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The Emergency Medicine Approach To The Evaluation And Treatment Of Pulmonary Embolism

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Abstract

Each year in the United States, up to 900,000 individuals will suffer from acute pulmonary embolism, resulting in an estimated 200,000 to 300,000 hospital admissions. Despite decades of research on the topic, the diagnosis remains elusive in many situations and the fatality rate remains significant. This issue presents a review of the current evidence guiding the emergency medicine approach to the diagnosis and treatment of pulmonary embolism. Key to this approach is the concept of risk stratification: using factors from the history and physical examination, plus ancillary tests, to guide clinical decision making. The pathophysiology of pulmonary embolism and decision-support tools are reviewed, and emergency department management strategies are described.

CME Objectives

Upon completing this article, you should be able to:

1. Describe current methods of risk stratification for PE.
2. Define the degree of risk for PE in patients prior to initiating a diagnostic plan.
3. Choose and appropriately interpret the results for diagnostic tests.
4. Assess a patient's severity of disease with clinical findings, focused cardiac ultrasonography, and cardiac troponin I measurement.
5. Choose among the various treatment options for PE.

Prior to beginning this activity, see "Physician CME Information" on the back page.

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Case Presentations

A 49-year-old male construction worker presents to the ED reporting a brief loss of consciousness 30 minutes prior to arrival while climbing through a crawlspace at work. He reports a prodrome of feeling short of breath, lightheaded, and dizzy, with associated midsternal chest pain. Family members at the bedside report that he was complaining of generalized weakness with mild shortness of breath at rest and on exertion for the past 3 to 4 days. His past medical history is significant for rectal cancer treated with resection, a traumatic fracture of L3, and deep vein thrombosis 9 months ago, after which he completed a 6-month course of warfarin. The patient denies use of tobacco, alcohol consumption, or use of illicit drugs. There is no family history of any medical problems. His vital signs upon arrival are: temperature, 36°C; blood pressure, 104/79 mm Hg; heart rate, 106 beats per minute; respiratory rate, 20 breaths per minute; and oxygen saturation, 95% on room air. He is in no distress, is sitting upright on the stretcher, and is speaking in full sentences. Aside from a regular tachycardia, his exam is normal. Initial ECG shows a sinus tachycardia at 106 beats per minute, rightward axis deviation, ST-segment depressions throughout, and deep T-wave inversions in the anterolateral leads. Laboratory analysis, including cardiac markers, electrolytes, CBC, and renal function are remarkable only for a platelet count of 115,000 x 10^9/L. Initial cardiac markers and electrolytes are normal. You put acute coronary syndromes on the top of your differential and admit the patient to the observation unit, but you wonder if there is anything else that should be done while waiting for the second troponin...

A short time later, a 58-year-old male with a history of hypertension presents to the ED with leg pain. He woke up 2 days prior with pain and discoloration of his right leg, which has progressively worsened. Although not initially reported in the chief complaint, upon review of systems, the patient reports that he has been dizzy and short of breath for the past couple of days. He denies chest pain, diaphoresis, or syncope. The patient further denies history of coagulopathy or prior blood clots. On exam, he is well-appearing and in no distress. He is afebrile, is tachycardic at 117 beats per minute, is breathing at a rate of 16 breaths per minute, and has a blood pressure of 155/93 mm Hg. His oxygen saturation is 97% on room air. The physical exam is remarkable only for the right lower extremity. The entire right leg is diffusely tender, with edema, erythema, and plethora. Laboratory results are unremarkable; ECG is normal sinus rhythm at a rate of 98 beats per minute with left axis deviation and no ST-segment abnormalities.

Introduction

Each year in the United States, it is estimated that between 600,000 and 900,000 individuals suffer from acute pulmonary embolism (PE), accounting for an estimated 200,000 to 300,000 hospital admissions.[1-4] In the United States, as many as 100,000 deaths are estimated to be caused by venous thromboembolism each year. Furthermore, numerous studies have found that approximately 1% of all patients admitted to hospitals die of acute PE, and an estimated 10% of all hospital deaths are PE related.[5-7] If left untreated, PE can be rapidly fatal.[2,8,9]

Improvements in detection and treatment of deep vein thromboses, venous thromboembolism prophylaxis protocols, and improvements in the sensitivity and specificity of diagnostic tests have resulted in a substantially decreased overall mortality from PE in the past decade.[3,10] Nonetheless, despite these advancements, PE still remains a fatal pathology, with a mortality rate of up to 10% of all patients diagnosed with an acute PE in the first 1 to 3 months following diagnosis.[11,12] While the mortality of PE is well publicized, the morbidity associated with undiagnosed PE is not, and it can be very disabling, leading to both pulmonary hypertension and post-thrombotic syndrome.[4,13-15] This issue of *Emergency Medicine Practice* presents a review of the current evidence guiding the emergency medicine approach to the diagnosis and treatment of PE.

Critical Appraisal Of The Literature

An extensive literature search was performed using the PubMed database, Ovid MEDLINE®, and the Cochrane Database of Systematic Reviews. Searches were limited to the English language. Search terms included, but were not limited to the following: *pulmonary embolism, venous thromboembolism, emergency department, treatment, risk stratification, prevention, deep vein thrombosis,* and *cancer.* Search results for *pulmonary embolism* returned 13,305 articles. The search was further limited to include only clinical trials, meta-analyses, practice guidelines, randomized controlled trials, and reviews, returning 3378 publications. The breadth of the available literature is extensive; thus, clinical trials and guidelines were only reviewed if published within the last decade. The National Guideline Clearinghouse (www.guidelines.gov) and the American College of Emergency Physicians (ACEP) Clinical Policies were referenced for PE management, risk stratification, and prevention guidelines and policies. The bibliographies of these guidelines were also reviewed. A total of 98 references were used in the preparation of this article.

As noted earlier, the number of publications on the topic of PE is extensive, with articles dating back over a century and multiplying exponentially in the last decade. There has been a great expansion in the literature around PE in the last 10 to 20 years. Studies typically focus on either the diagnosis or the treatment of PE, but there are several limitations in the literature regarding both of these types of stud-

ies. Diagnostic studies are typically limited by the relatively low prevalence of PE, so maintaining high sensitivity with narrow confidence intervals often requires a multicenter trial in order to enroll enough patients. Nonetheless, several recent meta-analyses have added validity to the findings of smaller studies. An additional limitation for studies regarding the diagnosis of PE is the variability in the definition of a "true negative." Studies vary widely regarding which "gold standard" (if any) is used to assess if the results of the diagnostic study in question are accurate. "Gold standard" tests vary from clinical follow-up to pulmonary angiography. Regarding treatment studies, the primary limitation is the lack of well-controlled studies in critically ill patients, where poor outcomes are most likely. The challenge of performing informed consent in this group is an important limitation of many studies aiming to evaluate treatment in the critically ill patient with PE. Consequently, studies evaluating the effectiveness of both medical and interventional treatments for those who are the most unstable are often small retrospective studies or large database reviews where the patient populations included in the various studies are difficult to compare or specifics regarding the patients are not available.

History And Pathophysiology

In 1761, Giambattista Morgagni, a prominent 18th century pathologist, published his classic book, *De Sedibus et Causis Morborum per Anatomen Indagatis* (*On the Seats and Causes of Diseases as Investigated by Anatomy*), asking "Ubi est morbus?" (Where is the disease?). He attempted to explain the presence of large blood clots in the pulmonary vasculature of patients who had experienced sudden death. A 19th century French pathologist, Jean Cruveilhier, gained notoriety by the publication of his books *Anatomie Pathologique du Corps Humain* and *Traite d'Anatomie Pathologique Generale,* in which he proposed the theory that phlebitis dominates all of pathology and concluded that venous inflammation seemed to be the common variable in all disease processes. It was later in the 19th century that the term "embolism" was coined by Rudolph Virchow, after observing blood clots wedged in the pulmonary arteries at autopsy.[16] Investigators later recognized Virchow's work by naming the now-classic risk factor triad—vascular endothelial injury, hypercoagulability, and blood stasis—in his honor.[17] Over the years, more specific risk factors have been described, but they all contribute in some way to one of the components of the Virchow triad. **(See Table 1.)**

All pulmonary emboli begin as a venous thrombus in another location. The most common sources of pulmonary emboli are the pelvic veins or the deep veins of the thigh.[14] As thrombi form in the deep veins of the legs, pelvis, or arms, they may dislodge and embolize to the pulmonary arteries. As the clot obstructs the pulmonary arteries, this causes a mechanical increase in pulmonary vascular resistance, with a resulting decrease in preload. In addition, vasoactive substances are released, which further elevate pulmonary vascular resistance. Alveolar dead space is thus increased with a resultant ventilation/perfusion mismatch, which impairs gas exchange. Outflow obstruction of the right ventricle, resulting in increased right-sided afterload, leads to elevated right ventricular wall stress, right ventricle dilatation, dysfunction, and potential ischemia of the right ventricle. This can cause decreased left-sided preload and a reduction in cardiac output. Particularly in the context of any underlying cardiopulmonary disease, the right ventricle may not effectively compensate for an increase in pulmonary vascular resistance, which is, ultimately, the major determinant of survival. Overall, these alterations in right ventricle mechanics result in decreased right-sided output (right ventricle failure), reduced left ventricular preload, and the spectrum of left heart failure, leading to hypotension or hemodynamic collapse.[18]

The symptoms related to PE are wide-ranging. The clinical triad of pleuritic chest pain, shortness of breath, and hemoptysis is rarely found. A large multicenter prospective trial found that hemoptysis is the least likely symptom of the triad, present in only 2.9% of patients with PE. Shortness of breath was the

Table 1. Venous Thromboembolic Risk Factors

Inherited predisposing factors include the following:

- Increased coagulation factor activity/function
  - Activated protein C resistance
  - Factor V Leiden mutation
  - Prothrombin gene mutation
  - Elevated factor VIII levels
- Defects of coagulation factor inhibitors
  - Antithrombin
  - Protein C
  - Protein S
- Defects in fibrinolysis
- Hyperhomocysteinemia
- Altered platelet function

Acquired predisposing factors include the following:

- Advancing age (particularly > 60 years)
- Previous episode of venous thromboembolism
- Obesity
- Malignancy
- Surgery
- Trauma
- Hormone replacement therapy
- Pregnancy
- Heparin-induced thrombocytopenia
- Autoimmune associated hypercoagulability (ie, lupus anticoagulant)

most common, present in 79% of the patients, and chest pain was the next most common symptom, present in 47% of patients with PE (in 1 study, 17% of chest pain arising from PE was nonpleuritic).[19] Cough, lower extremity pain, and lower extremity swelling are the next most common symptoms, with an incidence of 43%, 42%, and 39%, respectively.[20] Another symptom described by some patients is a sense of unease or anxiety that is difficult to describe: a feeling of "impending doom." Symptoms of more hemodynamically significant emboli may, paradoxically, be more difficult to attribute to PE unless the emergency clinician is vigilant about including PE in the differential. The sickest patients with PE may present with syncope, hypotension, or sudden death (often from sudden loss of cardiac output). Additionally, patients with massive or submassive PE may present with undifferentiated shock or syncope (also from either a permanent or temporary drop in cardiac output).

