

Diagnosis and management of acute pulmonary embolism

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ABSTRACT

Acute pulmonary embolism is a life-threatening diagnosis that can present with a multitude of nonspecific symptoms. Practitioners should maintain a high level of suspicion for acute pulmonary embolism in high-risk patients. Obtaining an appropriate diagnostic evaluation and choosing an adequate treatment method may reduce the morbidity and mortality of this devastating condition.

Keywords: pulmonary embolism, acute, anticoagulation, thromboembolism, deep venous thrombosis, saddle pulmonary emboli

Learning objectives

- Identify the clinical manifestations of PE.
- Develop a diagnostic evaluation strategy for patients with symptoms of PE.
- Create patient-specific treatment plans for PE.

Acute pulmonary embolism (PE) can be a life-threatening diagnosis that often presents with no overt signs or symptoms. In a review of clinical studies from 1939 to 2000, PE diagnosed at the time of autopsy ranged from 9% to 28%, with the exception of one study, which reported the incidence at 55%.¹ The CDC estimates that 300,000 to 600,000 people are affected annually by PE or deep venous thrombosis (DVT), although the precise number of cases is unknown.² Clinicians must approach suspected cases of PE with a heightened awareness and follow evidence-based recommendations for the diagnosis and treatment of acute PE. This article provides a general overview of the pathophysiology, clinical characteristics, diagnostic criteria, and noninvasive pharmacologic treatments for acute PE.

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PATHOPHYSIOLOGY

Acute PE caused by thromboemboli may be spontaneous and often originates in the deep venous system of the lower extremities, upper extremities, right side of the heart, or pelvis. Several factors increase patient susceptibility to thrombus formation. Virchow triad (stasis, vascular wall injury, and hypercoagulability) can be used to assess the patient's risk of developing thrombi.

Stasis is often considered the most prominent factor, which, in conjunction with either vessel damage or hypercoagulability, can lead to clot formation.³ Stasis can present in a variety of settings, including immobilization, chronic venous insufficiency, paresis secondary to stroke or other causes, and varicose veins.

Vascular damage results in the disruption of the vessel endothelium; causes include surgery, central venous catheterization or instrumentation, and trauma.

Hypercoagulability also can have multiple causes, including autoimmune diseases, malignancy, and genetic abnormalities of the clotting system such as impaired function of factor V Leiden, protein C and S deficiency, and the presence of lupus anticoagulant. The PIOPED II trial investigated diagnosing acute PE via multidetector CT angiography alone or combined with venous phase imaging of the pelvic and thigh veins.⁴ The researchers found that 92% of all patients with PE had one or more of the risk factors, including immobilization, surgery, malignancy, trauma, and central venous instrumentation.⁴

Pulmonary emboli are divided into two categories. *Massive PE* presents with hypotension characterized by either systolic BP less than 90 mm Hg or a reduction in systolic BP of over 40 mm Hg for more than 15 minutes. *Submassive PE* includes all PE that do not meet the criteria for massive PE. Anatomically, PEs that are identified at the bifurcation of the main pulmonary artery into the right and left pulmonary arteries are defined as saddle PEs. In a recent study, 27 of 297 patients (9.1%) were diagnosed with saddle PE with a 59.3% rate of major adverse events, including shock, intubation, mortality, fibrinolysis, and thrombectomy.⁵

CLINICAL PRESENTATION

Because the signs and symptoms associated with PE are nonspecific, the condition can be a diagnostic challenge.

Key points

- Acute PE affects 300,000 to 600,000 people in the United States annually.
- Clinicians should have a high suspicion for PE in high-risk patients.
- Signs and symptoms of acute PE are often nonspecific.
- Anticoagulation is the primary treatment for acute PE. Invasive interventions may be needed for massive PEs.

Many patients present atypically or have none of the preceding symptoms but are diagnosed postmortem. Because of the risk of sudden death from acute PE, clinicians should have a heightened awareness of PE when assessing patients. The most common signs and symptoms of PE in the PIOPED II study included dyspnea (73%), tachypnea (54%), pleuritic pain (44%), calf or thigh pain (44%), calf or thigh swelling (41%), cough (34%), orthopnea requiring more than two pillows (28%), tachycardia (24%), wheezing (21%), crackles (18%), decreased breath sounds (17%), accentuated heart sounds (15%), and jugular venous distension (14%).⁴

In a similar trial, 756 (94%) of 800 trial participants reported at least one of the following symptoms: sudden-onset dyspnea (78%), chest pain (39%), fainting or syncope (22%), and hemoptysis (5%). Of these patients, when the diagnosis of PE was delayed, the initial presenting symptom was sudden-onset dyspnea. Interestingly, in this evaluation of patients, only 3 of 800 patients (0.4%) complained of orthopnea; in the PIOPED II study, orthopnea was a presenting symptom in 28% of patients. The researchers believe that this stark difference lies in variability in the criteria used to describe orthopnea.

