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Pulmonary embolism: an unsuspected killer

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The accurate diagnosis of pulmonary embolism (PE) is crucial. PE is currently the third leading cause of death in the United States with 50,000 to 100,000 estimated deaths per year and an incidence of 0.5 to 1 per 1000 [1–4]. PE is a leading cause of unexpected deaths in hospitalized patients and a major source of medical malpractice lawsuits [5]. However, the diagnosis is missed more often than it is made. One author conservatively estimates that more than half of fatal PE cases are not even suspected antemortem [6]. Prior autopsy studies consistently have shown the rate to be even higher, at approximately 70% [7–11]. Conversely, in patients in whom the diagnosis is considered, the prevalence of PE is only 25% to 35% [12,13]. Therefore, clinicians generally miss PE when it is present and suspect it when it is not. PE is truly an unsuspected killer with profound clinical implications. Although patients in whom PE is diagnosed and treated have a mortality rate of only 3% to 8% [3,14,15], those in whom the diagnosis is missed have a fourfold to sixfold greater mortality [3,6,15].

Before the use of heparin, surgical interventions were the only treatment options available for PE with a mortality rate approaching 100% [16]. Heparin first was administered to treat PE in the 1930s, but concerns over its safety in this setting prevented more widespread use. It was not until 1960 that the benefits of anticoagulation therapy were confirmed [17]. Beginning

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in the 1960s, the use of fibrinolytics was studied; fibrinolytics were reserved primarily for unstable patients with PE [16]. With the advent of effective therapy, the accurate diagnosis of thromboembolic disease became vital.

Although many deaths are attributed to undiagnosed pulmonary emboli, the actual incidence of PE in the general population and the risk of mortality or morbidity from an individual pulmonary embolus are unknown. A high incidence of asymptomatic PE has been shown in patients with deep venous thrombosis (DVT) [18–22], suggesting that PE may be common and only infrequently may lead to death. Although some studies have found mortality rates from untreated PE ranging from 25% to 30%, these studies involved patients with other comorbidities that likely contributed to the adverse outcomes [17,23,24].Other studies involving patients without coexisting cardiopulmonary disease have found that mortality even with untreated or recurrent PE was significantly lower [22,24–27]. A follow-up study of the untreated patients with PE from the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) revealed a mortality rate from PE of only 5% (1 in 20) [27].

Given the fact that anticoagulation carries with it significant bleeding risks and that not all cases of PE cause morbidity or mortality, the risk of misdiagnosis of PE is not limited to missing the diagnosis. Incorrectly diagnosing PE in patients in whom it is absent or inconsequential unnecessarily exposes them to the risks inherent with long-term anticoagulation therapy. Because the accurate diagnosis of PE is crucial to maximizing patient outcomes, this article focuses on atypical presentations, unique challenges in certain patient populations, and current diagnostic strategies for PE.

Background

Venous thromboembolism (VTE) is a disease with a spectrum of manifestations that include thrombophlebitis, DVT, and PE. Most pulmonary emboli have their origin in clots in the iliac, deep femoral, or popliteal veins. Pulmonary emboli also can originate from sources in the upper extremities, central vascular access devices, heart, and vena caval filters [28–30]. The site of the DVT does not seem to be as important as previously was thought because PE can occur from any site of DVT formation [31]. Calf vein thrombosis, previously considered relatively benign, propagates above the knee in approximately 80% and may cause PE without first extending proximally [16]. Likewise, although superficial thrombophlebitis is generally benign, it can extend into the deep venous system and pose a risk for PE [32]. In many instances of PE, no peripheral source of thrombosis is ever identified.

Virchow first described the process of thrombosis as involving a triad of stasis, hypercoagulability, and endothelial injury [33]. Risk factors for PE can be inherited or acquired (Box 1) and must be considered when assessing a patient's probability of PE [29,30,35]. The strongest risk factor of

Box 1. Risk factors predisposing to venous thromboembolism

Inherited risk factors
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden mutation

Acquired risk factors
Prior history of venous thromboembolism
Malignancy
Surgery
Trauma
Central venous access devices
Pregnancy and the puerperium
Immobilization (travel, paralysis, bedridden state)
Congestive heart failure
Myocardial infarction
Stroke
Advanced age
Smoking
Obesity
Oral contraceptives/hormone replacement therapy

VTE seems to be a history of prior thromboembolic disease [35]. In addition, malignancy and surgery are well known to be associated with VTE. Certain malignancies, such as tumors affecting the lung, brain, ovaries, and pancreas, are especially prone toward predisposing patients to VTE [29], as are neurosurgical and orthopedic surgical procedures [34]. Major trauma patients are a high-risk patient population that deserves particular attention because PE is the third most common cause of death in these patients [2,36]. One study of victims of major trauma revealed that nearly 60% had a DVT, most of whom were asymptomatic [37].