Prehospital Care

Prehospital care for a patient with PE centers primarily around the presenting complaint and the patient's pulmonary and hemodynamic stability. As always, assessment and stabilization of the patient's airway, breathing, and circulation are paramount. Application of supplemental oxygen is often indicated. Room air oxygen saturation should be obtained, if possible, as this will provide helpful information to the emergency clinician. If present, chest pain should be treated, but the choice of treatments will depend on the suspicion for other potential causes of the chest pain. Caution should be used before treating patients with possible PE with vasodilating agents (such as nitroglycerin), as patients with PE may be preload dependent. Intravenous access may be obtained by emergency medical services (EMS), if possible, and hypotension may be treated with normal saline bolus infusion.

Emergency Department Evaluation

History, Physical Examination, And Risk Stratification

Risk stratification is key to the emergency medicine approach to diagnosing PE. Factors from the history and physical examination are used to determine how likely the diagnosis of PE is in an individual patient. As evidenced by the 2 cases presented earlier, the presentation of patients with PE varies widely. Despite much research on the utility of various decision support tools, gestalt clinical assessment remains a valid method of determining risk.[21-24] Clinical gestalt is the implicit, unstructured estimate of the pretest probability of disease and is based on the clinician's education, clinical experience, and, ultimately, overall judgment. The first study describing the use of clinical gestalt in predicting PE is the original PIOPED (Prospective Investigation Of Pulmonary Embolism Diagnosis) study. In PIOPED, the investigators divided 887 patients into 3 groups, based on this assessment: (1) low risk (probability of PE, 0%-19%), (2) intermediate risk (probability of PE, 20%-79%), and high risk (probability of PE, 80%-100%). PE was subsequently diagnosed in 9.2%, 29.9%, and 67.8% of the patients in the low-, intermediate-, and high-risk groups, respectively.[25] The impact of physician experience on the accuracy of gestalt clinical assessment has also been studied. In a 2005 study by Kabrhel, accurate determination of the pretest probability of PE appears to increase with clinical experience, but not significantly. Accuracy was 71% for PGY-1 residents, 74% for PGY-2 and PGY-3 residents, and 78% for PGY-4 and higher physicians.[26]

Although clinical gestalt remains a valid tool, the potential consequences of missing a PE, in combination with the risks of radiation and/or contrast exposure that accompany imaging studies to evaluate for PE, have led to considerable efforts in finding a decision tool that would be sensitive enough to find all significant pulmonary emboli while exposing the least number of patients to the risks of diagnostic testing. The fact that there continues to be so much effort to develop additional tools is evidence that the "holy grail" of diagnostic algorithms has yet to be identified. The ideal decision tool would be based solely on a relatively small number of easily remembered factors in the history and physical examination, would have a high degree of interrater reliability, and would be both sensitive and specific. To date, multiple decision support tools have been developed. The 5 tools most commonly referenced include the Wells score[27] **(see Table 2)**, the simplified revised Geneva score[28] **(see Table 3)**, the pulmonary embolism rule-out criteria (PERC) rule[18,29] **(see Table 4)**, the Charlotte (or Kline) rule,[30] and the Pisa model.[31] All 5 tools use very similar criteria, with various weighting and assigned point systems used. The Pisa model is the most complex and least discussed in the emergency medicine literature.

Although the Wells score is the most studied, it continues to be criticized for the lack of true objectivity. Most notably, the "an alternative diagnosis is less likely than PE" criterion is weighted heavily and, alone, can move someone from "no risk" to "moderate risk." In a 2011 meta-analysis of clinical decision rules for excluding PE, Lucassen et al reviewed the sensitivities and specificities of clinical gestalt, the Wells score, and the revised Geneva score using 52 studies comprising 55,268 patients; a summary of their findings is in **Table 5.**[32]

The PERC rule was developed by Kline et al with the specific objective of identifying patients who have more than trivial risk of PE but can be

safely discharged without any ancillary testing.[18] The PERC rule requires that the clinician already have a clinical impression of risk for PE < 15% ("very low risk"). It then asks a series of 8 yes/no questions **(see Table 4)**. If the answer to all 8 questions is "no," then the risk of having a PE is considered to be minimal. In a follow-up study, the authors found that none of the patients with a "very low" clinical risk and a negative PERC score assessment had PE.[29] The PERC rule was also externally validated by Wolf et al in a series of 134 patients. Although the sensitivity of an appropriately applied PERC score was 100%, the study was somewhat limited by the low prevalence of PE in general (12%), resulting in a 95% CI of 25% to 100%.[33]

Courtney et al published a prospective multicenter analysis of history and physical examination findings that increase or decrease the probability of PE. This study evaluated both previously used factors (explicit criteria) and criteria generally thought to be significant but never evaluated (implicit criteria). Three criteria were positively associated with venous thromboembolism (noncancer-related thrombophilia [odds ratio (OR) = 1.99], pleuritic chest pain

Table 2. Wells Score[27]

Criteria			Points
Suspected DVT			3.0
An alternative diagnosis is less likely than PE			3.0
Heart rate > 100 bpm			1.5
Immobilization or surgery in the previous 4 weeks			1.5
Previous DVT/PE			1.5
Hemoptysis			1.0
Malignancy (on treatment, treated in the last 6 months, or palliative)			1.0
Score Range (Points)	**Probability of PE (%)**	**% With This Score**	**Interpretation of Risk**
Traditional interpretation			
0-1	3.6 (2.0-5.9)	40.3	Low
2-6	20.5 (17.0-24.1)	52.6	Moderate
> 6	66.7 (54.3-77.6)	7.1	High
Alternative interpretation			
0-4	7.8 (5.9-10.1)	71.5	PE unlikely
> 4	40.7 (34.9-46.5)	28.5	PE unlikely

Abbreviations: bpm, beats per minute; DVT, deep vein thrombosis; PE, pulmonary embolism.

Used with permission. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients' probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost.* 2000; 83(3):416-420.

An online tool is also available to calculate the Wells score for PE: http://www.mdcalc.com/wells-criteria-for-pulmonary-embolism-pe/

Table 3. Simplified Revised Geneva Score[28]

Predictor	Point Score
Age ≥ 65	1
Active malignancy	1
Unilateral lower limb pain	1
Previous DVT/PE	1
Hemoptysis	1
Recent (< 4 wk) surgery or fracture	1
Tenderness over lower limb deep venous palpation and unilateral edema	1
Heart rate:	
75-94 bpm	1
> 94	2
Total Score	**0-8**

Low risk: ≤ 2 points; high risk: ≥ 3 points.

Abbreviations: bpm, beats per minute; DVT, deep vein thrombosis; PE, pulmonary embolism;

Table 4. Pulmonary Embolism Rule-Out Criteria (PERC)[18,29]

1. Is the patient > 49 years of age?
2. Is the pulse rate > 99 beats per minute?
3. Is the pulse oximetry reading < 95% while the patient breathes room air?
4. Is there a present history of hemoptysis?
5. Is the patient receiving exogenous estrogen?
6. Does the patient have a prior diagnosis of venous thromboembolism?
7. Has the patient had recent surgery or trauma requiring endotracheal intubation or hospitalization in the previous 4 weeks?
8. Does the patient have unilateral leg swelling (visual observation of asymmetry of the calves)?

This tool is used in a patient judged by the emergency clinician to be low-risk for PE. If the answer to all questions is "no," then no diagnostic testing is necessary.

Table 5. Sensitivity And Specificity Of Clinical Gestalt, Wells Score, And Revised Geneva Score[32]

Decision Tool	Sensitivity (%)	Specificity (%)
Clinical gestalt	85	51
Wells score (cutoff < 2)	84	58
Wells score (cutoff < 4)	60	80
Revised Geneva score	91	37

[OR = 1.53], and family history of venous thromboembolism [OR = 1.51]), and 3 were negatively associated with venous thromboembolism (female sex [OR = 0.60], current smoking [OR = 0.60], and substernal chest pain [OR = 0.60]). Both the presence of tachypnea (respiratory rate > 24 breaths/min) and patient perception of dyspnea were associated with increased likelihood of venous thromboembolism (OR = 1.26 for both), but with lower limits of the 95% confidence interval (CI) of 1.02 and 1.00, respectively. Several predictor variables often cited as providing rationale for test ordering were not statistically significant, including pregnancy or postpartum state, sudden onset of symptoms, obesity (body mass index $\geq 30\ kg/m^2$), and history of treated but currently inactive malignancy.[19] Validation studies are needed to confirm the utility of these variables in adjusting risk.

The remainder of the decision tools currently available are used to assist the clinician in deciding the depth of investigation necessary to safely rule out a PE. The Charlotte (Kline) rule, as well as recent revisions of the Wells score and the simplified revised Geneva score, now attempt to divide patients into only 2 distinct classes: one in which a negative quantitative D-dimer test can rule out PE and another in which further testing is needed.[27,28,30]

Some of the most recent research looked at the impact of a computerized decision support system on the work-up of patients with suspected PE. A 2011 study by Drescher et al showed that the use of an evidence-based entry-based computerized decision support system was associated with a higher yield of computed tomographic angiography (CTA) for PE. Implementation of this system resulted in a slight increase in the total number of CTAs ordered (229 vs 205); however, there was an overall increase in the positive CTA rate from 8.3% to 12.7% (95% CI, 1.4%-10.1%).[34] A limitation of this study was that it did not address missed cases of PE in which no CTA scan was ordered, raising a concern that the increase in specificity was at the cost of sensitivity. Further studies addressing both sensitivity and specificity are necessary to adequately assess these types of tools.