Also noteworthy is the presence of unilateral painful swelling of an upper or lower extremity in 38% of patients.⁶ If the diagnosis of PE is associated with DVT, signs and symptoms in the affected extremity will include erythema, edema, tenderness, and a palpable cord. Patients with concomitant right heart failure may present with increased jugular venous pressure and a right-sided S_3 .

DIAGNOSTIC EVALUATION

After assessing the patient's presenting symptoms and physical examination, the next step is to choose diagnostic imaging. Several clinical prediction models can be used to risk-stratify patients. The Pulmonary Embolism Rule Out Criteria (PERC) score, Wells Score, and Revised Geneva Score are three validated clinical decision rules that can help clinicians determine the need for imaging. These prediction models can be used in conjunction with clinical evaluation and suspicion of PE to guide diagnostics, but their limitations should be recognized. Those limitations include the possibility of not identifying very-low-risk

patients and variability between providers of identifying high-risk patients.

No definitive *laboratory* workup exists for patients suspected of having PE, further adding to the diagnostic challenge. Included in these are leukocytosis, elevated erythrocyte sedimentation rate, elevated lactate dehydrogenase, B-type natriuretic peptide, and troponin. An abnormality in any one of these tests will not specifically diagnose a PE and can be attributed to a variety of other medical comorbidities. Conversely, these values may be within normal limits in a patient with a PE. The level of D-dimer, a fibrin split product formed as a result of fibrin degradation, can be measured through a serum sample. The D-dimer level is best used as a negative predictive value with good sensitivity. In contrast, a positive D-dimer yields a poor positive predictive value with poor specificity. An arterial blood gas (ABG) analysis should be obtained to assess for oxygenation and to determine the possible need for advanced ventilation techniques.

An ECG is an integral part of the initial evaluation of patients with suspected PE. The ECG is useful in evaluating for myocardial infarction or atrial fibrillation, as well as characterizing right ventricular (RV) function and screening for right-sided heart failure. Normal sinus

Although ECG should be a part of the diagnostic evaluation, it likely will not confirm the diagnosis of PE.

rhythm was the most common rhythm observed in patients with PE evaluated in the ED, according to a retrospective cohort review evaluating the ECG results of 49 ED patients with PE and 49 controls (67.3% versus 68.6%). The most common abnormalities observed in the study and control groups were sinus tachycardia (18.8% versus 11.8%), incomplete right bundle branch block (4.2% versus 0.0%), complete right bundle branch block (4.2% versus 6.0%), and S1Q3T3 pattern (2.1% versus 0%).⁷ Other findings included atrial fibrillation, atrial flutter, left atrial enlargement, ST-segment abnormalities, and T-wave abnormalities.⁷ An important limitation of ECG in the evaluation of patients suspected of having PE is that ECG is neither a sensitive nor a specific study. Although ECG should be a part of the diagnostic evaluation, it likely will not confirm the diagnosis of PE. **Figure 1** shows an example of an S1Q3T3 pattern (prominent S wave in lead I, a Q wave in lead III and an inverted T wave in lead III).