Despite the clinical significance of risk factors for VTE, Morgenthaler and Ryu [9] found that 12% (11 of 92) of patients with PE as the cause of death at autopsy lacked any known risk factor. Risk factors must be taken into account in conjunction with the patient's history and presentation, but an absence of risk factors does not reliably exclude the diagnosis of PE.

Clinical presentation

The presentation of PE is occasionally dramatic, but more commonly patients present with subtle clinical findings, or they may be completely

asymptomatic. This situation contributes to the large number of cases that are missed on initial presentation. The classic findings of hemoptysis, dyspnea, and chest pain are insensitive and nonspecific for a diagnosis of PE, with fewer than 20% having this classic triad. The incidence of common symptoms in patients suspected of having PE is depicted in Table 1 [38]. One prospective observational study found that the single historical finding most sensitive for PE was unexplained dyspnea. Even this finding was absent, however, in 8% of the patients studied [39]. Although unexplained chest pain or dyspnea always should lead to the consideration of PE, the fact that presentations of PE are often subtle mandates that the clinician not overlook the diagnosis based on a lack of these symptoms.

No single physical examination finding is sensitive or specific for PE. Table 1 shows the prevalence of various signs in patients suspected of having PE [38]. Although other studies reveal tachypnea to be the most sensitive clinical sign, it is absent in 5% to 13% of cases of PE [34,40]. Tachycardia is even less sensitive, especially in younger patients, with 70% of PE patients younger than 40 years old and 30% of patients older than 40 having heart rates less than 100 beats/min [40]. Fever tends to be low grade, and its presence may mislead the clinician into suspecting an infectious etiology.

Table 1
Symptoms and signs in 500 patients with clinically suspected pulmonary embolism

	PE present n = 202		PE absent n = 298		
	No.	%	No.	%	*P*
Symptoms					
Dyspnea (sudden onset)	158	78	87	29	<.00001
Dyspnea (gradual onset)	12	6	59	20	.00002
Orthopnea	2	1	27	9	.00004
Chest pain (pleuritic)	89	44	89	30	.002
Chest pain (substernal)	33	16	29	10	.04
Fainting	53	26	38	13	.0002
Hemoptysis	19	9	16	5	.12
Cough	22	11	45	15	.22
Palpitations	36	18	46	15	.56
Signs					
Tachycardia >100/min	48	24	69	23	.96
Cyanosis	33	16	44	15	.73
Hypotension <90 mm Hg	6	3	5	2	.15
Neck vein distention	25	12	28	9	.36
Leg swelling (unilateral)	35	17	27	9	.009
Fever >38°C	14	7	63	21	.00003
Crackles	37	18	76	26	.08
Wheezes	8	4	39	13	.001
Pleural friction rub	8	4	11	4	.93

Abbreviation: PE, pulmonary embolism.

From Miniati M, Prediletto R, Fromichi B, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med 1999;159:866; with permission.

Stein et al [41] found fever with no other source present in 14% of patients with PE.

Data from the PIOPED found that in patients diagnosed with PE, 97% had the presence of dyspnea, chest pain, or tachypnea [13]. Dyspnea, chest pain, and tachypnea are all nonspecific symptoms, however, that are found more commonly with diseases other than PE. This finding is likely subject to considerable selection bias because only patients in whom the diagnosis was suspected were enrolled in the PIOPED study, whereas patients with silent or atypical presentations of PE would have been missed and their symptoms not recorded. The symptoms of dyspnea, pleuritic chest pain, and tachypnea are not only nonspecific, but also they may be insensitive when generalized to all patients with PE [4].

Patients traditionally have been described as having one of three classic syndromes: pulmonary infarction, isolated dyspnea, or circulatory collapse. This is an oversimplification of the clinical presentation of PE that does not account for atypical presentations and occult pulmonary emboli. Patients in whom the diagnosis is suspected tend to present, however, with one of these three syndromes. Although one should not limit clinical suspicion only to patients in these categories, it is extremely difficult to diagnose PE reliably in patients outside of this simplified scheme.