Pending further studies showing a significant difference between clinical gestalt and any particular decision support tool, we recommend using either clinical gestalt alone or one of the well-studied and validated decision support tools described here. For a summary of clinical features that predict the presence or absence of PE, **see Table 6.**

Diagnostic Studies

Although PE is well-studied, it continues to present a diagnostic challenge in many circumstances.[35] Several diagnostic studies are commonly utilized in the evaluation of patients with possible PE:

- Chest radiography (chest x-ray)
- Electrocardiogram (ECG)
- Arterial blood gas analysis
- Quantitative D-dimer
- Computerized tomographic pulmonary angiography (CTPA) of the chest
- Ventilation/perfusion (V/Q) lung scan
- Cardiac echocardiography
- Venous compression ultrasonography

In addition, other tests are often used to assess for the severity of disease, such as troponin and brain natriuretic peptide. Other modalities, such as magnetic resonance imaging (MRI) and pulmonary angiography, are indicated in specific circumstances.

Chest X-ray

The main benefit of chest x-ray in the evaluation of PE is to evaluate for alternative causes of presenting symptomatology.[36] Although chest x-ray is normal in < 25% of cases of PE, it is rare to see findings specific to PE, such as Fleischner sign (distended central pulmonary artery due to the presence of a large clot), Westermark sign (oligemia distal to the embolism), Hampton hump (a pleural-based wedge-shaped consolidation), or Fleischner lines (long bands of focal atelectasis seen in pulmonary infarction). Commonly seen abnormal findings include cardiomegaly, elevated hemidiaphragm, and pleural effusion.[37]

Electrocardiogram

ECG findings are nonspecific and of limited value in the evaluation of a patient with a potential PE. In a retrospective analysis of 117 patients without preexisting cardiac or pulmonary disease who were diagnosed with PE in the PIOPED study, Stein et al concluded that a normal ECG can be seen in 30% of patients with PE, whereas the classic S1Q3T3 has a sensitivity and specificity of 54% and 62%, respectively, and was found to occur in only 20% of patients with angiographically proven PE.[38] A review of 80 ECGs from a series of 80 consecutive patients diagnosed with PE found that anterior subepicardial ischemic pattern is the most frequent ECG sign of massive PE.[39] Surprisingly, sinus tachycardia is the most common presenting rhythm in patients with PE, although it was found in only 36% of the 117 patients evaluated in the retrospective analysis of PIOPED patients.[38] The most common ECG change is T-wave inversion in the anteroseptal and inferior leads, which is found in 68% of patients with PE.[39] **(See Figure 1, page 8.)**

The number of inverted T-waves in the anterior and inferior distribution increase with severity of right heart strain, cor pulmonale, and resulting subepicardial ischemia, and predicts early complications from PE.[40] In a retrospective review of 127

Table 6. Clinical Features From The History And Physical Examination That Predict The Presence Or Absence Of Pulmonary Embolism[19]

	Probability System	Patients With PE With This Finding, No. (%)	Adjusted Odds Ratio	95% Confidence Interval	*P*
Explicit Predictor Variables					
Unilateral leg swelling	W,G,C,P	710 (8.9)	2.60	2.05–3.30	< .001
Surgery within the previous 4 weeks (requiring general anesthesia)	W,G,C,P	520 (6.6)	2.27	1.70–3.02	< .001
Trauma within the previous 4 weeks (requiring hospitalization)	W,P	90 (1.1)	0.78	0.37–1.65	.520
Immobilization (any of the following): generalized body immobility for 48 hours in the prior 2 days, bedridden status, paralysis/paresis, or limb in cast/external fixator	W	763 (9.6)	1.72	1.34–2.21	< .001
Hemoptysis	W,G,C,P	227 (2.9)	0.78	0.46–1.32	.353
Patient history of VTE	W,G,P	858 (10.8)	2.90	2.32–3.64	< .001
Pulse > 94 beats/min*	G	3234 (40.7)	1.52	1.24–1.87	< .001
Active malignancy: current chemotherapy, radiation therapy, or palliative care	W,G	489 (6.2)	1.92	1.43–2.57	< .001
Shock index > 1.0 (pulse ÷ systolic blood pressure)	C	834 (10.5)	1.26	0.96–1.65	.093
Age > 50 years	C,P	3467 (43.7)	1.35	1.10–1.67	.005
Hypoxemia: oxygen saturation < 95% on pulse oximetry	C,P	1544 (19.4)	2.10	1.70–2.60	< .001
Estrogen (current use)	P	663 (8.4)	2.31	1.63–3.27	< .001
Implicit Predictor Variables					
Female gender		5328 (67.1)	0.57	0.47–0.69	< .001
Pregnancy or postpartum state		285 (3.6)	0.60	0.29–1.26	.180
Thrombophilic condition (not cancer related); any of the following known in the ED: factor V Leiden mutation, protein C or S deficiency, prothrombin mutation, antiphospholipid antibody syndrome, or sickle cell disease (both SS and SC variants)		149 (1.9)	1.99	1.21–3.3	.007
Smoking tobacco currently		1839 (23.2)	0.59	0.46-0.76	0.001
Sudden onset of symptoms		4407 (55.5)	0.88	0.73–1.06	.175
Substernal chest pain (located behind the sternum)		2909 (36.6)	0.58	0.46–0.72	< .001
Pleuritic chest pain (between clavicles and costal margin; changes with respiration)		3660 (46.1)	1.53	1.26–1.86	< .001
Dyspnea (patient perception of shortness of breath or difficulty breathing)		5587 (70.4)	1.26	1.00–1.58	.048
Inactive malignancy (not being treated with chemotherapy, radiation, or palliative care)		512 (6.4)	0.82	0.56–1.18	.284
Obesity (BMI ≥ 30)		2885 (36.3)	1.13	0.93–1.38	.214
Fever (temperature ≥ 38°C)		292 (3.7)	1.13	0.76–1.69	.536
Tachypnea (respiratory rate > 24 breaths/min)		1667 (21.0)	1.26	1.02–1.56	.035
Family history of VTE		820 (10.3)	1.51	1.14–2.00	.004

*Tachycardia was also part of the PERC rule (> 99 beats/min) and the Wells score (> 100 beats/min).

Abbreviations: BMI, body mass index; C, Charlotte (Kline) rule; ED, emergency department; G, Geneva score rule; P, PERC rule; PERC, pulmonary embolism rule-out criteria; VTE, venous thromboembolism; W, Wells score.

patients with confirmed PE by Kosuge et al, T-wave inversions in both leads V1 and V3 had a 99% positive predictive value for PE.[41] Although limited in its sample size, the 80 ECG reviews by Ferrari et al found that reversal of these findings before the sixth day was shown to be associated with a more favorable outcome.[39] As with chest x-ray, the primary utility of ECG in the evaluation of a patient with potential PE is to reveal other diagnoses such as acute ST-elevation myocardial infarction.

Arterial Blood Gas Analysis

Prior to the development and validation of more specific tests for PE, assessment of oxygenation and calculation of the alveolar-arterial (A-a) oxygen gradient was often used to increase or decrease the perceived risk for PE; however, in the current population of patients found to have PE, the arterial blood gas and pulse oximetry do not reliably predict the presence or absence of PE.[42] Studies have persistently demonstrated that blood gas analysis is insufficiently sensitive or specific to have a meaningful use in the evaluation of PE. Evaluation of 768 patients participating in the multicenter PIOPED study found that between 25% and 35% of patients with confirmed PE have a normal arterial blood gas, pulse oximetry, and A-a oxygen gradient.[43] A retrospective evaluation of 152 consecutive patients by Jones et al supported the finding that the absence of an A-a oxygen gradient with arterial blood gas results was insufficient to properly rule out PE.[44]

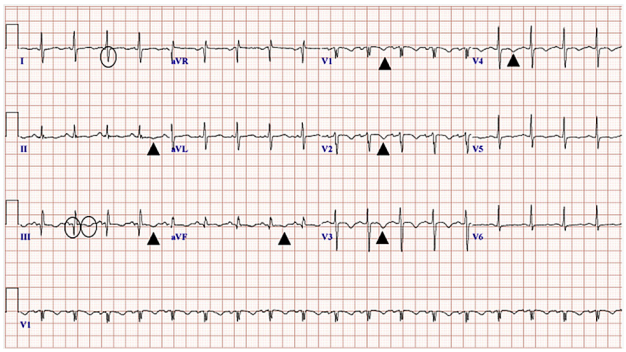
D-dimer

D-dimer is formed during the degradation of fibrin and is usually elevated in patients with PE.[45] D-dimer assays can be divided into 2 types: qualitative assays and quantitative assays. Qualitative assays have both a lower sensitivity for PE and lower inter-rater reliability, and they are not currently recommended for use in the evaluation of PE.[46] Highly sensitive quantitative D-dimer assays include the ELISA (enzyme-linked immunosorbent assay) and the turbidimetric assays. Both types of assays give a quantitative result that either falls above or below the cutoff. While the specificity of these tests is low (39% and 55%, respectively), they have reported sensitivities of > 93% (at a cutoff of 500 ng/mL) and are thus recommended to rule out the possibility of PE in appropriate patients.[47,48] Determining the appropriate population of patients in which this test can be applied is important, as PE was found within 3 months of presentation in > 2% of both intermediate- and high-risk patients with a negative D-dimer.[49,50] Another limitation of the D-dimer is that certain factors or situations will increase or decrease the result, potentially increasing the false positive or false negative rate.[51] **(See Table 7.)** Nonetheless, in otherwise low-risk patients who have conditions that may elevate the D-dimer, a negative result is useful. Given the risk of harm associated with advanced imaging, many of these patients should be evaluated with a D-dimer, similar to other low-risk patients.