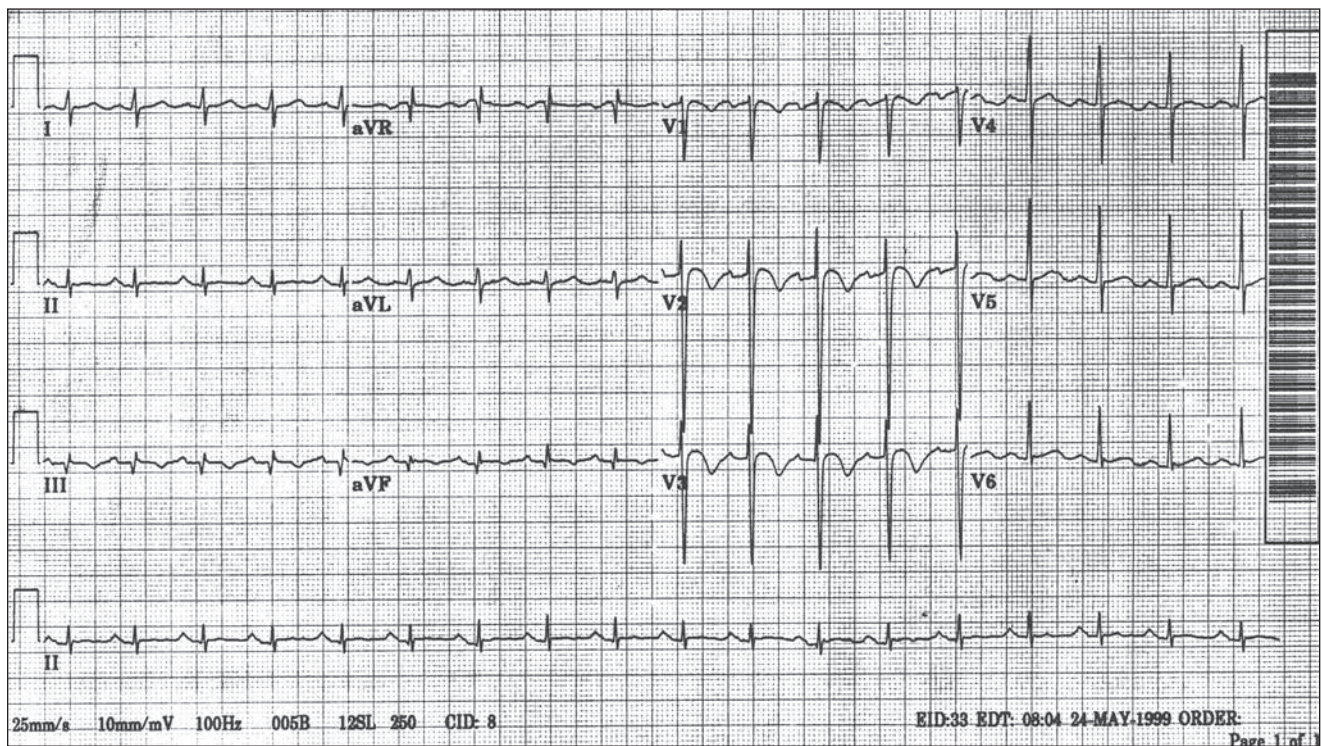


FIGURE 1. ECG displaying S1Q3T3 pattern

Chest radiographs may confirm or disprove varying differentials in acute PE but are not sensitive or specific to confirm PE. Several findings may be associated with acute PE, including pulmonary infiltrates, atelectasis, diaphragmatic elevation, pleural effusion, Westermark sign, and Hampton hump. The most useful finding, however, may be a normal-appearing chest radiograph in a patient with acute dyspnea or chest pain. This gives clinicians the ability to exclude other differential diagnoses in the evaluation of a patient presenting with signs and symptoms suggestive of acute PE.⁸

Spiral CT with IV contrast is one of the most widely used imaging studies in the evaluation of acute PE. Spiral CT is readily available and can be performed rapidly, so it is used frequently to diagnose acute PE. However, this test cannot be used in patients with IV contrast media allergy and should be used with caution in patients with renal impairment. Pulmonary artery filling defects signify an area of thrombus. Like pulmonary angiography, CT scanning can provide direct visualization of pulmonary emboli but at a more cost-effective value. CT also can distinguish the embolus as acute or chronic based on its location in the vessel lumen, degree of vessel occlusion, evidence of recanalization, and presence of an arterial web (remnants of an old organized thrombus). The embolus can be described as peripheral or central based on the results of CT scanning. CT also can often confirm other causes for the patient's presenting symptoms,

including nodules, masses, areas of consolidation due to infection, or pleural effusion. Multidetector CT scanning produces multiple slices of the scan simultaneously, allowing for more rapid completion of the CT scan with shorter duration of breath holding.

Ventilation-perfusion (\dot{V}/\dot{Q}) scanning can be used in patients with renal impairment or IV contrast media allergy who cannot tolerate CT scanning. Radioisotopes are used to assess air flow in the lungs (ventilation) and blood supply to the lungs (perfusion). Areas of adequate ventilation but poor perfusion are suspicious for thrombus. \dot{V}/\dot{Q} scan results are reported in probability: A patient with a high clinical suspicion of PE and a high-probability \dot{V}/\dot{Q} scan has a high likelihood of PE. A patient with a low clinical suspicion of PE and a low-probability \dot{V}/\dot{Q} scan has a low likelihood of PE. If the \dot{V}/\dot{Q} scan result is intermediate, the results should be combined with the clinical picture, although making a definitive diagnosis of PE or eliminating the diagnosis of PE is challenging.

