This chapter discusses the diagnosis and treatment of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), from the perspective of the emergency physician and provides a functional resource for the evaluation and treatment of VTE in the emergency department (ED).

**Pathophysiology of Thrombosis**

VTE forms as a result of excessive fibrin production from the action of thrombin on fibrinogen. Factors that enhance fibrinogen synthesis and promote its catalysis to fibrin include systemic inflammation, traumatic or immune-related vascular trauma, inherited thrombophilias and hemoglobinopathies, cancer, pregnancy, and sluggish blood flow. Venous injury, slow blood flow, and hypercoagulability are the cardinal inciting mechanisms for VTE, and most clinical decision rules for VTE incorporate these factors. In addition, each year of life independently increases the likelihood of imbalanced clot formation.2

**DEEP VEIN THROMBOSIS**

DVT represents a disease spectrum ranging from a minimally symptomatic isolated calf vein thrombosis to a limb-threatening iliofemoral venous obstruction. Although the true incidence is unknown in the ED population, DVT accounts for approximately 600,000 hospital admissions per year.

**Anatomy**

The venous anatomy of the lower extremity is divided into the deep and superficial systems. The superficial venous system consists primarily of the greater and short saphenous veins and the perforating veins. The deep venous system includes the anterior tibial, posterior tibial, and peroneal veins, collectively called the calf veins. The calf veins join together at the knee to form the popliteal vein, which extends proximally and becomes the femoral vein at the adductor canal. The femoral vein sometimes is called the superficial femoral vein, and this nomenclature contributes to confusion in interpreting radiology reports. A clot in the superficial femoral vein is indeed a DVT and should be treated as such. The femoral vein joins with the deep femoral vein to form the common femoral vein, which subsequently becomes the external iliac vein at the inguinal ligament. Proximal DVT refers to a clot in the popliteal vein or higher, whereas distal clot refers to an isolated calf vein thrombosis.

**Clinical Presentation**

The initial symptoms of DVT can be as subtle and nonspecific as a mild cramping sensation or sense of fullness in the calf, without objective swelling, and may be difficult to differentiate clinically from myriad other, unrelated disorders (Box 88-1). Many patients use the term charley horse to describe the sensation of an early DVT. It is precisely at this early stage, however, that DVT can be treated most effectively to minimize the potential morbidity and mortality associated with VTE. Because the left iliac vein is vulnerable to compression by the left iliac artery, leg DVT occurs with a slightly higher frequency in the left leg compared with the right; bilateral leg DVT is found in fewer than 10% of ED patients diagnosed with DVT. Likewise, the clinical signs of DVT vary and may include unilateral swelling, edema, erythema, and warmth of the affected extremity; tenderness to palpation along the distribution of the deep venous system; dilation of superficial collateral veins; and a palpable venous “cord.” The classic Homan’s sign (pain felt in the calf or posterior aspect of the knee on passive dorsiflexion of the foot while the knee is extended) is insensitive and nonspecific for DVT and has no role in clinical assessment of the patient. Upper extremity DVT refers to a thrombosis in the axillary vein and causes arm swelling on the same side as an indwelling catheter or recent intravenous infusion site. In the absence of a catheter, the most frequent location of arm DVT is on the dominant hand side. Patients frequently note that their rings become tight as an early sign of DVT.

**Diagnosis**

Diagnosis of DVT and PE starts with an estimation of the pretest probability (PTP). This estimation may be accomplished either by the clinical gestalt of an experienced practitioner or in conjunction with a clinical decision tool, such as that derived and validated by Wells and colleagues (Table 88-1). Patients with a low PTP can have DVT excluded with a normal quantitative D-dimer.

**Laboratory Evaluation**

The D-dimer is a protein derived from enzymatic breakdown of cross-linked fibrin, and an elevated plasma concentration indicates the presence of a clot formed somewhere in the body within the previous 72 hours. D-dimer concentration may be elevated with any condition that causes fibrin deposition, including malignancy, pregnancy, advanced age, prolonged bed rest, recent surgery, infection, inflammation, new indwelling catheters, stroke, and myocardial infarction. D-dimer concentration is proportionate to
Box 88-1 Differential Diagnosis of Deep Vein Thrombosis

- Muscle strain, hematoma
- Popliteal (Baker’s) cyst
- Lymphedema
- Cellulitis
- Vasculitis
- Fracture
- Superficial thrombophlebitis
- Chronic venous insufficiency
- Proximal venous compression (e.g., tumor, gravid uterus)
- Congestive heart failure (swelling usually bilateral)
- Hypoalbuminemia (swelling usually bilateral)

Table 88-1 Clinical Model for Estimating the Pretest Probability of Deep Vein Thrombosis

<table>
<thead>
<tr>
<th>CLINICAL FEATURE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treated within the previous 6 mo or currently receiving palliative treatment)</td>
<td>1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>1</td>
</tr>
<tr>
<td>Recently bedridden for ≥23 days or major surgery within 12 wk requiring general or regional anesthesia</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>1</td>
</tr>
<tr>
<td>Entire leg swollen</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling at least 3 cm larger than on the asymptomatic side (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>1</td>
</tr>
<tr>
<td>Previously documented deep vein thrombosis</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as deep vein thrombosis</td>
<td>-2</td>
</tr>
</tbody>
</table>


the size of the clot and decreases as the clot matures, so the test is less sensitive with small or chronic clots.

The D-dimer protein can be measured in plasma with several techniques, and the differences in D-dimer assay methodology greatly affect diagnostic accuracy. All commercially available assays share the concept of antibody capture followed by detection. The U.S. Food and Drug Administration (FDA) has approved over 75 different D-dimer assays for clinical use. One way to categorize the D-dimer assay format is as quantitative or qualitative (which includes semiquantitative assays). The two most common detection methods for quantitative assays are the enzyme-linked immunosorbent assay (ELISA) and the immunoturbidimetric technique. Because of variable properties of the test capture antibody and differences in test standardization, their cutoffs for the upper limit of normal vary for different quantitative D-dimer assays. For many assays, less than 500 ng/mL (or 1000 fibrinogen equivalent units (IFEUs)) is a negative test result and carries an 88 to 97% diagnostic sensitivity for symptomatic proximal DVT and 83 to 94% sensitivity for calf DVT or asymptomatic proximal DVT. A negative quantitative D-dimer assayed by the ELISA or immunoturbidimetric technique is sensitive enough to exclude the diagnosis of DVT in patients at low or moderate risk without further evaluation.

Qualitative D-dimer assays include whole-blood assays done on single-use cartridges that resemble home pregnancy tests and semiquantitative, manual latex fixation assays that use test cards containing several wells for plasma in various folds of dilution (note that latex fixation assays have lower sensitivity than automated latex agglutination assays). Because qualitative D-dimer assays have a diagnostic sensitivity of only 78 to 93% for symptomatic proximal DVT, a negative qualitative D-dimer excludes proximal DVT only in patients deemed to have a low clinical possibility by the physician.

Radiographic Evaluation

DVT evaluation is by a combination of D-dimer testing and duplex venous ultrasonography.

Venous duplex ultrasonography, performed by a certified sonographer and interpreted by a board-certified radiologist or similarly credentialed expert, has a sensitivity and specificity of approximately 95% for proximal DVT and is the diagnostic test of choice in most centers. It is important for emergency physicians to know the technique of the examination. Most radiology departments use the three point sequence (common and superficial femoral veins and popliteal vein, excluding the calf and saphenous veins). Although management of calf vein and saphenous clots remains controversial, the diagnostic sensitivity of a single venous ultrasound for the exclusion of a clot at risk of progressing to a proximal DVT is increased significantly by including the calf and saphenous veins. A patient at low risk may have the diagnosis of DVT effectively excluded by a negative three-point venous duplex ultrasound. However, for patients at higher than low risk, a single negative three-point ultrasound is inadequate as a sole method to exclude DVT, whereas a single normal whole-leg ultrasound (including normal calf and saphenous veins) is sufficient to exclude DVT with any PTP. A negative three-point ultrasound together with a negative quantitative D-dimer is sufficient to exclude DVT with any PTP. In a patient with a high PTP in whom the D-dimer is elevated (or not performed), a negative three-point ultrasound at the index visit should be followed by a repeat ultrasound in 2 to 7 days, which if negative is sufficient to exclude PE. An expertly performed and interpreted positive ultrasound is sufficient to confirm the diagnosis of DVT. Ultrasound cannot be used to rule out iliac or pelvic vein thrombosis.