Computerized Tomographic Pulmonary Angiography

CTPA has become the primary radiologic study ordered for the evaluation of PE[52,53] and is the overwhelming choice among both emergency clinicians

Figure 1. Electrocardiogram Of Patient With Massive Pulmonary Embolism



Sinus tachycardia, with an S1Q3T3 pattern noted by the circles and anterior-inferior T-wave inversions noted by the triangles.

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Table 7. Factors That Can Increase Or Decrease The Accuracy Of The D-dimer Assay In Diagnosing Pulmonary Embolism[48]

Can Cause False-Negative D-dimer
• Symptoms of PE for > 3 d
• Small PE
• Use of qualitative latex fixation tests
• Use of anticoagulants

Can Cause False-Positive D-dimer
• Cancer and malignancy
• Recent surgery
• Infection (eg, pneumonia, sepsis)
• Pregnancy
• Age > 70 years
• Disseminated intravascular coagulation
• Trauma
• Arterial thrombosis
• Acute coronary syndrome/myocardial infarction
• Vaso-occlusive sickle cell crisis
• Acute cerebrovascular event
• Atrial fibrillation
• Vasculitis
• Superficial phlebitis

Abbreviation: PE, pulmonary embolism.

and radiologists. The use of CTPA for the visualization of the pulmonary vasculature and the evaluation of PE was first described in 1992 by Remy-Jardin et al.[54] Their initial research showed a sensitivity of 100% and a specificity of 96%, which led to quick adoption of CTPA as the primary radiographic tool for diagnosing PE.[54] The 2011 ACEP Clinical Policy on PE summarizes the studies that have been done to date.[46] Single-detector scanners, as used in the Remy-Jardin study, show sensitivities ranging from 37% to 100% and specificities between 78% and 100%. Studies evaluating multidetector CT are fewer, but, as expected, they show improved accuracy, with sensitivities between 83% and 100% and specificities between 89% and 98%.[46]

Although CTPA alone does detect the majority of pulmonary emboli, it appears to be falsely negative in approximately 15% to 20% of cases, even with multidetector scanners. Factoring the pretest probability of PE into the utilization of CTPA results has been shown to increase the sensitivity of CTPA. In a follow-up study to PIOPED II, Stein et al found that, although the overall sensitivity of CTPA for PE is high, in those patients with a high pretest probability of PE and a negative CTPA result, the negative predictive value for PE was much lower (60%).[52] This study went on to assess whether the addition of venous phase imaging (CTA and computed tomographic venography [CTV]) added sensitivity to CTPA alone. The study found that CTA-CTV increases the test's sensitivity for PE from 83% (95% CI, 76%-92%) to 90% (95% CI, 84%-93%), with essentially no change in the specificity. With both types of imaging, however, it is noteworthy that the predictive value of either test was found to be high, with concordant clinical assessments. Among patients with a low clinical probability, the negative predictive value for PE was 96% (158 of 164 patients) in the CTA-only group and 97% (146 of 151 patients) in the CTA-CTV group. Among patients with a high clinical probability, 40% of results on CTA and 18% of results on CTA-CTV were false-negative.[52]

One of the limitations of CTPA is that it is not sensitive enough to detect all subsegmental emboli. In 2010, Carrier et al published a meta-analysis of the accuracy of single-detector and multidetector CT scans.[55] In patients who underwent a single- and multidetector CTPA, the overall rate of subsegmental PE was found to be 4.7% (95% CI, 2.5-7.6) and 9.4 (95% CI, 5.5-14.2), respectively. An unexpected finding, however, was that the 3-month thromboembolic risk in patients with suspected PE who were left untreated based on a diagnostic algorithm including a negative CTPA was the same (0.9% [95% CI, 0.4-1.4] for single-detector CTPA and 1.1% [95% CI, 0.7-1.4] for multiple-detector CTPA). The authors appropriately commented that, although the use of multidetector CTPA seems to increase the proportion of patients diagnosed with subsegmental PE, it does not lower the subsequent 3-month risk of thromboembolism, suggesting that subsegmental PE does not the confer the same risk to the patient as larger clots and raising questions about the utility of treating small emboli. These questions become more important as the resolution of CTPA increases with advancing technology.

A drawback to the use of CTPA is the exposure to radiation and iodinated intravenous contrast material. A CTPA subjects the patient to an average effective radiation dose of 15 mSv (ranges between 2 and 20 mSv), which is equivalent to approximately 150 2-view chest x-rays.[56,57] There are 2 primary adverse reactions to iodinated intravenous contrast media: (1) development of anaphylaxis or other immediate systemic allergic reaction, and (2) contrast-induced nephropathy. Therefore, a history of allergy to intravenous contrast iodine and a history of renal insufficiency may make V/Q scan the better choice.

Ventilation/Perfusion Scanning

V/Q scanning continues to be an option to diagnose PE, but there are drawbacks to its use. The time needed to perform the study, the lack of continuous availability, and the significant number of indeterminate V/Q results have relegated this study to being primarily used in patients who have a contraindication to CTPA. V/Q scanning is completed in 2 steps: the ventilation scan and the perfusion scan. During the ventilation scan, the patient breathes radioactively tagged air and several images are taken in varying positions, essentially outlining the parts of the lung that are ventilated. The perfusion scan utilizes a radioactively tagged tracer that is injected into the vascular system, and then the same images taken during the ventilation scan are repeated. This outlines the areas of the lungs that are adequately perfused. By comparing these images to each other, the nuclear medicine physician or radiologist can discern areas lacking both blood flow and ventilation (a "matched" defect) and areas with adequate ventilation but not perfusion (a ventilation/perfusion "mismatch").

The translation of the magnitude and quantity of these 2 types of defects into a continuum of risk for PE is inconsistent across institutions and nuclear medicine physicians and radiologists. This is particularly true in the low- and intermediate-probability readings, which may cause uncertainty among emergency clinicians regarding what to do with the results. A normal V/Q scan essentially excludes the diagnosis of PE, while in a patient population with a 25% prevalence of disease, a high-probability scan has an 85% to 90% positive predictive value.[35,58] In patients where PE is suspected and there is a low- or intermediate-probability reading on V/Q scan, the actual incidence of PE is between 10% and 40%, thus

illustrating the limitations of V/Q scanning in ruling the disease in or out.[35,58]

Bedside Cardiac Echocardiography

With the increase in emergency physician-performed bedside ultrasonography, focused bedside cardiac echocardiography is becoming an important tool in the assessment of the patient with possible PE.[59] The role of ultrasound in patients with suspected pulmonary embolus is to prioritize further testing, assess the differential diagnosis, and assist with treatment decisions for hemodynamically significant emboli in the severely compromised patient.[59-64] In an acute massive (hemodynamically significant) or submassive (hemodynamically stable with enlargement of the right ventricle) pulmonary embolus, the right ventricle can be dilated and have reduced function or contractility. In patients with hemodynamically significant pulmonary embolus, the left ventricle can be underfilled and hyperdynamic. The presence of right ventricular enlargement and dysfunction in patients with pulmonary embolus is prognostically important and associated with significantly higher inhospital mortality. It is also one of the best predictors of poor early outcome.[59-63,65]

Venous Compression Ultrasonography

Venous compression ultrasonography (CUS) of the lower extremities is another diagnostic tool utilized to increase or decrease suspicion for PE in certain clinical situations. Specifically, they can be used as an initial diagnostic in pregnant patients with an elevated D-dimer[57] and, if positive, can potentially eliminate the need to expose the patient to the radiation from either a CTPA or V/Q scan. CUS can also be used in patients with a moderate to high clinical risk of PE with a negative or inconclusive CTPA or an inconclusive V/Q scan.[51] Classically, CUS has been used following a nondiagnostic V/Q scan. For single negative CUS following nondiagnostic V/Q scans in patients with low pretest probability of PE, early studies showed a PE rate of 1.7% at 3 months.[66] Nonetheless, Daniel and colleagues later showed that a single CUS had a sensitivity of only 54%, a specificity of 97%, and a posttest probability of approximately 12% (95% CI, 6%-17%).[67] A single CUS should not be used to rule out PE, particularly when the test results are discordant with the clinical assessment of risk.[68] For these reasons, follow-up CUS examinations are obtained approximately 5 to 7 days later to assess for clot progression. Two negative CUS examinations following a nondiagnostic or indeterminate V/Q scan result in a 3-month risk of PE of < 1%.[69,70] Early studies with single-slice or 4-slice multidetector CTPA showed that CUS diagnosed an additional 3.1% to 6% of deep vein thromboses and, therefore, a likely PE in patients with suspected PE but negative CTPA.[69] Nonetheless, there are few studies addressing the necessity of CUS after a negative multidetector CTPA.

The diagnostic workup of PE must be closely linked to the emergency clinician's pretest probability of disease. The authors recommend using the 2 clinical pathways for patients with low pretest probability and moderate-to-high pretest probability. **(See pages 12 and 13.)**

Risk Stratification Post Diagnosis

Once the diagnosis of PE has been made, further risk stratification is indicated to guide treatment and disposition. This is based upon perceived risk of clinical deterioration or mortality management plans, and disposition can vary from prescribing subcutaneous low-molecular-weight heparin in patients discharged from the ED to systemic thrombolytics or embolectomy and admission to the intensive care unit. Key to choosing the appropriate therapy and disposition is an assessment of the risk in an individual patient for deterioration and death. Several factors are useful in this assessment. The most important tool in prognostication is ultrasonographic assessment of the right ventricle, as discussed previously.