Pulmonary angiography is the gold-standard test for diagnosing PE, although it is used infrequently because of its high cost and invasive nature (Figure 2). Subsets of pulmonary angiography, each with their own risks, benefits, limitations, and contraindications, include digital subtraction pulmonary angiography and pulmonary CT angiography. In digital subtraction pulmonary angiography, a catheter is inserted via a distal vein and

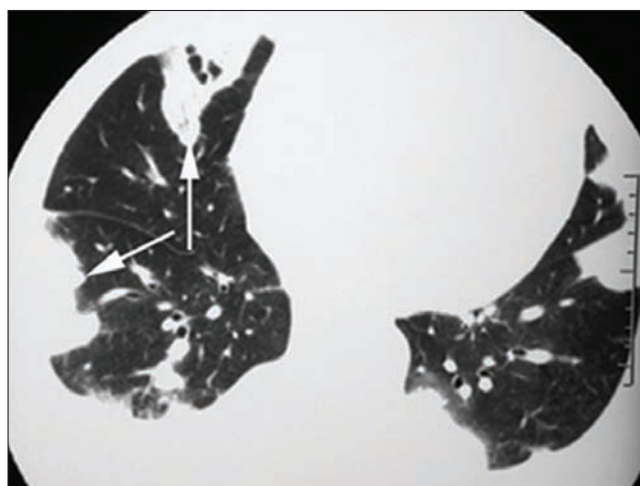


FIGURE 2. Pulmonary infarction caused by PE displayed on pulmonary angiography CT image.

threaded through the right side of the heart into the pulmonary artery, where contrast media can be used to produce images of the pulmonary vasculature. Digital subtraction angiography can accurately record pulmonary artery pressures, and can be used to perform embolectomy or embolization of arterial venous malformations. Risks associated with this intervention include cardiac arrhythmias, elevated pulmonary artery pressure, and cor pulmonale.

Echocardiography to assess RV function is an important supplemental test in assessing the patient's overall prognosis and comorbidities. Common findings on echocardiogram in patients with PE include increased RV size, decreased RV function, tricuspid regurgitation, RV thrombus, and regional wall abnormalities.

Venous Doppler ultrasound may be used to assess for thrombi in the extremities. This noninvasive test may be useful in patients who cannot undergo studies with contrast media. Diagnosis of a venous thrombosis can give practitioners evidence for starting anticoagulation early and can assist in determining the cause of the PE. Ultrasound also can help determine if other means of aggressive treatment are warranted, including inferior vena cava (IVC) filter placement, thrombectomy, or fibrinolysis.

TREATMENT

In an acute setting, the initial treatment of PE focuses on stabilizing the patient. Provide supplemental oxygen to ensure adequate oxygenation, and monitor pulse oximetry continually, with a reasonable goal of 92%.⁹ In severe cases of respiratory compromise, patients may require more invasive management of their oxygen capacity with either noninvasive bilevel positive airway pressure ventilation or intubation and mechanical ventilation. Assess the patient's vital signs and establish cardiac telemetry monitoring. In the event of hemodynamic compromise,

initiate IV fluids. Proceed with caution when replacing fluid volume as RV stress and dilation from increased pulmonary vascular resistance can lead to fluid overload. If adequate hemodynamic support cannot be attained with appropriate IV fluid resuscitation, vasopressors including norepinephrine, dopamine, or epinephrine may be considered.

The mainstay therapy for PE is anticoagulation. Treatment options include unfractionated heparin, low-molecular-weight heparin (LMWH), fondaparinux, warfarin, and rivaroxaban. The American College of Chest Physicians (ACCP) suggests LMWH as the initial anticoagulant; however, treatment should be individualized based on the patient's characteristics and comorbidities. The ACCP describes the phases of anticoagulation as:

- *initial (0 to about 7 days)*, during which parenteral heparin, LMWH, rivaroxaban, or fondaparinux is given. A vitamin K antagonist (warfarin) also will be started in this time frame if the goal is to transition the patient from IV heparin, LMWH, or fondaparinux to an oral agent.
- *long-term (about 7 days to about 3 months)*, during which the patient is prescribed a vitamin K antagonist or other agent such as a LMWH, fondaparinux, or rivaroxaban.
- *extended (from about 3 months on)*, during which treatment is the same as the long-term phase described above. Which patients will need extended therapy depends on multiple factors, including risk factors, recurrence of thrombosis, and comorbidities.¹⁰