Many emergency physicians use bedside ED ultrasound in their daily practice, but at present the data are conflicting as to whether emergency physician–performed ultrasound (EPPU) for lower-extremity DVT has adequate diagnostic accuracy. Follow-up with formal diagnostic duplex ultrasound seems reasonable.

Indirect computed tomography (CT) venography (CTV) is not a primary imaging modality for DVT but may be performed in conjunction with CT pulmonary angiography (CTPA) of the chest during the evaluation of suggested PE. Adding CTV to CTPA provides an incremental increase in the sensitivity for VTE, identifying DVT in approximately 2% of patients in whom the CTPA is read as negative for PE but at the expense of significant additional radiation exposure to the pelvis and lower extremities.

Interobserver agreement among radiologists interpreting CTV appears to be less than that for the CTPA portion of the study, possibly because of poor venous opacification in many cases. At this time, routine use of CTV is not necessary when CTPA is performed. Magnetic resonance imaging (MRI) can evaluate the pelvic vasculature and vena cava, which is not possible with ultrasound. MRI does not produce ionizing radiation, making it an attractive option for pregnant patients but limited by cost, availability, patient size, and tolerance to close quarters. MRI is not a primary diagnostic test for patients with suspected DVT.
Treatment

When the diagnosis of DVT has been established, anticoagulation should be initiated, unless contraindicated, with a low-molecular-weight heparin (e.g., enoxaparin 1 mg/kg subcutaneously [SQ] every 12 hours), fondaparinux (5-10 mg SQ once daily, depending on patient weight), or unfractionated heparin (70-80 units/kg intravenous bolus followed by 17-18 units/kg/hr infusion), assuming normal renal function. The treatments work equally well and are safe in the absence of contraindications to anticoagulation. Treatment requires transition to oral anticoagulation with warfarin for at least 3 months. Hospital admission is obviated by initiation of outpatient low-molecular-weight heparin or fondaparinux therapy in the ED or ED observation unit, followed by self-administration at home (with appropriate patient teaching) or home administration by a visiting nurse. If admission is contemplated, after heparin has been given, the first dose of warfarin can be given in the ED to help reduce overall length of stay in the inpatient unit. Patients should be encouraged to ambulate after anticoagulation for DVT. Bed rest promotes DVT extension, increases the risk of embolization, and ultimately predisposes the patient to the postphlebitic syndrome. Patients who cannot be given anticoagulants or who have a recurrence of VTE despite anticoagulation therapy should be considered for vena caval intervention.

Superficial Leg Thrombophlebitis

Based on the results of a large randomized controlled trial, patients with a clot in the greater saphenous vein that extends above the knee are at risk for progression to DVT via the saphenous-femoral vein junction and may require an abbreviated course of anticoagulation. The published evidence suggests that saphenous vein thrombophlebitis can adequately be treated with nonsteroidal anti-inflammatory drugs, heat, and graded compression stockings (fitted to exert 30-40 mm Hg of pressure at the ankle) followed by a mandatory repeat ultrasound in 2 to 5 days. If the clot is extending, then anticoagulation is indicated. The duration of anticoagulation treatment remains uncertain, but full-dose low molecular weight heparin or fondaparinux for 10 days followed by repeat ultrasound seems reasonable.

Isolated Calf Vein Thrombosis

The optimal management strategy for thromboses of the tibial or peroneal veins remains controversial. Approximately 25% of isolated calf vein thromboses propagate proximally, prompting recommendations for treatment with anticoagulation as for proximal leg DVT. However, most of these data were from hospitalized or postoperative patients with a higher risk of propagation than ambulatory patients. For tibial or peroneal vein thrombosis in an otherwise healthy, ambulatory patient with no other indication for anticoagulation, I recommend antiplatelet therapy with aspirin (325 mg of enteric-coated acetylsalicylic acid per day) and close follow-up with repeat duplex ultrasound scan at 2 to 5 days to evaluate for clot propagation.

Phlegmasia Cerulea Dolens (Painful Blue Leg)

Massive iliofemoral occlusion results in swelling of the entire leg with extensive vascular congestion and associated venous ischemia, producing a painful, cyanotic extremity. There may be an associated arterial spasm resulting in phlegmasia alba dolens (painful white leg or milk leg), which may mimic an acute arterial occlusion. Prompt consultation with a vascular surgeon should be obtained because patients with phlegmasia cerulea dolens may require emergent thrombectomy. If timely consultation is not possible, early thrombolytic therapy may be a limb-salvaging procedure in the absence of contraindications. One strategy is to infuse alteplase (1 mg/min to a total dose of 50 mg) via a peripheral intravenous catheter placed distal to the thrombus.

Upper Extremity Venous Thromboses

DVTs of the upper extremity have become more common in association with increased use of indwelling venous catheters and wires for electronic cardiac devices. Upper extremity DVT can cause PE, and all patients with DVT above the elbow require definitive treatment. About one half of all upper extremity DVTs are associated with an indwelling catheter. Upper extremity DVT is diagnosed and excluded with venous ultrasound. The use of D-dimer testing in this population is inadequately studied.

In the absence of pain or infection, catheter-associated DVT does not automatically warrant catheter removal if the catheter serves a current, vital purpose. However, these patients should receive anticoagulation if they do not have contraindications. The duration of anticoagulation after catheter removal for DVT remains controversial, but most published guidelines recommend at least 3 months.

The rate of PE from axillary vein DVT appears to be similar to that for femoral vein DVT, although many experts believe the severity of PE tends to be less with upper extremity DVT.

Isolated upper extremity DVT, especially axillary-subclavian vein thrombosis, also can be seen in relatively young, active, otherwise healthy patients. Although standard DVT risk factors, such as hypercoagulable state or malignancy, may be present, most of these patients have no apparent predisposing condition. Some patients with arm DVT have inherited or acquired subclavian vein stenosis or extrinsic compression. It is not known whether strenuous, repetitive activity (“effort DVT”) causes the DVT by exacerbating the anatomic compromise through movement of the arm or hypertrophy of adjacent muscles, or whether effort simply brings out the symptoms of an otherwise occult upper extremity DVT. Optimal treatment of isolated brachial vein thrombosis, often the result of a recent intravenous infusion (“infusion phlebitis”), also remains uncertain. No study has demonstrated clear benefit for systemic anticoagulation, but a good strategy is to use the same management plan as described for superficial thrombophlebitis of the leg.

Complications

Although the most feared complication of DVT is fatal PE, DVT damages venous valves, causing venous insufficiency. Venous insufficiency, in turn, manifests as a spectrum ranging from painless varicosities to severe postphlebitic syndrome, which can cause unremitting pain and swelling, varicose veins, skin changes, and nonhealing ulcers. Figure 88-1 shows the leg of a construction worker with a femoral DVT that produces swelling on the job, impairing his ability to work.