Scoring systems such as the European Society of Cardiology (ESC) model for predicting early mortality from PE[71] and the simplified Pulmonary Embolism Severity Index (sPESI)[72] have attempted to provide objective and quantitative assessments of risk. **(See Tables 8 and 9.)** The ESC model is available online at: http://www.icirculation.com/Special/ESCNew/Pdf/guidelines-APE-FT.pdf. An April 2012 study by Lankeit et al looked at these systems by comparing the performances of test characteristics of these 2 scoring systems in predicting 30-day outcomes.[73] The study examined a cohort of 526 patients with objectively confirmed PE. The primary endpoint of the study was all-cause mortality. The secondary endpoint was a combination outcome including all-cause mortality, nonfatal symptomatic recurrent venous thromboembolism, or nonfatal major bleeding. Overall mortality in this cohort of 526 patients was 7.6%. The sPESI classified fewer patients as low risk (31% [165 of 526], 95% CI, 27%-35%) compared with the ESC model (39% [207 of 526], 95% CI, 35% to 44%; $P < .01$). Importantly, however, low-risk patients based on the sPESI had no 30-day mortality, compared with 3.4% (95% CI, 0.9-5.8) in low-risk patients by the ESC model. The secondary endpoint occurred in 1.8% of patients in the sPESI low-risk group and 5.8% in the ESC low-risk group (difference, 4.0 percentage points; 95% CI, 0.2-7.8). The prognostic ability of the ESC model remained significant in the subgroup of patients at high risk, according to the sPESI model (OR 1.95; 95% CI, 1.41 to 2.71; $P < .001$).

The value of the cardiac troponin (cTnI) in post-diagnosis risk assessment has been investigated and found to be useful in identifying a subset of patients at increased risk of complications.[74] Autopsy data have shown myocardial necrosis in patients with acute PE and normal coronary arteries, suggesting that a large clot burden causes myonecrosis with resultant increase in cTnI.[75] Elevations in troponin are related to acute right ventricular strain or failure. A 2007 study by Aksay et al sought to determine if elevated troponin I levels can predict complicated clinical course and inhospital mortality in patients with acute PE.[76] This study revealed that elevated cTnI levels are associated with higher rates of inhospital mortality (approximate 3-fold increase) and a complicated clinical course in patients with PE (approximate 9-fold increase). The need for mechanical ventilation in patients with elevated cTnI was 5 times that of patients with normal cTnI, and inotropic support was necessary approximately 3 times as often. Finally, patients with elevated cTnI received thrombolysis approximately 6 times as often as patients with normal cTnI. Brain natriuretic peptide has also been evaluated as a marker for increased severity of disease, but it has not been shown to be specific enough to be useful at this point.[77]

Based on the current literature available, we recommend utilizing the simplified PE severity index together with focused bedside echocardiography and troponin measurements to further risk stratify patients following the diagnosis of PE.

Table 8. Accuracy Of sPESI In Predicting 30-Day Mortality Among Different Risk Groups[73]

		Deaths, Any Cause, at 30 Days	
	Number of Patients (%)	Yes (n = 40)	No (n = 486)
sPESI Risk Class			
Low risk	165 (31%)	0	165
High risk	361 (69%)	40	321
ESC Model Risk Class			
Low risk	207 (39%)	7	200
Intermediate risk	277 (53%)	18	259
High risk	42 (8%)	15	27

This table compares mortality for 526 patients who were classified in each of the 2 systems (sPESI and ESC). Using the sPESI rule, none of the 165 patients classified as low risk died; 40 out of 361 patients classified as high risk died. For the ESC model, 7 out of 207 patients classified as low risk died, 18 out of 277 patients classified as intermediate risk died, and 15 out of 42 patients classified as high risk died.

Abbreviations: ESC, European Society of Cardiology; sPESI, simplified pulmonary embolism severity index.

Treatment

Systemic Anticoagulation

Systemic anticoagulation remains the mainstay of treatment for all patients with PE. This does not lessen clot burden initially, but it does prevent any extension of a clot and allows the body's own fibrinolytic processes to dissolve an existing clot. In hemodynamically stable patients, low-molecular-weight heparin or unfractionated heparin alone are effective and remain the standard of care for initial anticoagulation.[78,79] Initial short-term therapy with unfractionated or low-molecular-weight heparin is generally used until oral therapy with warfarin or another oral anticoagulant reaches therapeutic levels. There has been extensive research showing the safety, efficacy, and appropriate dosing for both unfractionated heparin and low-molecular-weight heparin. Currently recommended dosing of unfractionated heparin is 80 U/kg of ideal body weight as an initial bolus, followed by a constant infusion, which is

Table 9. Original And Simplified Pulmonary Embolism Severity Index (PESI)[72]

Variable	Score	
	Original PESI*	Simplified PESI†
Age > 80	Age in y	1
Male sex	+10	Not included
History of cancer	+30	1
History of heart failure	+10	1‡
History of chronic lung disease	+10	
Pulse ≥ 110 beats/min	+20	1
SBP < 100 mm Hg	+30	1
Respiratory rate ≥ 30 breaths/min	+20	Not included
Temperature < 36°C	+20	Not included
Altered mental status	+60	Not included
Arterial oxyhemoglobin saturation level < 90%	+20	1

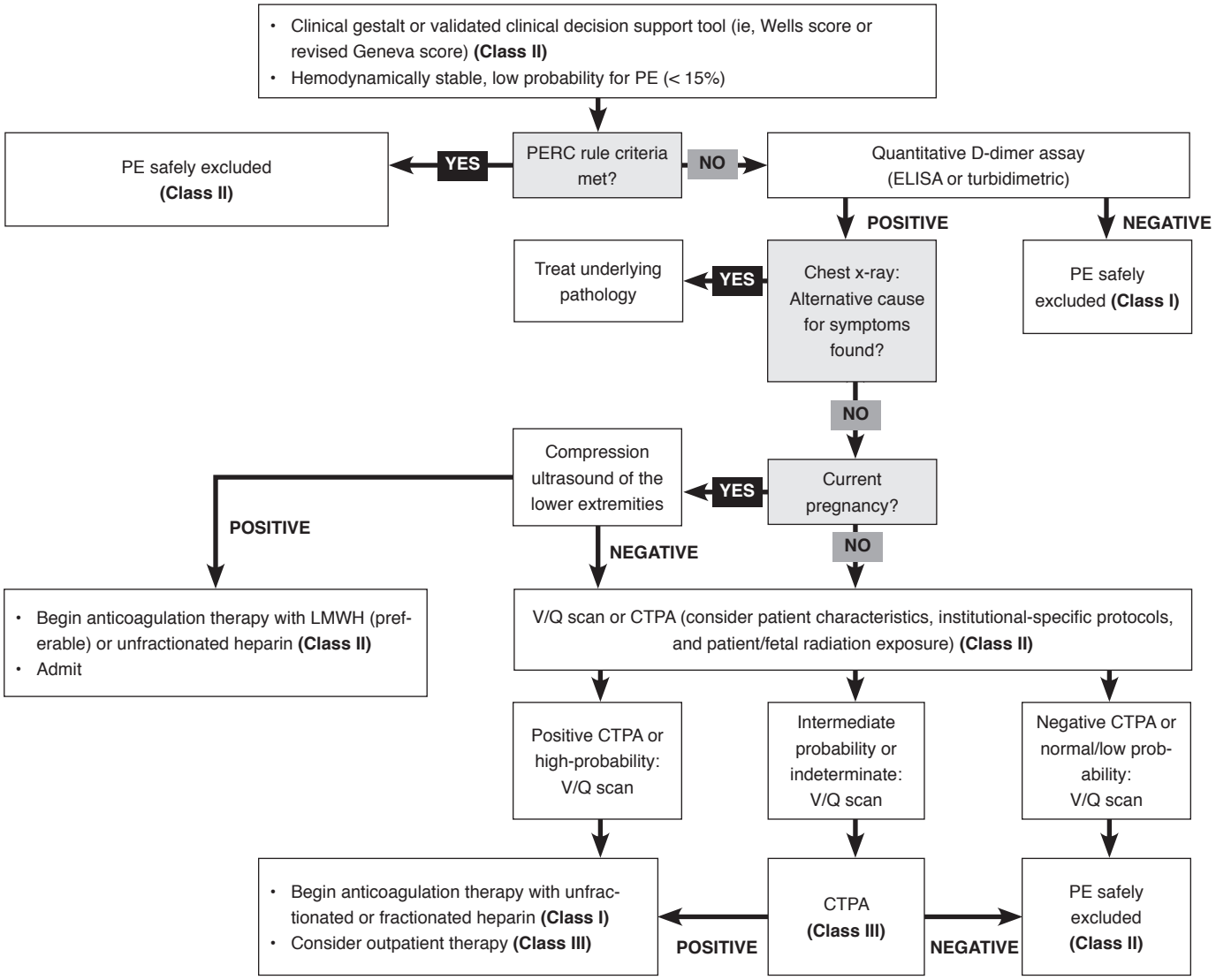
*A total point score for a given patient is obtained by summing the patient's age in years and the points for each predictor, when present. The score corresponds with the following risk classes: ≤ 65, class I; 66-85, class II; 86-105, class III; 106-125, class IV; and > 125, class V. Patients in risk classes I and II are defined as being at low risk.

†A total point score for a given patient is obtained by summing the points. The score corresponds with the following risk classes: 0, low risk; ≥ 1, high risk.

‡These variables were combined into a single category of chronic cardiopulmonary disease.

Abbreviations: PESI, pulmonary embolism severity index; SBP, systolic blood pressure.

Clinical Pathway For Suspected Low-Probability Pulmonary Embolism



Abbreviations: CTPA, computerized tomographic pulmonary angiography; ELISA, enzyme-linked immunosorbent assay; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; PERC, pulmonary embolism rule-out criteria; V/Q, ventilation/perfusion.

Class Of Evidence Definitions

Each action in the clinical pathways section of *Emergency Medicine Practice* receives a score based on the following definitions.