Unfractionated heparin enhances the activity of anti-thrombin III, an intrinsically occurring anticoagulant that inhibits several activated coagulation factors, including factor IIa, factor VIIa, factor IXa, and factor Xa. Heparin is administered IV and should be initiated with an 80 unit/kg bolus followed by an infusion rate of 18 units/kg/hour. This rate should be monitored with partial thromboplastin time (PTT) every 4 hours to assess for appropriate therapeutic levels. Levels that do not fall in the therapeutic range may significantly increase patient morbidity and mortality. A benefit of unfractionated heparin is that it can be used in patients with renal impairment, and its short peak plasma time and half-life mean that it can be more rapidly reversed if necessary. Also, therapeutic levels can be assessed easily with PTT level. Unfractionated heparin often is the treatment of choice in patients who are hemodynamically unstable. Risks associated with unfractionated heparin include heparin-induced thrombocytopenia and hemorrhage.

LMWHs including enoxaparin, dalteparin, and tinzaparin, which inhibit factor Xa, are the treatment of choice for hemodynamically stable patients.¹⁰ These drugs are administered subcutaneously once or twice daily via weight-based dosing and do not require PTT monitoring. LMWHs

are not an appropriate choice in patients who are morbidly obese, are extremely low weight, renal insufficiency, or are pregnant. According to the ACCP, the last dose of LMWH should be given 24 hours before a procedure or surgery to reduce the risk of bleeding.¹⁰ In patients who require fibrinolysis, LMWH use limits the ability to perform this procedure in a timely manner.

Fondaparinux, a synthetically produced agent, inhibits factor Xa without affecting thrombin and is also administered once daily. This drug also is contraindicated in patients with severe renal impairment.

Warfarin is an oral vitamin K antagonist that antagonizes the vitamin K clotting factors (II, VII, IX, and X). Warfarin requires frequent monitoring via prothrombin time (PT) and internationalized ratio (INR). Although warfarin can be initiated simultaneously with LMWH or UFH, it should not be used as monotherapy before starting other anticoagulants because it can increase the patient's risk of recurrent PE or DVT. For warfarin to be effective, current clotting factors should be cleared by the bloodstream before warfarin attains its full effectiveness. This process can take 36 to 72 hours, so warfarin and other anticoagulants should overlap for 5 days or until the patient's INR is therapeutic for 24 hours. The goal of therapy is to maintain a PT/INR between 2 and 3 for the best risk-to-benefit profile.

Rivaroxaban, another oral anticoagulant, is a factor Xa inhibitor that subsequently inhibits platelet activation. Rivaroxaban does not require overlap or bridging therapy with heparin or enoxaparin when initially begun. Unlike patients on warfarin, those on rivaroxaban do not require monitoring with PT/INR. As a newly approved agent, rivaroxaban is significantly more expensive than warfarin.

In its guidelines on antithrombotic therapy, the ACCP concludes that a select group of patients may benefit from fibrinolysis.¹⁰ The guidelines recommend fibrinolytic therapy for patients with acute PE, hypotension (systolic BP less than 90 mm Hg or a documented drop in systolic BP of more than 40 mm Hg), and low risk of bleeding. Fibrinolytic therapy is not recommended for patients with acute PE who are not hypotensive, but is recommended in select patients with acute PE and a low risk of bleeding who are not hypotensive but at high risk of developing hypotension. For all patients receiving fibrinolytic therapy, the guidelines recommend short infusion times (for example, 2 hours) through a peripheral vein rather than a pulmonary artery catheter, regardless of the choice of medication.¹⁰

Invasive techniques may be needed for unstable patients diagnosed with massive PE. The specifics of each technique are beyond the scope of this article and will only be briefly mentioned. Fibrinolysis, catheter-directed therapies, and surgical embolectomy may be used to reverse the obstruction of the pulmonary artery in such

cases. The risk-benefit profile should be weighed in each case and the techniques should be performed by highly skilled practitioners. Placement of an IVC filter for prevention of future clots often is reserved for patients who are at high risk of clot recurrence and have contraindications to anticoagulation.

CONCLUSION

In an acute or ambulatory care setting, providers will likely be faced with patients who present with signs and symptoms suspicious of PE. Due to the poor specificity of these presenting cases, providers must be vigilant about suspecting PE in patients at increased risk. Prompt triage, imaging, and treatment can improve morbidity and mortality significantly. Discovering the underlying pathology can assist providers in determining the length of therapy and need for continued treatment and prevention. Recent pharmaceutical and technological advances have added to the treatments available for PE and will continue to evolve as scientific research continues, with a goal of further improving identification, diagnosis, and treatment of acute PE. **JAAPA**

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