PULMONARY EMBOLISM

PE results from a clot that formed hours, days, or weeks earlier in the deep veins and dislodged, traveled through the venous system, and traversed the right ventricle into the pulmonary vasculature. What the patient experiences during this process varies widely, ranging from no symptom to cardiovascular collapse. No one knows exactly how many patients pass through the ED with PE because there is no reliable way of identifying missed cases. Assuming that ED populations have a risk for PE somewhere between that of hospitalized patients (who are at high risk for PE)
and outpatients (who are at lower risk), approximately 1 in every 500 to 1000 ED patients has PE. About 8% of ED patients with PE die within 30 days, even when PE is promptly diagnosed and treated.\textsuperscript{10}

**Pathophysiology of Pulmonary Vascular Occlusion**

The pulmonary vascular tree normally has a low resistance to fluid flow, and young persons without cardiopulmonary disease (e.g., congestive heart failure, chronic obstructive lung disease, advanced sarcoidosis, pulmonary fibrosis, scleroderma, and primary pulmonary hypertension) can tolerate at least 30% obstruction, often with minimal symptoms or signs. Pulmonary infarction is a more dramatic exception. Although a segmental pulmonary artery constitutes only about one sixteenth of the entire pulmonary vascular circuit, a clot lodged deeply in a segmental artery can obstruct blood flow to a sufficient degree to cause tissue necrosis. The patient can feel focal, sharp, pleuritic pain and exhibit a splinting response to breathing. Over several days the infarcted segment becomes consolidated on chest radiography and exudes a pleural effusion, manifesting an intense underlying inflammatory process. Chest pain from noninfarcting PE can be highly variable and vague. About 30% of patients with definite PE have no perception of chest pain.

In contrast, if asked in a detailed and structured way, about 90% of patients with noninfarcting emboli admit to the sensation of dyspnea. The dyspnea may be constant and oppressive or may be intermittent and perceived only with exertion, possibly because of an exercise-induced increase in pulmonary vascular resistance. Rest dyspnea seems to be the clinical manifestation of distorted and irregular blood flow within the lung, referred to as ventilation-perfusion inequality. With each breath a patient with PE wastes ventilation because of increased alveolar dead space (alveoli that are ventilated but not perfused). A lodged clot can redistribute blood flow to areas of the lung with already high perfusion relative to ventilation and therefore cause more blue blood to pass through the lung without being fully oxygenated. This venous admixture is probably the primary cause of hypoxemia with PE and the increased alveolar-arterial oxygen difference (the A-a gradient). About 15% of patients with PE have a normal A-a gradient of oxygen (with normal defined as age in years/4 + 4), however, and the A-a gradient is abnormally high in most patients who are evaluated for PE but ultimately found to not have PE. In a multicenter registry of 348 patients with PE, 37 (10.6%) had a pulse oximetry reading of 100% at the time of arrival to the ED, while breathing room air. Despite its shortcomings as a single diagnostic step, the presence of hypoxemia (pulse oximetry <95%, breathing room air) that cannot be explained by a known disease process increases the probability of PE. Conversely, a normal oxygen saturation can be used only when considered together with multiple other clinical features and should not alone or independently be used to forego testing for PE (Box 88-2).\textsuperscript{13,19} In addition, when PE is diagnosed, the severity of hypoxemia represents a powerful independent predictor of patient outcome.

PE also causes highly variable effects on vital signs. In the ED, about half of all patients with PE have a heart rate greater than 100 beats/min.\textsuperscript{11} Tachycardia from PE probably results from impaired left ventricular filling, leading to a pathophysiologic process that parallels that of hemorrhagic shock. In one study, the probability of PE was not reduced in patients who normalized any vital sign while in the ED.\textsuperscript{12} When PE obstructs more than 50% of the vasculature, it usually causes an acute increase in right ventricular pressure. In contrast to the left ventricle, the right ventricle does not show an elastic response to acutely increased afterload; it quickly dilates, showing echocardiographic hypokinesis early in the course. In about 40% of cases, the right ventricular damage persists for at least 6 months and probably longer. Arterial hypertension represents an ominous hemodynamic consequence of PE; it occurs in only about 10% of patients but signifies a fourfold increase in risk of death compared with normotensive patients.\textsuperscript{20} In its most extreme form, PE can obstruct the right ventricular outflow entirely, either by casting the entire pulmonary vascular tree (Fig. 88-2) or by acutely occluding the main pulmonary artery. Pulseless electrical activity (PEA) is the most common electrocardiogram (ECG) result from obstructive PE. The survival rate for cardiac arrest from PE is abysmally low, even if the arrest is witnessed and heroic treatment is initiated.

**Clinical Presentation**

Table 88-2 presents a listing of factors that significantly increase the probability of PE in the ED population.\textsuperscript{11} As is the case for cardiac risk factors in the evaluation of acute chest pain, variables that increase the probability of PE in epidemiologic studies are not useful for individual ED patients with signs and symptoms suggesting PE. From an epidemiologic standpoint, people who smoke are at a significantly higher risk for venous clots than are people who do not smoke. However, in the ED, smoking by a given patient does not seem to increase that person’s risk for PE over that of a nonsmoker with an otherwise identical clinical presentation. It is possible that smokers are simply more likely to have other lung problems that manifest a clinical presentation similar to PE. As many as 50% of patients diagnosed with PE have no apparent...
clinical risk factors for VTE, but testing for genetic thrombophilia has no value in the ED setting.\textsuperscript{13}

Virtually any ED visit related to weakness, shortness of breath, dizziness or syncope, pain, extremity discomfort, or nonspecific malaise or functional deterioration could represent a potential PE; however, this does not mean that every patient with one of these symptoms should be worked up for PE, and these symptoms should be considered in the context of the entire clinical picture. A patient with PE typically presents with 2 to 3 days of shortness of breath, now worsened enough to seek care. The chest pain usually is vaguely described. A few patients have focal pleuritic chest pain, but many say nonspecifically that their chest hurts with breathing, usually on the lateral aspects. Purely substernal chest pain is a rare presentation for PE and in general suggests a cardiac or other origin. The presence or absence of sudden onset of symptoms neither increases nor decreases the probability of PE.\textsuperscript{11} When the antemortem histories of patients who die suddenly and unexpectedly from PE are reconstructed by interviewing family and examining medical records, most have complained of nagging symptoms for weeks before collapse, and 40% already had seen a physician for care.\textsuperscript{14} PE with lung infarction can result in a clinical picture that is similar to lobar pneumonia, including focal chest pain, fever, and unilateral rales on auscultation. However, a temperature greater than 101.5° F suggests infection rather than infarction. An occasional clue to pulmonary infarction is the onset of pain and blood-red hemoptysis on the same day, whereas lobar pneumonia usually causes productive cough for a few days before rust-tinged sputum.

The physical examination can sometimes provide specific information about the presence of PE, including unilateral leg asymmetry, suggesting presence of DVT. Jugular venous distention in