Patients with pulmonary infarction commonly present with chest pain secondary to irritation of the pleura. It may be difficult to differentiate between PE and pneumonitis or pleuritis. Hemoptysis usually is self-limited and occurs in approximately one third of these patients. Pulmonary infarction is much more common in older patients with underlying cardiopulmonary disease, and they tend to present with pleuritic chest pain more frequently [30,42]. PE may be present in 20% of young patients, however, without specific risk factors for VTE who present with a complaint of pleuritic chest pain [16]. Pulmonary infarct is associated with submassive and less severe PE than isolated dyspnea or circulatory collapse [42,43].

In patients with isolated dyspnea, the severity of symptoms is related to the degree of vascular obstruction and their underlying cardiopulmonary reserve. Even with obstruction of 50%, patients may remain asymptomatic [42]. PE may be difficult to distinguish from other causes of dyspnea, such as congestive heart failure (CHF), hyperventilation, reactive airway disease, or obstructive lung disease. Patients with circulatory collapse have the most severe form of PE. They may present with syncope, hemodynamic instability, or full cardiopulmonary arrest.

Atypical presentations

Atypical presentations of PE are common, with symptoms such as abdominal pain, back pain, fever, cough, atrial fibrillation, and hiccoughs [16]. As noted earlier, most fatal pulmonary emboli are never suspected and

go undiagnosed. Many of these misses may involve patients with other significant comorbid disease to which their symptoms are attributed incorrectly. A significant percentage of these misses may be due to clinically silent or occult presentations and pulmonary emboli causing sudden cardiopulmonary arrest. Given that only a few cases of PE are suspected, these "atypical" presentations seem to represent most fatal cases of PE. Atypical presentations that are explored in more detail include occult PE, syncope, and PE in the setting of cardiopulmonary arrest.

Occult PEs are known to exist in asymptomatic patients in high-risk groups. Of asymptomatic surgical patients, 15% have been shown to have evidence of PE on lung scans [24]. In patients with known DVT but without symptoms suggesting PE, 40% to 60% have lung scan or angiogram findings suggesting PE [19–21]; this has led some authors to propose that all patients diagnosed with DVT have a baseline ventilation-perfusion (V/Q) scan [18,21]. Because the risk of recurrent VTE is low in patients adequately treated and because of the unclear clinical significance of these abnormal V/Q scans, other authors do not think that baseline lung scans are indicated for all patients diagnosed with DVT [20,44–46]. The rate of asymptomatic PE in the general population or in patients with occult DVT is unknown. It is possible that healthy individuals frequently have small emboli that dissolve rapidly and never become symptomatic.

Of patients presenting with syncope, Sarasin et al [47] found PE to be the cause in about 1%. Meanwhile, syncope is present in 8% to 13% of all patients with PE [48]. It is presumed to be secondary to right ventricular outflow obstruction causing transient hypotension. In a study of 92 patients at autopsy with PE as the cause of death, more than one quarter had a history of syncope [9]. Patients with PE who present with syncope carry a worse prognosis than patients who do not [48]; this may be due to the fact that larger pulmonary emboli are necessary to cause the outflow obstruction required to induce syncope. In a study by Bell et al [49], syncope occurred in 20% of patients with massive PE compared with only 4% of patients with submassive PE.

PE may cause right ventricular outflow obstruction with subsequent decreased left ventricular filling and cardiac output, leading to hypotension, shock, and cardiac arrest. One study found that of all patients presenting to the emergency department in cardiac arrest, PE was responsible in 4.8% [50]. In younger patients, who tend to have a lower baseline risk of cardiac disease, the percentage of cardiac arrests due to PE is likely even higher, with one author estimating it at 10%. In this study, patients with PE were more likely to have pulseless electrical activity and witnessed arrest than patients with other causes of death [51]. In another study, 63% of patients with PE-induced cardiac arrest had pulseless electrical activity as the presenting rhythm [52]. It is theorized that patients have time to seek aid during a gradual progression to pulselessness with maintained electrical activity. Conversely, in patients presenting with pulseless electrical activity

and cardiac arrest, approximately one third to one half have been found to have PE at autopsy [51,52].

