to entertain the diagnosis of PE in the setting of cardiac arrest with concomitant elevated central venous pressures. Early diagnosis

Table 1 Factors used in the assessment using the Well's criteria

Well's criteria	
Clinical assessment	Points
Clinical signs and/or symptoms of DVT	3
Alternate diagnosis is less than PE	3
Heart rate greater than 100 beats per min	1.5
Surgery or immobilization in past 4 wk	1.5
History of prior DVT or PE	1.5
Hemoptysis	1.0
Malignancy	1.0
Less than 2 points—low probability of PE	
2–6 points—moderate probability of PE	
Greater than 6—high probability of PE	

of massive PE and treatment is associated with decreased mortality and will be discussed later.

Due to the complexity of the clinical diagnosis of PE, various decision-making algorithms and clinical decision-making schemes have been proposed. Two common clinical predictive rules are the Wells score and the Geneva score which have demonstrated similar predicative accuracy for PE^{16,17} (→Tables 1 and 2). Each scoring algorithm, however, has its shortcomings, with the Geneva score requiring arterial blood gas on room air and the Wells score requiring clinical judgment which cannot be standardized.¹⁸ Some authors contend that PE algorithms offer very little aid and have proven that physician gestalt or judgment is best and has been validated as the best preclinical judgment.^{19–21}

Table 2 Factors used in the assessment using a revised Geneva Score

Revised Geneva Score	
Predisposition	Points
Age: greater than 65 y	1
History of DVT or PE	3
Surgery or fracture in the past 30 d	2
Active malignancy	2
Symptoms	
Unilateral lower extremity pain	3
Hemoptysis	2
Clinical assessment	
Heart rate 75–94 beats per min	3
Heart rate greater than 95 beats per min	5
Pain with deep palpation of lower extremity	4
0–3 points—low probability	
4–10 points—intermediate probability	
Greater than 11—high probability	

Given the inherent difficulty of clinical diagnosis of PE, imaging plays a central role in its diagnosis. The American College of Radiology (ACR) issues national guidelines for the appropriate use of imaging via their Appropriateness Criteria (ACR-AC) which is continually updated and represents the most up-to-date evidence for choosing appropriate imaging modality via expert panels and most current data.²² The ACR-ACs are divided into “conditions” for which imaging modalities are scored 1 (usually not appropriate) to 9 (usually appropriate). For suspected PTE in the setting of intermediate probability with positive D-dimer or high pretest probability, the ACR-AC advocates for chest radiograph, CT angiography of the chest with IV contrast, or CT chest with IV contrast, giving these studies their highest numbered recommendation of “9.” Technecium-99m ventilation perfusion (V/Q) scan and ultrasound duplex Doppler of the lower extremities garnered a 7 on their scale from 1 to 9.^{23,24}

For most patients, chest radiograph is indicated to exclude other etiologies of chest pain or shortness of breath such as pneumonia or pneumothorax. Subsequent imaging is dependent on patient stability. In hemodynamically stable non-pregnant patients, representing the majority of patients, pulmonary artery CT is the best test. V/Q scan may be obtained in cases where CT is contraindicated due to contrast allergy or renal failure. Hemodynamically unstable patients with suspected PE may be evaluated with emergent lower extremity ultrasound or echocardiogram to evaluate for right ventricular strain as evidenced by RV dilation, poor RV contractility, or McConnell’s sign (RV free wall akinesia with hyperdynamic apex) or even evaluate for thrombus in the right ventricular outflow. In some instances, empiric thrombolytic or anticoagulant without imaging is necessary and should be evaluated on a case-by-case basis, ideally by a PERT if one is available which will be discussed later.

Simply making the diagnosis of PE on CT is not sufficient. One must also evaluate for evidence of right heart dysfunction, as this plays a major role in helping to triage patients to various therapies as discussed later. The right ventricular diameter is divided by left ventricular diameter; a quotient greater than 0.9 on either transthoracic echocardiogram or CT represents right heart strain which has been demonstrated to be predictor of increased mortality both in hospital and at 30 days.^{25–27} Additionally, otherwise unexplained elevation of troponin or B-type natriuretic peptide in the setting of PE signals the presence of right heart strain.