**Table 88-2 Classic Risk Factors and Physiologic Findings for Pulmonary Embolism**

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>MECHANISMS</th>
<th>STRENGTH OF ASSOCIATION WITH PE IN ED POPULATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inherited thrombophilia</td>
<td>Hypercoagulability</td>
<td>++</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>Inflammation</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acquired thrombophilia</td>
<td>Hypercoagulability</td>
<td>Unknown</td>
</tr>
<tr>
<td>Active cancer (under treatment)</td>
<td>Hypercoagulability</td>
<td>+</td>
</tr>
<tr>
<td>Inactive cancer (considered in remission)</td>
<td>Presumed hypercoagulability</td>
<td>Not significant</td>
</tr>
<tr>
<td>Limb or generalized immobility</td>
<td>Stasis</td>
<td>++</td>
</tr>
<tr>
<td>Prior PE or DVT</td>
<td>Multiple</td>
<td>+</td>
</tr>
<tr>
<td>Trauma within previous 4 wk requiring hospitalization</td>
<td>Inflammation, venous injury and stasis</td>
<td>+++</td>
</tr>
<tr>
<td>Surgery within previous 4 wk requiring general anesthesia</td>
<td>Inflammation, venous injury and stasis</td>
<td>++++</td>
</tr>
<tr>
<td>Smoking</td>
<td>Inflammation</td>
<td>Not significant</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Hypercoagulability</td>
<td>++</td>
</tr>
<tr>
<td>Pregnancy or postpartum</td>
<td>Hypercoagulability</td>
<td>Minimal</td>
</tr>
<tr>
<td>Family history of VTE</td>
<td>Inherited condition</td>
<td>Not significant</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleuritic chest pain</td>
<td>Lung ischemia, muscle strain</td>
<td></td>
</tr>
<tr>
<td>Subternal chest Pain</td>
<td>Presumed cardiac ischemia</td>
<td>Not significant</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>V/Q mismatch</td>
<td>+</td>
</tr>
<tr>
<td>Sudden onset of symptoms</td>
<td>Vascular obstruction</td>
<td>Not significant</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>Infarction</td>
<td>+++</td>
</tr>
<tr>
<td>Syncope</td>
<td>Vascular obstruction</td>
<td>Minimal</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate &gt;100 beats/min</td>
<td>Cardiac stress, baroreceptors</td>
<td>+++</td>
</tr>
<tr>
<td>Pulse oximetry reading &lt;95%</td>
<td>V/Q mismatch</td>
<td>+++</td>
</tr>
<tr>
<td>Unilateral leg or arm swelling</td>
<td>Venous obstruction</td>
<td>++++</td>
</tr>
<tr>
<td>Normalization of vital signs</td>
<td>Presumptive from treatment or Hawthorne effect</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

DVT, deep vein thrombosis; PE, pulmonary embolism; V/Q, ventilation-perfusion ratio; VTE, venous thromboembolism.
a patient with severe dyspnea and clear lung fields on auscultation suggests pure right-sided heart failure. The presence of wheezing suggests bronchospasm, which is not common in PE and makes the diagnosis less likely (but does not exclude it). Bilateral rales suggest the diagnosis of left ventricular failure, although localized rales often are heard over infarcted lung tissue. Astute clinicians may hear an accentuated pulmonic component of the second heart sound, or a right ventricular S₃ sound.

Diagnosis

Chest radiography seldom provides specific information but is useful to suggest alternative diagnoses, such as pneumonia, congestive heart failure, or pneumothorax. Unilateral basilar atelectasis on the chest radiograph increases the probability of PE. If symptoms have been present for 3 days or more, pulmonary infarction sometimes shows an apex-central, pleural-based, wedge-shaped area of infiltrate, producing the Hampton’s hump finding. Unilateral lung oligemia (Westermark’s sign) is a rare radiographic manifestation of a large PE.

Likewise, a 12-lead ECG provides more information about the presence of alternative diagnoses, such as pericarditis or cardiac ischemia, than the presence of PE. When PE causes ECG changes, this is usually a result of acute or subacute pulmonary hypertension. The most common effects of pulmonary hypertension on ECG are rapid heart rate, symmetrical T-wave inversion in the anterior leads (V₁-V₃), the McGinn-White S₁Q₃T₃ pattern, and incomplete or complete right bundle branch block (Fig. 88-3); any one of these findings approximately doubles the probability of PE in a symptomatic patient. In the ED, inability to identify a cause of otherwise unexplained symptoms and signs is an important stimulus to evaluate the patient for PE. Because as many as 50% of patients diagnosed with PE have no identifiable classic risk factors for thrombosis, the decision to pursue the diagnosis of PE is based on that particular patient’s presentation and should not rely on the presence or absence of population risk factors.

In some cases PE can be excluded with reasonable certainty based on data that are available at the bedside, gathered only via the medical history and physical examination. Multicenter studies of urban academic EDs have suggested that emergency physicians currently evaluate about 1 to 2% of all patients for PE. Each year more than 16 million patients come to the ED with chest pain or dyspnea. Although numerous cases of PE are probably still missed, overtesting for PE can also be harmful. Specific risks include exposure to the ionizing radiation and intravenous contrast necessary for CTPA and CTV and the risk of false-positive interpretation, which may occur in as many as 10% of scans read as positive for PE. The appropriate use of D-dimer testing decreases the need for imaging in all but patients at high risk.

Accordingly, there should be a rational, reproducible strategy to guide the decision-making and diagnostic processes. This strategy should begin with estimation of PTP. Methods for estimating PTP can be implicit (meaning the clinician’s best guess) or explicit (meaning use of a scoring system or flow algorithm to categorize the probability).

One approach to the workup for PE is to compare the PTP with the “test threshold” for PE. The test threshold represents the point above which some type of workup should be initiated and below which the clinician can justifiably not starting the workup. For PE the test threshold is 1 to 2.5%. Patients with a PTP less than 2.5% are more likely to be harmed than benefited by a workup and vice versa for patients with a PTP greater than 2.5%.

The question becomes how to quantify the PTP accurately. Clinical judgment alone is subject to cognitive error inherent to medical diagnosis, including framing heuristic and conditions in the ED at the time (e.g., is one less likely to pursue a relatively low-likelihood diagnosis when the department is very busy), conditions of the patient (e.g., fatigue, dysphoria, subjective feelings about the patient), and the availability of diagnostic studies (e.g., daytime vs. nighttime, weekday vs. weekend). In addition, there is variability among clinicians who may not agree that a 19-year-old with cough and pleuritic chest pain, a normal chest radiograph, and no other risk factors has less than a 2% probability of PE.

Decision rules help to deal with these problems because they are structured and more transparent. Several rules have been derived and validated for the risk stratification of patients with possible PE; however, difficulty with spontaneous recall and a preference for gestalt reasoning by clinicians may limit their use in clinical practice. Fortunately, clinical reasoning appears to be comparable to at least two of the validated decision rules. In a large single-center study of 2603 ED patients evaluated for PE, the

Figure 88-3. Initial electrocardiogram tracing from an 18-year-old woman on oral contraceptives in the ED with syncope. Several findings consistent with pulmonary embolism are shown, including tachycardia, the S₁Q₃T₃ pattern, and an incomplete right bundle branch block. Computed tomography angiography revealed extensive bilateral pulmonary emboli, and echocardiography showed severe right heart dysfunction.
treating clinician’s unstructured estimate of PTP was equivalent to that provided by the Wells score and the Charlotte rule. This finding was independent of training level.21

Although gestalt reasoning and clinical decision rules may provide adequate stratification to guide the workup (i.e., D-dimer vs. pulmonary vascular imaging), they have not been able to reproducibly identify the “very low-risk” population whose PTP lies below the 2% test threshold. In one validation study, patients with Wells score less than 2 had a 1.3% probability of PE,30 but this finding has not been repeated. To identify the very low-risk group in whom PE could be safely excluded at the bedside with no diagnostic testing, the PE rule-out criteria (the PERC rule) were derived and prospectively validated in 8138 patients in 13 different hospitals across the United States and in New Zealand (see Box 88-2).16

When the physician’s unstructured clinical suspicion for PE is low and each of the eight elements of the rule is satisfied, the PERC rule identifies a very low-risk population among whom no patient has a PTP for PE of greater than 2%. In the large validation series, the rule excluded PE at the bedside in 20% of cases and yielded a false-negative rate of 1% (95% confidence interval [CI] 0.6-1.6%). This finding supports a rational and reproducible method for avoiding unnecessary testing in a low-risk patient with a sign or symptom partially suggestive of PE. Patients with risk factors but without any symptoms or signs of PE (e.g., no chest pain, no shortness of breath, no dyspnea on exertion, normal vital signs, and no recent syncope) do not warrant workup for PE unless there is some compelling clinical indication to the contrary.

PE is also less likely when some other disease process can explain the patient’s complaints and findings (e.g., asthma causing bronchospasm proven by a low peak expiratory flow rate, or findings of wheezing and prolonged expiration on auscultation) in a patient otherwise not believed to be at high risk for PE. A tangible alternative diagnosis reduces the probability of coincident PE. The flow algorithms provided here are predicated on the following goals: (1) to identify as many ED patients as possible who have PE; (2) to avoid mislabeling (and administering anticoagulants to) patients who do not have PE; and (3) to use available resources efficiently and effectively (Fig. 88-4).