Class I
- Always acceptable, safe
- Definitely useful
- Proven in both efficacy and effectiveness

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

Class II
- Safe, acceptable
- Probably useful

Level of Evidence:
- Generally higher levels of evidence
- Nonrandomized or retrospective studies: historic, cohort, or case control studies
- Less robust randomized controlled trials
- Results consistently positive

Class III
- May be acceptable
- Possibly useful
- Considered optional or alternative treatments

Level of Evidence:
- Generally lower or intermediate levels of evidence
- Case series, animal studies, consensus panels
- Occasionally positive results

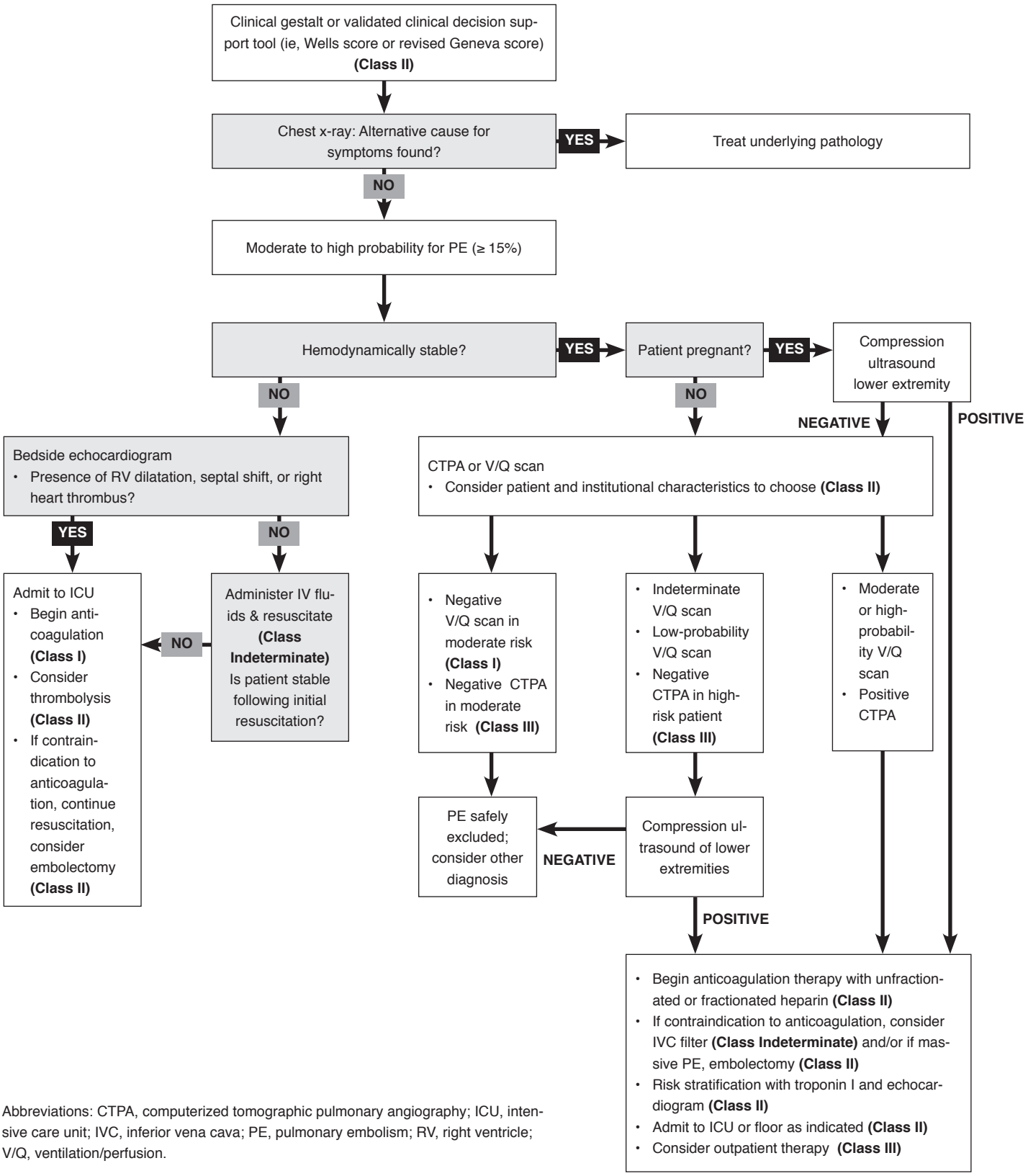
Indeterminate
- Continuing area of research
- No recommendations until further research

Level of Evidence:
- Evidence not available
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Significantly modified from: The Emergency Cardiovascular Care Committees of the American Heart Association and representatives from the resuscitation councils of ILCOR: How to Develop Evidence-Based Guidelines for Emergency Cardiac Care: Quality of Evidence and Classes of Recommendations; also: Anonymous. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IX. Ensuring effectiveness of community-wide emergency cardiac care. *JAMA.* 1992;268(16):2289-2295.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient's individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Clinical Pathway For Moderate- To High-Probability Pulmonary Embolism



Abbreviations: CTPA, computerized tomographic pulmonary angiography; ICU, intensive care unit; IVC, inferior vena cava; PE, pulmonary embolism; RV, right ventricle; V/Q, ventilation/perfusion.

For Class of Evidence definitions, see page 12.

usually initiated at approximately 16 to 18 U/kg of ideal body weight per hour. Close monitoring of the partial thromboplastin time is necessary, with most algorithms calling for serial measurements every 6 hours until the activated partial thromboplastin time is approximately twice baseline. The various low-molecular-weight heparins are dosed according to weight and administered subcutaneously once or twice per day. No monitoring is necessary.

With the safety of low-molecular-weight heparin therapy well established, selected patients with PE may be managed as outpatients. A prospective study demonstrating the safety of outpatient treatment in hemodynamically stable patients with PE was published in 2010 by Agterof.[80] Patients were considered for outpatient therapy as long as they met none of the following exclusion criteria:

- Hemodynamic or respiratory instability (collapse, systolic blood pressure < 90 mm Hg, pulse rate > 100 beats per minute, or the need for oxygen therapy to maintain oxygen saturation > 90%)
- Unrelated illness for which the patient would require hospitalization for more than 24 hours
- Pain requiring intravenous analgesia
- Need for acute thrombolysis at presentation
- Active bleeding or known hemorrhagic diathesis
- Pregnancy
- Hospitalization
- Likelihood of poor compliance
- No support system at home
- Renal insufficiency (defined as a creatinine level > 1.7 mg/dL/L)

In the Agterof study, there were 152 patients who fulfilled the inclusion criteria and were treated as outpatients. There were no reported deaths, major hemorrhages, or recurrent venous thromboembolisms in the first 10 days of treatment or in the follow-up period of 3 months. Only 3 patients (1.9%) required readmission in the first 10 days because of complaints that could be related to PE. Further prospective studies are needed to confirm the promising results of this study, but it appears that outpatient treatment of a select population of patients with PE may be feasible.

Reperfusion Treatments

In addition to systemic anticoagulation, reperfusion treatments for hemodynamically unstable patients with PE may restore pulmonary arterial flow and cardiac output. This can be accomplished in 1 of 2 ways: mechanical removal of the clot (embolectomy) or chemical dissolution of the clot (thrombolysis).

Multiple studies have evaluated the various methods of reducing clot burden. A 2006 study by Kucher[81] reviewed 2392 patients with acute PE from the International Cooperative Pulmonary Embolism Registry (ICOPER). They evaluated the effectiveness of multiple therapies, including thrombolysis, surgical embolectomy, catheter embolectomy, and emergent placement of an inferior vena cava filter. In this study, patients were categorized as either having "massive PE" (systolic arterial blood pressure < 90 mm Hg, n = 108) or "nonmassive PE" (systolic arterial pressure ≥ 90 mm Hg, n = 2284). Reperfusion therapies were not performed in 73 of the 108 patients (68%) with massive PE. In the 33 patients who received thrombolysis, there was no statistically significant improvement in 90-day mortality when compared to patients in which thrombolysis was not used. The 90-day mortality for patients receiving thrombolysis was 46.3% (95% CI, 31.0%-64.8%). The 90-day mortality for patients not receiving thrombolysis was 55.1% (95% CI, 44.3%-66.7%); hazard ratio, 0.79; (95% CI, 0.44-1.43). In addition, there was not a reduction in recurrent PE rates at 90 days (12% for both; $P > 0.99$).[81]

The utility of thrombolytics in the treatment of PE has been studied since the 1960s. In 1970, a landmark trial funded by the National Heart and Lung Institute known as the Urokinase in Pulmonary Embolism Trial (UPET), reported an increased PE resolution rate in the thrombolytic group when compared to the group that received heparin alone. No survival benefit was noted in the patient groups; however, patients were not stratified based on the severity of the event.[82] Phase II of the trial (Urokinase-Streptokinase Pulmonary Embolism Trial [USPET]) was completed in 1973 and showed comparable results for the utilization of streptokinase and urokinase. In this study, thrombolytics were administered within 24 hours of presentation, and although it was not documented, patients did experience major physiologic improvements.[83]

Recombinant tissue plasminogen activator (rt-PA) became available in the 1980s, and off-label uses of rt-PA for unstable patients with PE ensued.[84] To assess its effectiveness (particularly compared to the preferred treatment agent at the time, urokinase), a randomized controlled trial was performed.[85,86] It was found that rt-PA was not only safer, but it was more effective, with a more-rapid onset of action. Meyer et al performed a multicenter study that included 63 patients comparing rt-PA and urokinase.[87] Pulmonary artery mean pressure, cardiac index, and total pulmonary resistance were compared, and they improved in both groups over time; however, they improved more rapidly in the alteplase rt-PA group. Right ventricular function and pulmonary perfusion were rapidly improved in the rt-PA group. Fibrinogen also decreased faster in the rt-PA-treated patients. Another study compared treatment with rt-PA to heparin in patients with acute PE. There were no episodes of recurrent PE among rt-PA patients; however, there

were 5 clinically suspected recurrent PEs within 14 days in patients randomized to heparin alone.[88]

In a *New England Journal of Medicine* study in 2002, in patients with submassive pulmonary emboli, rt-PA plus heparin was compared to heparin alone. It was reported that the group receiving heparin alone had a significant increase in the number of subjects requiring inhospital escalation of treatment for clinical deterioration and 3 times the risk of death.[89]

A recent study of the effectiveness of thrombolysis in unstable patients with PE was published in May 2012 by Stein and Matta.[90] The inhospital all-cause case fatality rate, according to treatment, was determined in unstable patients with PE who were discharged from short-stay hospitals throughout the United States from 1999 to 2008. Among unstable patients with PE, 21,390 of 72,230 (30%) received thrombolytic therapy. The inhospital all-cause case fatality rate in unstable patients who received thrombolytic therapy was 15%, and the rate was 47% in the patients who did not receive thrombolytic therapy ($P < .0001$).[90] **(See Figure 2.)**