PE in the setting of pregnancy presents its own challenges and controversies for which significant discussion is outside the scope of this article. V/Q scan has been advocated as the first test.^{28,29} Other authors have argued that while V/Q scan and CT pulmonary angiography may have similar diagnostic characteristics for PE, CT angiography can offer alternative diagnoses when PE is not found but does have higher radiation to the mother.³⁰

Patient Triage: Imaging and Clinical Criteria

Depending on institutional guidelines and practices, proceduralists may be one of the first physicians called after a

Table 3 Factors used in the assessment using the Pulmonary Embolism Severity Index

Pulmonary Embolism Severity Index	
Variable	Points
Age	1 point/y
Male	10
Heart failure	10
Chronic lung disease	10
Arterial O ₂ saturation <90%	20
Pulse >110 beats per min	20
Respiratory rate— > 30 breaths per min	20
Temperature <36°C	30
Malignancy	30
Systolic blood pressure <100 mm Hg	30
Altered mental status	60
Score—sum	Risk classification
≤ 65	I
66–85	II
86–105	III
106–125	IV
>125	V

diagnosed PE. It is important to delineate if a patient is hemodynamically stable and, if so, is there evidence of right ventricular strain on imaging, as this will allow subclassification of PE (►Table 3). PE is considered low risk when patients are hemodynamically stable and there is no evidence of right heart strain by imaging or laboratory markers. PE is considered to be submassive when there is right heart strain, but the patient remains hemodynamically stable. Massive PE is diagnosed in the setting of PE with hemodynamic instability, defined as systolic blood pressure less than 90 mm Hg or decrease in systolic blood pressure of greater than 40 mm Hg from patient’s baseline for more than 15 minutes which cannot be attributed to another cause.²⁵

Patients with low risk or nonmassive PE who are asymptomatic or minimally symptomatic (Pulmonary Embolism Severity Index [PESI] score of I or II; ►Table 3) should be placed on anticoagulation without requirement for additional thrombolytic—catheter-directed or systemic^{31,32} (►Table 4).^{25,33}

There has been a great deal of controversy regarding treatment guidelines for submassive and massive PE. The goal of any therapy in this patient population is to decrease the obstructive burden of the PE, thereby decreasing right ventricular strain/dysfunction with the ultimate goal of lowering patient mortality.^{34,35} Meyer et al who authored the Pulmonary Embolism Thrombolysis (PEITHO) trial demonstrated that systemic fibrinolysis with tenecteplase significantly reduced risk of death or cardiovascular collapse by 56% in the setting of submassive (normotensive patients)

Table 4 European Society of Cardiology guidelines

European Society of Cardiology (ESC) Guidelines (2014)				
Risk of early mortality	High	Intermediate: High	Intermediate: Low	Low
AHA guideline equivalent	Massive	Submassive	Submassive	Low risk
Criteria	Shock or hypotension	No shock or hypotension	No shock or hypotension	No shock or hypotension
	PESI class III–V	PESI class III–IV	PESI class III–IV	PESI class < III
	RV dysfunction	RV dysfunction	RV dysfunction or abnormal cardiac markers	No RV dysfunction or abnormal cardiac markers
	Abnormal cardiac markers (troponins or BNP)	Abnormal cardiac markers		

Abbreviations: AHA, American Heart Association; BNP, B-type natriuretic peptide; cardiac markers, myocardial injury—troponins or RV dysfunction; PESI, Pulmonary Embolism Severity Index; RV, right ventricle.

PE; however, this was counterpoised by a 5-fold increase in risk of major bleeding (6.3% tenecteplase group vs. 1.2% placebo group; $p < 0.001$) and 10-fold increase (2.4% tenecteplase vs. 0.2% placebo; $p = 0.003$) in hemorrhagic stroke.³⁶ Thus, systemic fibrinolytics have been relegated mainly to massive PE.^{37,38} The European Society of Cardiology (ESC) classifies systemic thrombolysis in acute high-risk PE as 1B recommendation and 2016 CHEST guidelines classify as 2B recommendation.^{32,39,40}

There are a myriad of studies which demonstrate benefit of thrombolytics—the earliest was the MAPPET-3 trial performed in 2002 comparing heparin with alteplase thrombolytic versus heparin plus placebo over 2 hours which demonstrated increased 30-day event-free survival in the alteplase plus heparin cohort than the heparin alone.⁴¹ Multiple additional studies followed including TIPES trial demonstrating statistical significance in the reduction of right ventricular dilatation (a surrogate for right heart failure/dysfunction) in tenecteplase versus placebo which was corroborated by the TOPCOAT trial where heparin plus tenecteplase demonstrated statistically significant superiority over heparin plus placebo.^{32,42,43}

Due to the well-validated improvement in patient outcome but unacceptably high rates of major bleeding events from systemic thrombolysis, catheter-directed thrombolysis (CDT) to decrease systemic dose of thrombolytics or thrombus fragmentation via mechanical forms such as rheolytic therapy or rotational embolectomy have garnered much interest.

CDT has long been used in the arterial or venous thrombosis especially as it pertains to native arterial, bypass conduits, or grafts where the thrombolytic is delivered into the thrombus via a multi-sidehole catheter via prolonged drip or a combination of pharmacologic thrombolytic and mechanical thrombolectomy.^{44–46} Many of these techniques have been implemented and augmented for use in the pulmonary artery.