For a patient for whom suspicion is implicit or with explicit score suggesting a PTP over 40%, clinicians should skip the D-dimer, order pulmonary vascular imaging, and strongly consider initiating anticoagulation in the absence of contraindications. Because the half-life of circulating D-dimer is less than 8 hours, the sensitivity of the D-dimer may decrease if the patient’s symptoms have been present for longer than 3 days. False-negative D-dimer measurements may also be seen with ongoing warfarin therapy and in the subset of patients with pulmonary infarction.

<table>
<thead>
<tr>
<th>ED patients</th>
<th>Sufficient suspicion for PE to warrant testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest probability assessment (Decision rule or implicit)</td>
<td></td>
</tr>
<tr>
<td>Non-high (&lt;40%)</td>
<td></td>
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<tr>
<td>D-dimer</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTA</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PE</td>
<td></td>
</tr>
<tr>
<td>Consider further testing*</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ED patients</th>
<th>Sufficient suspicion for PE to warrant testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretest probability assessment (Decision rule or implicit)</td>
<td></td>
</tr>
<tr>
<td>High (&gt;40%)</td>
<td></td>
</tr>
<tr>
<td>D-dimer</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>V/Q</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Low, moderate, or intermediate probability</td>
<td></td>
</tr>
<tr>
<td>PTP &gt;40%</td>
<td></td>
</tr>
<tr>
<td>No PE</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td></td>
</tr>
<tr>
<td>Further testing*</td>
<td></td>
</tr>
</tbody>
</table>

*May require patient admission. Additional testing—Option 1: “Crossover” to perform either scanning or computed tomography for algorithms A and B. Option 2: Perform lower extremity venous ultrasound, and if initial venous ultrasound is negative, repeat the lower extremity venous ultrasound in 1 week. Option 3: Perform formal pulmonary angiography.
As was discussed in the DVT section, quantitative D-dimer assays are more reliable for the exclusion of PE than are qualitative assays.12-35

The post-test probability to safely exclude the diagnosis of PE must be equal to 1%, which is at least equivalent to that of a normal scan or a negative CTPA. This combination can be achieved by the combination of a PTP assessment less than 40% (i.e., a patient not at high risk) and a quantitative D-dimer concentration less than 500 ng/mL. When the PTP is high or the screening D-dimer is positive, pulmonary vascular imaging by CTPA or scanning is advised. Although CTPA is not perfect, it has multiple advantages over scanning and usually can confirm or exclude the presence of PE.

Most academic centers now use CTPA as the primary method of evaluating for PE. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study evaluated the test characteristics of CTPA for the diagnosis of PE in a prospective, multicenter study of 824 patients imaged primarily with four-row multidetector scanners.3 CTPA images were deemed adequate for interpretation in 773 (94%), and the sensitivity in these patients was 83% (95% CI 76-92%) with a specificity of 96% (95% CI 93-97%).

When CTPA fails to identify PE in a situation of high clinical suspicion, the clinician should review with the radiologist any issues of image acquisition quality that adversely affected diagnostic accuracy. As with any imaging study, if CTPA quality was poor and the results do not match the clinical picture, more testing should be performed.

The importance of isolated subsegmental pulmonary embolus either missed or detected by CTPA can arise because of a radiologist’s statement that “subsegmental clot cannot be excluded by CTPA.” More recently, increased detection of isolated subsegmental filling defects has occurred, with more thinly collimated images acquired with a higher number multidetector scanner.17 No firm evidence yet exists to guide these circumstances. When two radiologists independently evaluate CTPA, their agreement on the presence of isolated subsegmental filling defects is poor.17 The same lack of agreement with regard to subsegmental clots holds for formal pulmonary angiography. It is reasonable that if the patient has no evidence of DVT, no signs of cardiopulmonary stress, and no ongoing major risk for thrombosis (e.g., active malignancy), isolated subsegmental findings are the equivalent of no findings, and anticoagulation is not indicated. If a patient with negative CTPA has signs of pulmonary hypertension or hypoxemia without an apparent alternative cause, or has a known thrombophilia, further testing is advised. Subsequent testing after negative CTPA is individualized by institution in consultation with radiology. Most commonly, if venous studies were not performed as part of the CTPA, duplex ultrasonography of both lower extremities should be undertaken. Positive sonographic evidence of DVT is considered confirmation of the presence of PE. A negative sonogram does not exclude the diagnosis, however, and the procedure should be repeated in 2 to 7 days.

CTPA can provide additional information to enhance its usefulness in the ED. Although the scan can be extended to include the leg veins, this is not recommended as a routine (see earlier discussion.) CTPA often provides information about alternative processes that might explain the patient’s symptoms (Box 88-3). Pneumonia is the most common alternative diagnosis found in ED patients. In about 10% of ED patients evaluated for PE, CT as a single test could (1) show absence of PE; (2) provide evidence of alternative disease, which can be used with other evidence to reduce the probability of PE to a reasonably low level to stop the workup; and (3) facilitate treatment for the alternative disease.

The scintillation scan remains a good diagnostic option for patients with contraindications to iodinated intravenous contrast. The accuracy and precision of the scan were shown in the PIOPED study, which compared the results of scanning with the most accurate criterion standard test available at the time—formal pulmonary angiography (Table 88-3).22 This multicenter study showed that a high-probability scan can be used to diagnose PE, and a normal scan (i.e., no perfusion defect) excludes the diagnosis of PE with an acceptable degree of certainty. A moderate probability or indeterminate scan requires additional formal pulmonary angiography or a CTPA. Even in patients with a low PTP, a low-probability scan usually indicates a need for additional testing, such as either CTPA or venous duplex ultrasonography of the legs. The latter should be repeated at least once, 2 to 7 days later, if negative at the initial presentation. In patients with a chest radiograph that shows airspace disease, the specificity of scanning can be expected to decrease, and the relative diagnostic utility of CTPA can be expected to increase.

Management

Anticoagulation

Either unfractionated heparin (80 units/kg intravenous bolus, followed by 18 units/kg/hr intravenous infusion), fractionated

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**Table 88-3** Prevalence of Pulmonary Embolism Stratified by Ventilation-Perfusion Scan Result and Pretest Probability Estimate

<table>
<thead>
<tr>
<th>V/Q Ratio Scan Result</th>
<th>80-100%</th>
<th>20-79%</th>
<th>0-19%</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>High probability</td>
<td>28/29 (96%)</td>
<td>70/80 (88%)</td>
<td>5/9 (56%)</td>
<td>103/118 (87%)</td>
</tr>
<tr>
<td>Intermediate probability</td>
<td>27/41 (66%)</td>
<td>66/236 (28%)</td>
<td>11/68 (16%)</td>
<td>104/345 (30%)</td>
</tr>
<tr>
<td>Low probability</td>
<td>6/15 (40%)</td>
<td>30/191 (16%)</td>
<td>4/90 (4%)</td>
<td>40/296 (14%)</td>
</tr>
<tr>
<td>Near-normal or normal</td>
<td>0/5 (0%)</td>
<td>4/62 (6%)</td>
<td>1/61(2%)</td>
<td>5/128 (4%)</td>
</tr>
<tr>
<td>Total</td>
<td>61/90 (68%)</td>
<td>170/569 (30%)</td>
<td>21/228 (9%)</td>
<td>252/887 (28%)</td>
</tr>
</tbody>
</table>

Adapted from the PIOPED Investigators: Value of the ventilation/perfusion scan in acute pulmonary embolism. JAMA 263:2753, 1990.