Inferior Vena Cava Filters

Insertion of a temporary or permanent inferior vena cava filter is another intervention that has been recently studied to assess its effect on mortality from pulmonary emboli, with preliminarily favorable results.[81] The American College of Radiology created Appropriateness Criteria® of permanent and retrievable inferior vena cava filters, in part, to determine effectiveness in the setting of PE.[91] They found that the only definitive indications for vena cava filter placement are as described in the American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy guidelines. These indications include: (1) patients with contraindications to anticoagulation, (2) those who have complications from the use of anticoagulation, and (3) those who fail to attain adequate anticoagulation while undergoing treatment.[92]

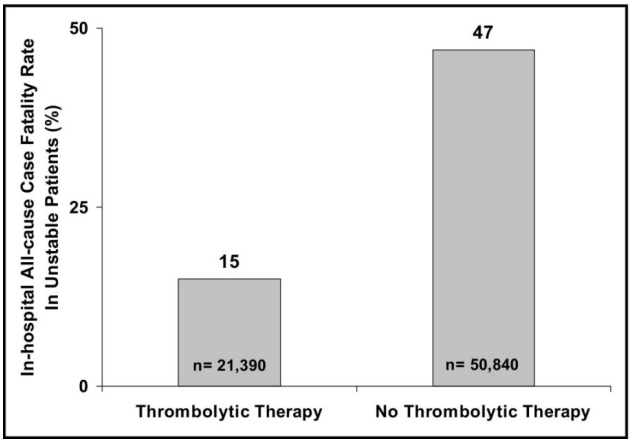
The 2012 study by Stein and Matta demonstrated the impact of vena cava filters in specific situations.[90] There was a marginal decrease in the case fatality rate in stable patients who received a vena cava filter: 21,420 of 297,700 (7.2%) versus 135,240 of 1,712,800 (7.9%) ($P < 0.0001$). A small percentage of these stable patients (1.4%) received thrombolytic therapy, and the patients who also received a vena cava filter had a lower case fatality rate than those who did not: 550 of 8550 (6.4%) versus 2950 of 19,050 (15%) ($P < .0001$).

Unstable patients who received a vena cava filter fared better whether they received thrombolysis or not. The inhospital case fatality rate for unstable patients who received both thrombolytic therapy and a vena cava filter was 7.6% (505 of 6630), significantly less than that of patients who had thrombolytic therapy without vena cava therapy, at 18% (2600 of 14,760) ($P < .0001$). Unstable patients who did not receive thrombolytic therapy also had a lower inhospital case fatality rate with a vena cava filter: 33% (4260 of 12,850) versus 51% (19,560 of 38,000) ($P <.0001$).[90] The retrospective design of this study significantly limits the ability to draw conclusions regarding the true impact of inferior vena cava catheter placement. Further investigation into the risks and benefits of inferior vena cava filter placement is needed and should include a prospective clinical trial comparing anticoagulation to the use of permanent and retrievable filters.

Treatment Summary

Based on the currently available evidence, we recommend that stable patients with a diagnosis of PE be treated with low-molecular-weight heparin unless they have contraindications such as severe renal insufficiency. Patients appropriate for low-molecular-weight heparin therapy should be considered for outpatient therapy, using the criteria described in the Agterof study[80] **(see page 14)** to identify potential candidates. Patients diagnosed with PE who are hemodynamically unstable should be provided aggressive supportive care and treated with systemic unfractionated heparin. Emergent embolectomy or thrombolytic therapy with rt-PA should be considered in patients who have a systolic blood pressure < 90 mm Hg or who otherwise clinically deteriorate further. Systemic thrombolytic therapy should be administered in arrested patients with confirmed or strongly suspected PE who develop pulseless electrical activity.

Figure 2. Association Of Thrombolytic Therapy With A Decrease In Mortality For Unstable Patients With Pulmonary Embolism[90]



Risk Management Pitfalls For Pulmonary Embolism

1. **"PE wasn't a part of this patient's differential."**
   Consider PE in patients with the most-common complaints (chest pain and shortness of breath), but also with less-common complaints such as syncope, dizziness, or anxiety. PE can present with a multitude of complaints, and it is essential to keep a low threshold when deciding to include it in the differential.

2. **"This patient was in shock. I thought he was septic."**
   Always consider massive PE in the differential of undifferentiated atraumatic shock.

3. **"Her PERC score was negative, so I didn't think I had to order any tests."**
   Application of the PERC rule must be confined to a patient population already deemed by the practitioner as low risk. A negative PERC score does not have a negative predictive value high enough to be utilized in any other risk category.

4. **"The D-dimer at triage was negative, so I didn't think I had to worry about PE."**
   Reliance on D-dimer tests other than the quantitative turbidimetric or ELISA assays is inappropriate. Interrater reliability with the qualitative assays used in many point-of-care assays is inadequate, and the sensitivity of this test is not adequate, particularly in the undifferentiated patient.

5. **"I knew the quantitative D-dimer test is much better than the bedside assays. Since it was negative, I stopped the work-up there."**
   As with the PERC rule, interpretation of a negative D-dimer assay must be done in the context of the clinician's pretest probability for disease. Current evidence shows that only in patients considered to have a low clinical risk for PE can a negative quantitative D-dimer safely exclude PE.

6. **"The CTPA was negative, so I discharged the patient."**
   As with prior tests mentioned, a negative CTPA (or indeterminate V/Q scan) does not rule out the possibility of PE in a patient considered high risk for emboli. The clinician must interpret the negative results in the context of pretest probability of disease.

7. **"I started the heparin, and his vitals were fine, so I admitted him to the floor."**
   A significant percentage of initially stable patients with pulmonary emboli will deteriorate during their hospital course, requiring escalation of therapy. Evaluation of the patient's potential for deterioration will aid the clinician in admitting the patient to the correct setting.

8. **"I held the heparin pending the results of his diagnostic tests. I knew he was really tachycardic, but I haven't confirmed the diagnosis yet."**
   In a patient with a high clinical suspicion for disease and signs of hemodynamic instability, initiate anticoagulation therapy immediately. Delayed treatment is associated with increased mortality in these patients.

9. **"I started the patient on 120 mg of enoxaparin. She was dialyzed yesterday."**
   Failure to evaluate for contraindications to specific treatment options can cause significant complications. Patients with renal compromise should be treated with unfractionated heparin. As with all therapeutics, the emergency clinician must have a good understanding of both the indications and contraindications for any therapy initiated.

10. **"I know she was stable, but I thought she would benefit from thrombolytics."**
    Although controversy exists regarding the use of thrombolytic therapy in patients with PE, they are not recommended in stable patients, since the risks outweigh the benefits.

Controversies And Cutting Edge

Computerized Tomographic Pulmonary Angiography Versus Ventilation/Perfusion Scanning

Important considerations when comparing CTPA to V/Q scanning include their sensitivity and specificity and the differences in radiation exposure. The increased use of CT in patients with suspected PE has resulted in an increase in the diagnosis of PE but without an associated mortality benefit.[93,94] It is possible that the falling threshold to rule out PE using CTPA has resulted in overdiagnosis.

In a study published in 2010 evaluating the effectiveness of V/Q scan versus CTPA, while accounting for radiation exposure, the authors found that they were able to decrease the number of CT scans by 25% and increase the number of V/Q scans utilized by more than 50%, with similar diagnostic outcomes.[95] CTPA has become the default test of choice for PE; however, the effective radiation dose, which is approximately 4 times that of a V/Q scan, must be considered. The authors reported that the number of CTPA examinations performed decreased from 1234 in 2006 to 920 in 2007, and the number of V/Q scans increased from 745 in 2006 to 1216 in 2007. The mean effective dose of radiation was reduced by 20%, from 8.0 mSv in 2006 to 6.4 mSv in 2007 ($P < 0.0001$). The patients who underwent CTPA and V/Q scanning in 2006 were of similar age. In 2007, the patients who underwent V/Q scanning were significantly younger. There was no significant difference in the false-negative rate (range, 0.8%–1.2%) between CTPA and V/Q scanning in 2006 and 2007.[95]

In 2007, Anderson et al published the first randomized noninferiority study comparing CTPA to V/Q scan in the diagnosis of PE.[96] Of the 694 evaluable patients randomized to the CTPA group, 133 (19.2%) were diagnosed with PE or deep vein thrombosis in the initial evaluation period (94 isolated PE, 29 PE and deep vein thrombosis, and 10 isolated deep vein thrombosis [7 proximal]). Of the 712 evaluable patients in the V/Q scan group, 101 (14.2%) were diagnosed with PE or deep vein thrombosis in the initial evaluation period (64 isolated PE, 19 PE and deep vein thrombosis, and 18 isolated deep vein thrombosis [11 proximal]). The overall rate of venous thromboembolism (composite of deep vein thrombosis and PE) found in the initial diagnostic period was significantly greater in patients randomized to the CTPA strategy (difference, 5.0%; 95% CI, 1.1%-8.9%, $P = .01$). Mortality or recurrent venous thromboembolism events in the ensuing 3 months were the same in both groups.[96] It is unclear whether this finding is secondary to an increase in false positive studies by CTPA or whether it is secondary to the diagnosis of clinically insignificant emboli. As noted previously, perhaps it is not essential that we identify as many PEs as we are currently identifying with CTPA; continued research on this question is needed. Particularly in light of the continued improvements in CT scan technology, key directions for future research will include an appraisal of which patients with PE benefit from treatment (and, therefore, diagnosis).