The Prospective Single-Arm Multicenter Trial of Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism: SEATTLE II Study used a multi-sidehole drip catheter with

concomitant ultrasound waves (high frequency, low power 2.2 MHz; 0.5 Watt per element) to theoretically allow thrombolytics to further penetrate into the thrombus to perform CDT.^{35,47} The study succeeded in demonstrating that the CDT was able to significantly decrease thrombus burden, decrease right ventricular dilatation, and reduce pulmonary hypertension in the setting of both massive and submassive PE. Moreover, the risk of major bleed was decreased (10%), none of which was intracranial or fatal; interestingly patients with massive PE were still at higher risk of bleeding event than submassive PE (23 vs. 7%, respectively).³⁵ The reduction in right ventricular dilatation was assessed with CT at 48 hours.³⁵ The average dose of t-PA was 23.7 mg, whereas systemic alteplase is usually 100 mg infusion over 2 hours.^{32,35}

The SEATTLE II study followed the ULTIMA trial which also pertained to ultrasound-assisted CDT and was entitled Randomized Controlled Trial of Ultrasound-Assisted Catheter Directed Thrombolysis for Acute Intermediate-Risk Pulmonary Embolism. This multicenter study demonstrated statistically significant improvement in right ventricular dilatation versus heparin alone. There were no major bleeding events in either arm.⁴⁷

In the Pulmonary Embolism Response to Fragmentation, Embolectomy and Catheter Thrombolysis (PERFECT) registry, 100 patients were enrolled in a multicenter trial with both massive and submassive PE and were treated with either catheter-directed mechanical thrombectomy or pharmacomechanical thrombectomy with infusion of tissue plasminogen activator (t-PA). The study demonstrated clinical success of 85.7% for massive PE and 97.3% for submassive PE without any major procedure-related complications such as major bleeding.⁴⁸ This trial also called into question the necessity for auxiliary ultrasound in CDT, as it found no significant improvement in outcome with placing sidehole catheters versus ultrasound-aided catheters in the setting of CDT.

The ULTIMA, SEATTLE II, and PERFECT studies have all similarly demonstrated the applicability and effectiveness of catheter-directed therapies while simultaneously demonstrating significant reduction in major complications composed of

both systemic bleeding and stroke. While long-term evidence is certainly lacking, CDT in the setting of submassive and even massive PE demonstrates much promise.

Role of Pulmonary Embolism Response Team

The introduction of the PERT was largely born out of the controversial multifaceted treatment of both submassive and massive PE which is composed of multiple specialties who are able to quickly respond and convene to discuss treatment for patients with PTE. Specialties which may compose a PERT include interventional radiology, cardiology, vascular surgery, cardiothoracic surgery, pulmonary/critical care, hematology, and emergency medicine.⁴⁹ Provias et al first described the composition and role of PERT from Massachusetts General Hospital which was established in 2012. Once the PERT is activated via paging system, the on-call physician responds and initiates a web-based video conference with the aforementioned specialties resulting in a coherent plan based on multiple experts with various medical and technical skills.^{50,51} Many variations of this practice have been implemented and have demonstrated success. Rather than one individual such as an emergency room physician placing consultations for myriad services and working to formulate the best plan, all specialties are able to meet simultaneously and devise an appropriate plan based on the available literature and recommendations from each specialty. The readiness and rapidity of convening several subspecialized physician in a timely fashion, especially in the setting of massive PE, is essential because any delay in management may result in poor outcomes. Additionally, as new multimodality treatments for high-risk PE emerge, each subspecialty may offer the latest cutting edge technique and arrive to an immediate consensus tailored for the patient at hand.⁵¹ Moreover, Kabrhel et al documented underutilization of thrombolysis in the absence of a multidisciplinary team, with published literature demonstrating use of thrombolytics in only 2 to 9% of patients with hypotension versus up to 23% in their experience with a PERT without increase in hemorrhagic risk.⁴⁹ Sista et al corroborated the increase in thrombolysis, especially CDT rates, utilizing CDT in 36% of cases which they partially ascribed to the increased appreciation of severe PE and the inclusion of a multidisciplinary team, including an interventional radiologist.⁵² The end goal of the PERT is ultimately to reduce morbidity and mortality via the employment of a multimodality, multidisciplinary team who is able to tailor treatment specific to each patient above and beyond an oversimplified algorithm while employing the latest innovations in each field to treat this morbid disease.

Conclusion

PE is a major cause of morbidity and mortality. Its diagnosis is difficult to make clinically, making imaging central in importance. Imaging, laboratory values, and clinical parameters can be used to subclassify PE severity. A PERT is a relatively new concept, first started in 2013, but has gained

widespread acceptance. This multidisciplinary team makes timely and unified recommendations, thereby expediting, optimizing, and individualizing the care of these patients afflicted by PE.

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