PE, pulmonary embolism; V/Q, ventilation-perfusion ratio.
Low-risk PE

- SBP >90 mm Hg at all times and all of the following:
  - Shock index <1
  - SaO₂ almost always > 94%
  - Daniel score <3
  - Normal troponin or BNP or proBNP level
  - PESI score <66

Begin low-molecular-weight heparin
Optional admission to unmonitored regular bed
Consider outpatient treatment if adequate
compliance and follow-up can be ensured

Moderate-risk PE

- SBP >90 mm Hg at all times and any one of the following:
  - Shock index 1 or greater at any time
  - SaO₂ persistently <94%
  - Daniel score >3
  - Elevated troponin or BNP or proBNP level
  - PESI score >65 and <125
  - Echocardiography with any degree of right ventricular hypokinesis

Begin heparin treatment
Fibrinolytics in the minority of cases
Admission to a telemetry bed

More severe (submassive)

- Moderate-risk PE

- Appearance of at least moderate distress AND
  - Shock index >1 and severe right ventricular hypokinesis on
    echocardiography
  - Worsening Daniel score, particularly a new incomplete right bundle
    branch block (RBBB) or progression of iRBBB to complete RBBB
  - SaO₂ <90% and serum troponin level clearly elevated
  - PESI score >124

Begin heparin treatment
Fibrinolytic treatment in the majority of patients
without contraindications in the ED
Admission to a step-down or intensive care unit

High-risk (major) PE

- Any SBP <90 mm Hg or <20 mm Hg below documented baseline and
  appearance of distress
- Any persistent SBP <90 mm Hg regardless of appearance

Begin heparin treatment
Fibrinolytic treatment in all patients without
contraindications in the ED
Admission to intensive care unit

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Table 88-4 Risk-Stratification and Associated Treatment Recommendations for Acute Pulmonary Embolism (PE)

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>CRITERIA</th>
<th>ACTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk PE</td>
<td>SBP &gt;90 mm Hg at all times and all of the following:</td>
<td>Begin low-molecular-weight heparin</td>
</tr>
<tr>
<td></td>
<td>Shock index &lt;1</td>
<td>Optional admission to unmonitored regular bed</td>
</tr>
<tr>
<td></td>
<td>SaO₂ almost always &gt; 94%</td>
<td>Consider outpatient treatment if adequate compliance and follow-up can</td>
</tr>
<tr>
<td></td>
<td>Daniel score &lt;3</td>
<td>be ensured</td>
</tr>
<tr>
<td></td>
<td>Normal troponin or BNP or proBNP level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PESI score &lt;66</td>
<td></td>
</tr>
<tr>
<td>Moderate-risk PE</td>
<td>SBP &gt;90 mm Hg at all times and any one of the following:</td>
<td>Begin heparin treatment</td>
</tr>
<tr>
<td></td>
<td>Shock index 1 or greater at any time</td>
<td>Fibrinolytics in the minority of cases</td>
</tr>
<tr>
<td></td>
<td>SaO₂ persistently &lt;94%</td>
<td>Admission to a telemetry bed</td>
</tr>
<tr>
<td></td>
<td>Daniel score &gt;3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated troponin or BNP or proBNP level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PESI score &gt;65 and &lt;125</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Echocardiography with any degree of right ventricular hypokinesis</td>
<td></td>
</tr>
<tr>
<td>More severe (submassive) moderate-risk PE</td>
<td>Appearance of at least moderate distress AND</td>
<td>Begin heparin treatment</td>
</tr>
<tr>
<td></td>
<td>Shock index &gt;1 and severe right ventricular hypokinesis on echocardiography</td>
<td>Fibrinolytic treatment in the majority of patients without contraindications in the ED</td>
</tr>
<tr>
<td>High-risk (major) PE</td>
<td>Any SBP &lt;90 mm Hg or &lt;20 mm Hg below documented baseline and appearance of distress</td>
<td>Begin heparin treatment</td>
</tr>
<tr>
<td></td>
<td>Any persistent SBP &lt;90 mm Hg regardless of appearance</td>
<td>Fibrinolytic treatment in all patients without contraindications in the ED</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Admission to intensive care unit</td>
</tr>
</tbody>
</table>

BNP, B-type natriuretic peptide; ED, emergency department; iRBBB, incomplete right bundle branch block; PESI, Pulmonary Embolism Severity Index; proBNP, pro-B-type natriuretic peptide; SaO₂, arterial oxygen saturation; SBP, systolic blood pressure.

low-molecular-weight heparin (e.g., enoxaparin, 1 mg/kg SQ or intravenously [IV] every 12 hours), or the pentasaccharide factor Xa inhibitor fondaparinux (5-10 mg, depending on body mass) can be used for treatment of most patients with PE. Low-molecular-weight heparin is recommended over unfractionated heparin because meta-analyses clearly indicate a lower rate of major hemorrhage with low-molecular-weight heparin, a lower rate of heparin-induced thrombocytopenia, and a lower rate of VTE recurrence compared with unfractionated heparin, and a similar overall economic cost. However, the anticoagulant effect of unfractionated heparin can be almost completely and rapidly reversed with protamine, whereas low-molecular-weight heparin can be neutralized only about 50% with protamine, and protamine has no effect on fondaparinux. Both forms of heparin work equally well, and both are safe in the absence of contraindications to anticoagulation. Heparin provides several immediate benefits, including the reduction in clot extension (which can occur rapidly); reduces the transient hypercoagulable effect of warfarin treatment; and over a period of days to weeks allows the natural fibrinolytic system to reduce clot size.

A large registry found that emergency physicians begin heparin in approximately 10% of patients who are diagnosed with PE, before knowing the results of pulmonary vascular imaging ("empirical heparin"). Only 15% of patients who died from PE received empirical heparin, but this fact in the absence of other published data can be used to assert that empirical heparin administration can improve outcomes from PE. In consideration of its risks and benefits, empirical treatment probably confers more benefit than harm in a hemodynamically stable patient when the PTP of PE exceeds 30%, the patient has no major contraindication to anticoagulation, and the clinical circumstances predict that imaging will not be available for several hours. All patients with a high PTP, no contraindication to anticoagulation, and evidence of hemodynamic instability, including recent syncope, any hypotension, hypoxemia, or clinical evidence of right-sided heart strain (criteria defined in Table 88-4 as more severe moderate PE or high-risk PE), should receive immediate empirical heparin.

Recent evidence has indicated that up to 50% of outpatients diagnosed with PE may be stable enough to be treated as outpatients. A multicenter trial that randomized patients with low-risk PE (see Table 88-4 for definition) found equivalent outcomes for patients who were discharged from the ED compared with hospital admission. It should be noted that more than 95% of patients in that study were enrolled from Europe, where the public health resources for initiation and maintenance of high-quality anticoagulation generally exceed those of the United States. In settings where good follow-up can be obtained, the patient can be taught to self-administer low-molecular-weight heparin, and the patient can access an anticoagulation clinic within 48 hours, a low-risk patient with PE can be discharged from the ED.

For a patient diagnosed with PE in the presence of a major contraindication to anticoagulation, such as a recent cerebral hemorrhage or large cerebral infarction, the appropriate consultant should be contacted for urgent placement of an inferior vena cava filter. If vena caval interruption cannot be performed within 12 hours, one option is to perform a baseline head CT scan, then start an unfractionated heparin infusion at 18 units/kg/hr (without a bolus) and admit the patient to the intensive care unit for close neurologic monitoring and frequent partial thromboplastin time determinations. The rationale for use of unfractionated heparin is that it can be reversed more reliably (by discontinuing the heparin drip and administering protamine, 1 mg/kg IV) than fractionated heparin. Case reports and series have suggested that inhaled nitric oxide might be helpful for patients with severe PE and an absolute contraindication to anticoagulation, but this treatment has not been subjected to rigorous study.