Time- And Cost-Effective Strategies

- Minimizing unnecessary testing is one of the primary ways to limit costs and time. This begins with utilizing either clinical gestalt or clinical decision rules to identify the pretest probability of PE and those specific patients who require no diagnostic testing to evaluate for PE. Once the decision to pursue diagnostic testing has been made, only those tests with the ability to significantly alter pretest probability should be considered. Arterial blood gas sampling, qualitative D-dimer tests, and pro-brain natriuretic peptide levels do not have the ability to affect pretest probability in any risk group, so these tests should not be used in the risk assessment for PE.
- Several other diagnostic tests are helpful in certain situations but not in others. For example, a negative quantitative D-dimer assay is helpful in low-risk patients but not high-risk patients. A cardiac troponin I is not helpful in the diagnosis of PE, but it is helpful in the assessment for severity of disease. When choosing between CTPA or V/Q scans, take the patient's chest x-ray into consideration, as the presence of an abnormal chest x-ray increases the potential for an indeterminate result. Also pertinent to the decision between CTPA or V/Q is the significantly increased time to perform a V/Q scan. The time to obtain a result should also be taken into account, as it is institutional dependent.
- Regarding the treatment of PE, the ease of administration of low-molecular-weight heparin versus unfractionated heparin is clear. Treatment with unfractionated heparin includes a more complicated dosing calculation, maintenance of a continuous infusion, and frequent blood tests to monitor therapeutic effectiveness.
- Although not validated by prospective studies, the option of outpatient treatment of stable patients with pulmonary emboli has the potential to significantly decrease costs.

Diagnostic Testing In Pregnancy

There is controversy over which test – CTPA or V/Q scan – is better in the setting of pregnancy. While radiation exposure to the patient is clearly higher with CTPA, radiation exposure to the fetus is higher with V/Q scanning, as radioactive tracer accumulates in the bladder.[57] The Fleischner Society guidelines recommend CTPA as the next imaging test in pregnant patients after a negative lower-extremity ultrasound.[97] Conversely, more than two-thirds of the PIOPED investigators recommend V/Q scan over CTPA for imaging pregnant patients with suspected PE.[36] Therefore, the decision as to which imaging test to choose may ultimately rest on the specific patient circumstances and individual judgment of the physician. In 2011, the American Thoracic Society made recommendations regarding diagnostics in pregnant patients with suspected PE; however, the evidence for their recommendations is primarily a consensus of experts without significant data to support it.[98] Based on the evidence, we agree with their recommendation for a chest radiograph as the initial chest imaging study, but we do not feel it is appropriate to make concrete recommendations following a normal chest x-ray. Many institutions have limitations with respect to availability of nuclear medicine studies or the availability of radiologists who have expertise in interpreting a V/Q scan; therefore, each emergency physician must make that decision with respect to his or her institution's resources and ability to give a meaningful interpretation of the diagnostic study performed. The least desirable scenario is one in which both a V/Q scan and a CTPA are needed to complete the diagnostic evaluation.

Disposition

The current standard of care for any patient diagnosed with a PE is admission to the hospital. As discussed in the Risk Stratification Post Diagnosis section **(see page 10),** the exact admission location varies, depending on the patient's clinical status and potential for complications. Patients who are hemodynamically unstable clearly require admission to an intensive care unit. Patients who are hemodynamically stable but have a greater potential to deteriorate (such as those with an elevated troponin I or abnormal right-sided heart function seen on echocardiography) may also require admission to in intensive care unit. Patients who are hemodynamically stable and do not have risk factors for increased mortality may be safe to manage on a general medical floor; however, patients with coexisting acute and chronic medical conditions have the potential to require admission to a higher level of care. Recent research has raised the possibility of outpatient management of a select group of patients with PE and is discussed in the Treatment section on **page 14**.

Summary

PE results most often from the presence of a clot in the pulmonary vasculature, and is an important cause of significant morbidity and mortality in ED patients. For centralized PEs, outflow obstruction of the right ventricle, resulting in increased right-sided afterload, leads to elevated right ventricular wall stress, right ventricle dilatation, dysfunction, and potential ischemia of the right ventricle. This can propagate further to cause a decreased left-sided preload and reduction in cardiac output. While there are many causes of PE, the clinical signs and symptoms are nonspecific, and the emergency clinician must decide which patients must undergo diagnostic tests until PE is ruled in or out or an alternative diagnosis is found. Many clinical decision tools have been devised to assist in the decision-making process, including (but not limited to) the Wells score, PERC rule, simplified revised Geneva score, Kline rule, and Pisa rule. For the most part, the tools use similar criteria, with various weighting and assigned point systems. A large weight, however, is given to clinical gestalt, resulting in further diagnostic subjectivity. Therefore, the diagnostic workup of PE must be closely linked to the emergency clinician's pretest probability of disease, which is the impetus for further stratifying the presenting patient population as low probability or moderate to high probability and allowing for more concrete decision making. The use of emergency bedside echocardiography to determine patients requiring immediate intervention has been included as a mainstay of PE workup in the ED. Admission versus outpatient management is also an important issue; however, more evidence is necessary before outpatient therapy as a mainstay of PE management can be recommended. While much of the disease process of PE has been elucidated with our understanding of the etiology and pathophysiology, it remains an insidious threat. Future investigators must determine whether all PEs are necessary to diagnose and find a way to limit testing while preserving the safety of the patient.

Case Conclusions

In the 48-year-old construction worker, acute coronary syndromes was your primary concern; however, given the patient's recent history of deep vein thrombosis, a CTPA was ordered to assess for PE. This showed multiple central pulmonary emboli, including a saddle embolism. The exact wording at the end of this preliminary reading was, "clinically correlate if patient still alive." You performed bedside cardiac ultrasound and saw a dilated right ventricle. Based on these findings, the patient was admitted to the ICU. Approximately 6 hours later, the patient became increasingly dyspneic and tachycardic. A repeat bedside ultrasound showed increased dilatation of the right ven-

tricle. The patient was taken emergently to angiography, where rt-PA was administered into the central pulmonary vasculature. The patient's hemodynamics improved, as did his symptoms. He was eventually discharged from the hospital on warfarin therapy.

In the patient with right lower extremity swelling, deep vein thrombosis was your primary concern. A bedside lower extremity ultrasound was performed, and a large right common femoral vein thrombosis was visualized. The patient was started on heparin and sent for a CTA of the chest, where bilateral pulmonary emboli were visualized. The patient was anticoagulated with unfractionated heparin, admitted to the medical floor, and discharged approximately 1 week later on warfarin therapy. A full hematologic and malignancy work-up was conducted, and no evidence of cancer or hypercoagulability was found.

This Month In *EM Practice Guidelines Update*

The December 2012 issue of *EM Practice Guidelines Update* reviews the American College of Emergency Physicians (ACEP) 2012 Clinical Policy, "Critical Issues in the Initial Evaluation and Management of Patients Presenting to the Emergency Department in Early Pregnancy." This 2012 revision of the 2003 ACEP Clinical Policy reviews 3 Critical Questions on management of patients who present to the ED in early pregnancy with abdominal pain and/or vaginal bleeding. Historically, quantitative beta-hCG levels and the concept of the "discriminatory threshold" have been used to help discriminate early intrauterine pregnancy from ectopic pregnancy. When beta-hCG levels are above a defined threshold, it is expected that an intrauterine pregnancy should be visible on sonography, and when it is not, a presumptive diagnosis of ectopic pregnancy is made. This issue of *EM Practice Guidelines Update* excerpts the Clinical Policy revision and comments on the implications for emergency clinicians. Subscribers to *Emergency Medicine Practice* have free access to this online publication at www.ebmedicine.net/EarlyPreg.

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Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, are noted by an asterisk (*) next to the number of the reference.

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CME Questions

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1. Which of the following symptoms is most common in a patient with pulmonary embolism?
a. Chest pain
b. Hemoptysis
c. Shortness of breath
d. Syncope

2. Which of the following is NOT a validated tool that can be used in the evaluation of a patient's risk for PE?
a. Clinical gestalt
b. PERC
c. Revised Geneva score
d. San Francisco rule

3. A 39-year-old female presents with 2-day history of shortness of breath, nonproductive cough, and right-sided chest pain. She has no past medical history, takes no medications, and has never been hospitalized or had any surgery. She denies tobacco, alcohol, or drug use. Her vital signs are as follows: oral temperature of 36.8°C, pulse of 88 beats per minute, respiratory rate of 20 breaths per minute, and a saturation of 96% on room air. Her examination is normal except for scattered rhonchi on the right chest. You have decided that although PE is in your differential, her risk is very low. Using the PERC criteria, can PE be safely excluded without any additional testing?
a. No
b. Yes

4. **Which ECG finding is most common in a patient with a PE?**
   a. Sinus bradycardia
   b. T-wave inversions in V2-V4
   c. U-waves
   d. Wide QRS

5. **Which of the following diagnostics has been found to be neither sensitive nor specific enough to be helpful in the evaluation of PE?**
   a. Arterial blood gas sampling
   b. CTPA
   c. Echocardiogram
   d. V/Q scan

6. **You have evaluated a patient presenting for chest pain, and although your clinical gestalt suggests a very low risk of PE, the patient does not meet the PERC criteria. Which of the following would be the most appropriate next step?**
   a. CTPA
   b. Compression ultrasonography of the lower extremities
   c. Quantitative D-dimer
   d. V/Q scan

7. **Which of the following predicts increased mortality in a patient with PE?**
   a. Elevated brain natriuretic peptide
   b. Normal troponin I
   c. Dilated right ventricle on echocardiography
   d. Pregnancy

8. **In the 2010 study by Agterof, which of the following excluded patients from being considered for outpatient treatment of PE?**
   a. Good access to follow-up care
   b. Hemodynamic stability
   c. Pain relieved by oral medications
   d. Pregnancy

9. **Regarding treatment for PE, which finding would favor treatment with unfractionated heparin versus fractionated heparin?**
   a. Concurrent heart failure
   b. Hyperglycemia
   c. Renal failure
   d. Thrombocytopenia

10. **Which of the following is TRUE regarding diagnostic imaging for PE in pregnant patients?**
    a. Choice of testing should be made on an institution- and patient-specific basis.
    b. Computed tomographic pulmonary angiography is preferred.
    c. Negative compression ultrasonography of bilateral lower extremities is adequate to rule out PE.
    d. V/Q scanning is preferred.

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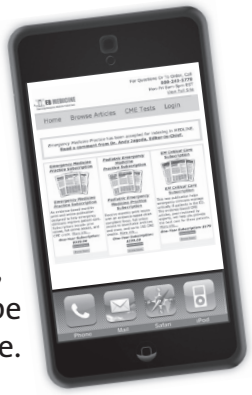

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