Most patients with PE look and feel better the day after starting heparin anticoagulation, and more than half go on to a nearly full...
Thrombolytic Therapy

Thrombolytic therapy in PE is controversial. Administration of alteplase to patients with PE results in more rapid symptomatic improvement than standard antithrombotic therapy alone and causes more rapid and complete normalization of right ventricular function. Alteplase also increases the risk of hemorrhage, especially minor hemorrhage. It is not known with certainty how many patient lives would be saved, or definitively improved, by the addition of thrombolytic therapy to heparin therapy versus the many patient lives would be saved, or definitively improved, by the addition of thrombolytic therapy to heparin therapy versus the number of patients who would experience a fatal or life-threatening bleeding event as a result of thrombolytic therapy. On balance, the benefit-risk analysis suggests that fibrinolysis is of greatest value in the subset of patients with proven, massive PE. Massive PE is defined by hypotension with a systolic blood pressure below 90 mm Hg for more than 15 minutes. In patients with preexisting hypertension, the threshold is adjusted to below 100 mm Hg or a reduction in the baseline systolic blood pressure of more than 60 mm Hg. In the absence of contraindications, patients with proven massive PE probably benefit from fibrinolysis. There is insufficient evidence to recommend initiation of empirical fibrinolysis in the absence of confirmatory pulmonary vascular imaging or the presence of otherwise unexplained shock in a patient with known DVT and high clinical suspicion for PE.

A subset of patients with submassive PE may benefit from fibrinolysis, including those with moderate-to-severe respiratory distress and hypoxia (oxygen saturation less than 95%) and those with echocardiographic evidence of right ventricular dysfunction. When echocardiography is unavailable in a timely manner, surrogate laboratory markers of right ventricular dysfunction may be useful, including an elevated troponin level or a brain natriuretic peptide concentration portend a worse outcome. Echocardiography demonstrating right ventricular hypokinesis or dilation also increases the probability of death from PE. Table 88-4 summarizes the criteria that can be used to risk stratify patients with PE into four groups. Table 88-4 also shows how consideration of these criteria may help guide the decision to place the patient in an ICU versus an intermediate or regular inpatient bed, and whether to administer heparin only or consider escalated therapy.

Table 88-5

<table>
<thead>
<tr>
<th>Food and Drug Administration–Approved Fibrinolytic Regimens for Acute Treatment of Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptokinase</td>
</tr>
<tr>
<td>Urokinase</td>
</tr>
<tr>
<td>Alteplase</td>
</tr>
</tbody>
</table>

Tenecteplase (TNKase) is a recombinant plasminogen–activating enzyme with several pharmacologic properties that may favor its use for fibrinolysis of acute PE; it has been studied in one randomized controlled trial. Tenecteplase does not have FDA approval for PE treatment. Tenecteplase differs from alteplase because it has a longer half-life, resistance to plasminogen activator inhibitor–1, and increased fibrin specificity, which results in less fibrinogenolysis and less coagulopathy.

The clinical course of patients with obstructive PE can be unpredictable. Many patients with massive PE remain stable in the ED. Other patients are stable on arrival but progressively deteriorate over hours as right ventricular function declines. Three percent of ED patients without hypotension while in the ED experience cardiac arrest and die within 24 hours. A patient can be stable and then hypotensive within minutes because of the highly variable effect of the clot on right ventricular outflow obstruction, especially when it is perched in the main pulmonary artery (Fig. 88-5). Additional mechanisms of rapid instability include new embolization of clot material, release of mediators of pulmonary vasoconstriction, sudden bradycardia or asystolic arrhythmias, and respiratory failure. Clues to oncoming cardiopulmonary decompensation include worsening respiratory distress and worsening hypoxemia, a rising shock index (the heart rate divided by the systolic blood pressure), systolic arterial blood pressure less than 90 mm Hg, and syncope or a seizure-like convulsive episode while in the ED. A particularly ominous finding is the evolution on ECG from a narrow-complex tachycardia to an incomplete right bundle branch block to a complete right bundle branch block (Fig. 88-6) as evidence of life-threatening pulmonary hypertension and incipient cardiac arrest.

Clinical evidence of impending or actual respiratory failure indicates the need for prompt endotracheal intubation with use of mechanical ventilation. In the absence of hypotension, children with obstructive PE can usually be treated with a single low-dose bolus of dabigatran or rivaroxaban or a weight-adjusted bolus of apixaban, followed by label-directed dosing, rather than the usual full bolus of alteplase. Low-dose rivaroxaban (15 mg) has been approved for the treatment of acute PE in patients who have been infused with alteplase (100,000 units) or tenecteplase (125 mg) within 24 hours of onset of symptoms unless the patient is in extremis. This regimen, which incorporates the safe use of thrombolysis for certain patients, is similar to the use of rivaroxaban in patients with acute symptomatic venous thromboembolism. In our institution, we have implemented the use of a thrombolytic regimen that includes the use of low-dose rivaroxaban with the alteplase regimen.
Catheter-directed thrombectomy also may be lifesaving but requires that the patient be sent to the relatively uncontrolled environment of the interventional radiology suite. No data support the use of catheter intervention for treatment of PE. PE can manifest as cardiac arrest. Most patients with incipiently fatal PE have overt respiratory distress, syncope or seizure-like activity, or a high heart rate relative to the systolic blood pressure before arrest. First responders who observe a patient dying from PE most commonly observe PEA as the initial cardiac arrest rhythm (>20 depolarizations per minute without palpable pulses). The mechanism for PEA manifests from right ventricular outflow obstruction and impaired right ventricular contractility. Ultrasound performed during PEA arrest from PE usually shows weak cardiac contractions with a swollen right ventricle and small left ventricle. Some patients manifest slow agonal rhythms with fatal or near fatal PE possible owing to septal wall tension leading to ischemia or ischemic-equivalent effect on the atrioventricular node and infranodal conducting pathways.

Regardless of the initial rhythm, pulselessness from PE imparts a published mortality rate exceeding 70%. Numerous case reports of standard rapid sequence intubation technique, preferably with either ketamine or etomidate for induction of anesthesia with neuromuscular blockade. Other induction agents that depress cardiac function or reduce preload may precipitate severe hypotension and should be avoided or their dosage reduced. In the case of impending respiratory or cardiac arrest, fibrinolytic therapy should be strongly considered.

Surgical Embolectomy

For patients with known floating thrombi in the right side of the heart or for patients with severe refractory hypotension, surgery is the most likely intervention to save the patient’s life. Surgical embolectomy requires extracorporeal cardiopulmonary bypass and an experienced cardiothoracic surgeon. Surgical embolectomy may be the best option for patients who have severe PE with a contraindication to fibrinolysis; however, extracorporeal perfusion requires intensive heparin anticoagulation, and the patient’s mental status cannot be monitored during surgery—a key concern in patients with high risk of intracranial hemorrhage. Catheter-directed thrombectomy also may be lifesaving but requires that the patient be sent to the relatively uncontrolled environment of the interventional radiology suite. No data support the use of catheter intervention for treatment of PE. PE can manifest as cardiac arrest. Most patients with incipiently fatal PE have overt respiratory distress, syncope or seizure-like activity, or a high heart rate relative to the systolic blood pressure before arrest. First responders who observe a patient dying from PE most commonly observe PEA as the initial cardiac arrest rhythm (>20 depolarizations per minute without palpable pulses). The mechanism for PEA manifests from right ventricular outflow obstruction and impaired right ventricular contractility. Ultrasound performed during PEA arrest from PE usually shows weak cardiac contractions with a swollen right ventricle and small left ventricle. Some patients manifest slow agonal rhythms with fatal or near fatal PE possible owing to septal wall tension leading to ischemia or ischemic-equivalent effect on the atrioventricular node and infranodal conducting pathways.

Regardless of the initial rhythm, pulselessness from PE imparts a published mortality rate exceeding 70%. Numerous case reports

**Figure 88-6.** Serial electrocardiograms obtained 2 minutes apart show the progression from a narrow complex rhythm (A) to a right bundle branch block pattern (B) in a patient with massive bilateral pulmonary emboli. Shortly after the second tracing was obtained, the patient developed cardiovascular collapse refractory to vigorous resuscitation efforts.

of standard rapid sequence intubation technique, preferably with either ketamine or etomidate for induction of anesthesia with neuromuscular blockade. Other induction agents that depress cardiac function or reduce preload may precipitate severe hypotension and should be avoided or their dosage reduced. In the case of impending respiratory or cardiac arrest, fibrinolytic therapy should be strongly considered.

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Box 88-4 Unique Questions That Commonly Arise in the Emergency Department (ED)

1. I cannot get imaging at night. Is it reasonable to treat the patient with heparin until morning? The short answer to this question is yes, if the patient has no contraindications. Many smaller hospitals routinely use this method and use a single dose of enoxaparin.

2. How do I manage the patient who is being treated for pulmonary embolism who returns to the ED for chest pain? If the patient has a therapeutic international normalized ratio (1.5–2.5) and returns with symptoms only (e.g., chest pain, dyspnea) and without syncope, appears relatively comfortable, has normal vital signs, and has no new changes suggesting pulmonary hypertension on ECG (in particular, no S1Q3T3 pattern and no T wave inversion in leads V1 through V3), follow-up imaging is probably not needed. Other causes of chest pain (especially acute coronary syndrome) should be considered. In the absence of an identified alternative diagnosis, symptomatic care with an anti-inflammatory agent is safe and reasonable therapy for the return complaint of chest pain. Persistent dyspnea at rest raises more concerns of unresolved or recurrent thrombosis with secondary effects, including bronchospasm or, worse, pulmonary vascular hyperplasia with pulmonary hypertension. Repeat pulmonary vascular imaging may provide evidence of an unresolved or new clot. More important, a transthoracic echocardiogram can disclose evidence of persistent right ventricular dysfunction and pulmonary hypertension. Symptomatic patients with unresolved filling defects and pulmonary hypertension can progress to chronic thromboembolic pulmonary hypertension. Prevention of this decline, patients who return to the ED with persistent rest dyspnea and have unresolved filling defects and pulmonary hypertension should be admitted or referred to a program that offers the option of pulmonary thrombectomy.

3. How can I rule out pulmonary embolism in a pregnant patient without use of ionizing radiation? One clinical conundrum is the fact the pregnancy is accompanied by both an increased risk of PE and a predictable elevation in D-dimer, even in the absence of PE. Given that PE is the most common nontraumatic cause of death in pregnant women, clinicians are justified in adopting a liberal “rule-out PE” approach to all pregnant women with dyspnea.

To evaluated suspected PE in pregnancy, I recommend the following sequence. First, assess the PERC rule criteria and apply a modified version of the PERC rule with a slightly elevated top limit for the pulse rate (normal up to 104 beats/min instead of 99 beats/min). If the result of this modified PERC rule is negative, then order a quantitative D-dimer. Use thresholds to define a normal D-dimer that is elevated on the basis of trimester (first trimester, 5.5x; second trimester, 2x; and third trimester, 2.5x standard threshold). If the result of the modified PERC rule is positive or the D-dimer is above the adjusted threshold, then order bilateral lower extremity ultrasound; if this is positive for DVT, then treat for PE. If the bilateral ultrasound is negative, proceed to pulmonary vascular imaging.

The issue of the optimal imaging procedure in pregnancy remains controversial. A 2003 survey of radiologists indicated an almost equal split (53% in favor of CTPA, 47% in favor of V/Q scanning) in their choice for imaging in PE in pregnancy. Very few published data are available to compare outcomes after V/Q scanning with those after CTPA scanning in pregnancy. Facts to consider include the following:

1. No empirical data are available to accurately measure the radiation dose absorbed by the fetus in utero during imaging, as dosimeters cannot be placed on the fetal body. Thus estimates of fetal radiation dose come from models and simulations. These studies generally suggest that the radiation dose from CTPA is lower than that from V/Q scanning, but the dose is approximately equal between CTPA and perfusion-only “Q” scanning.

2. Available data show that the overall rate of indeterminate studies is about 10-15% for both V/Q and CTPA, but for the subset of pregnant patients with a plain film chest radiograph that is normal, the indeterminate rate is lower for V/Q scanning than for CTPA scanning.

3. CTPA may show alternative diagnoses that V/Q scanning does not, although one study showed that most alternative diagnoses were pneumonia, which were also seen on plain film chest radiography.

4. CTPA may increase the risk of breast cancer in the mother by about 1.5%, whereas V/Q scanning is not believed to confer this risk.

5. Nonionic contrast media readily cross the placenta, and the long-term risks of contrast exposure to the fetus remains unknown.

6. Tube voltage modulation and other technology can significantly reduce fetal radiation exposure with CTPA, possibly even to a greater extent than does shielding with lead or antimony-bismuth aprons.

7. Fetal radiation exposure with CTPA increases with each trimester, although this effect is mitigated with 64-channel scanners, as they produce less scatter radiation than 16- or 4-channel CT scanners.

Taken together, these facts suggest no clear benefit to either procedure for any trimester of pregnancy. I recommend that a plain film chest radiograph be taken first, and if this radiograph shows no air space disease, that scintillation scanning can be considered—but only the perfusion phase is performed, the radiation “dose” is halved, and the patient receives prehydration, and consideration is given to placement of a Foley catheter to accelerate removal of radiolabel in the bladder. If the chest radiograph has any evidence of airspace disease, CTPA scanning should be performed and the abdomen should be shielded. Obviously, these recommendations must be considered in the clinical context of availability of equipment and personnel and the opinion of the responsible radiologist. Scintillation perfusion scanning, if normal, excludes the diagnosis. A perfusion scan with two or more segmental perfusion defects in the presence of a normal chest radiograph establishes the diagnosis, and heparin (which does not cross the placental barrier) can be initiated. If is the perfusion scan is nondiagnostic, CTPA scanning will be required.

4. How do I evaluate the patient with possible pulmonary embolism who is too obese to fit in a CT scanner? Each CT scanner has a maximum patient weight that it will accommodate. When a patient’s weight exceeds the scanner limit and a larger capacity scanner is not available, I recommend duplex venous ultrasonography of the lower extremities to rule out DVT. Although often technically suboptimal in a massively obese patient, venous ultrasonography occasionally provides positive evidence of DVT, ostensibly clinching the diagnosis. Another option is to anticoagulate empirically based on a moderate-to-high pretest probability and a D-dimer concentration that exceeds 1000 ng/mL. The adequate regimen for anticoagulation is uncertain, but many experts recommend subcutaneous enoxaparin, 1 mg/kg of actual body weight up to a maximum of 200 µg/kg.

CT, computed tomography; CTPA, CT pulmonary angiography; DVT, deep vein thrombosis; ECG, electrocardiogram; PE, pulmonary embolism; V/Q, ventilation-perfusion ratio.
have suggested heroic results from bolus administration of thrombolytic therapy to patients with cardiac arrest from PE. The administration of fibrinolytic therapy does not absolutely preclude surgical intervention. Patients who have been treated with a fibrinolytic agent can undergo sternotomy or thoracotomy for embolectomy and survive without fatal hemorrhage. The decision to perform embolectomy ultimately resides with the cardiac surgeon.

Box 88-4 details questions that commonly arise regarding the diagnosis and treatment of PE in the ED.

**KEY CONCEPTS**

- Deep vein thrombosis often manifests as a nonspecific crampy sensation in the upper or lower extremity without obvious swelling.
- The absence of a sudden onset of symptoms is of no value in excluding PE as the cause of the patient's presentation.
- An ELISA or immunoturbidimetric D-dimer concentration below 500 ng/mL can rule out PE or DVT in all but high-risk patients. Patients with low or moderate pretest probability should not undergo imaging without a screening D-dimer test.
- A patient with a pretest probability below 2% need not be tested for PE.
- A patient with PE and a pulse oximetry reading below 95% is at increased risk for a bad outcome.
References