Despite the frequency with which they occur, most missed PEs are unsuspected (Fig. 1) [4]. Some authorities argue, as expressed in an editorial by Egermayer [53], "There can be only a limited advantage to encouraging increased alertness for a disease that is usually asymptomatic." Egermayer's recommendation was to place an increased emphasis on prevention rather than diagnosis and treatment [53]. Although no amount of increased alertness would allow a clinician to diagnose all cases of PE, it is only with increased cognizance and development of improved diagnostic algorithms that clinicians can enhance their ability to diagnose this deadly but treatable disease.

Specific patient populations

Pediatrics

VTE in children usually is associated with hereditary or acquired coagulation abnormalities. Hereditary deficiencies include factor V Leiden mutation; sickle cell disease; and deficiencies of protein C, protein S, and antithrombin III. Thrombosis tends to be most pronounced in the neonatal period and at adolescence. There are numerous causes of acquired VTE, including surgery, malignancy, trauma, central venous catheter placement, infection, renal disease, autoimmune diseases, vasculitis, congenital heart disease, and severe inflammatory bowel disease [54]. Central vascular access devices seem to be the most common acquired risk factor in children [55]. A

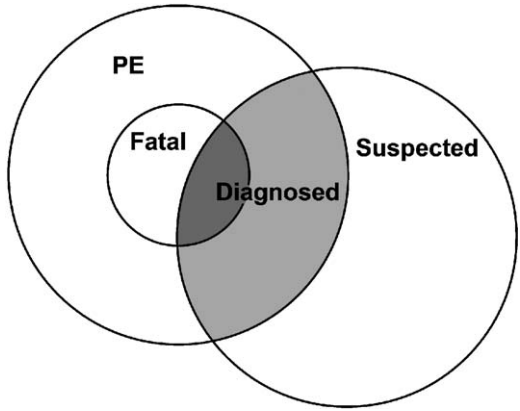

Fig. 1. Schema of relationship between suspected and actual cases of pulmonary embolism (PE). (*From* Ryu JH, Olson EJ, Pellikka PA. Clinical recognition of pulmonary embolism: problem of unrecognized and asymptomatic cases. Mayo Clin Proc 1998;73:877; with permission.)

retrospective study of 61 children with thrombosis found an association with central vascular access in 25% [56].

Overall, VTE is rare in children. Rohrer et al [57] found an incidence of lower extremity DVT of only 0.05% (1 of 93 cases, in a 17-year-old) in hospitalized children with at least two independent risk factors for thrombosis. A study of pediatric intensive care unit patients found 4% to have DVT [58], whereas at autopsy the rate of PE in children was approximately 4% [59]. A review of the literature on VTE in children revealed that 98% had a precipitating factor, although it was not always known on initial presentation [60]. Although rare, the diagnosis of PE should be considered in children manifesting suspicious symptoms, especially in older children and children with risk factors. Children diagnosed with VTE require anticoagulation and an extensive workup in search of a potential underlying cause.

Pregnancy

PE is the leading cause of maternal mortality in developed countries [61,62]. Although the incidence of PE in individuals older than age 45 is higher in men than in women, numerous studies have shown that in young adults, women have a significantly higher rate of PE [29]. Pregnancy and the postpartum period are well-known risk factors for PE [63], with the risk of PE five times higher in pregnant compared with nonpregnant women [34]. During the postpartum period, there is an even greater risk of thrombosis than during pregnancy [29]. Although a high level of suspicion is necessary, the prevalence of PE in pregnant patients in whom the diagnosis is considered is quite low [64].

The diagnosis of PE in pregnancy is particularly difficult because dyspnea may be a normal finding. Causes of dyspnea in pregnancy include upward pressures on the diaphragm secondary to an intra-abdominal mass effect and increased oxygen consumption requiring increased cardiac output. By the third trimester, 75% of pregnant women have dyspnea, and most women have symptoms beginning by the 20th week. The physiologic dyspnea of pregnancy may be difficult to differentiate from more worrisome causes such as PE. Physiologic dyspnea tends to be mild without limiting daily activities, it tends to be absent at rest, and it generally does not worsen as pregnancy progresses. Symptoms such as syncope, hemoptysis, and chest pain should not be attributed to physiologic dyspnea [65]. Likewise, dyspnea that has a rapid onset should raise suspicion for PE.

During pregnancy, failure to diagnose PE places the mother and the fetus in jeopardy. Likewise, overdiagnosing PE places both patients at risk by exposing them to anticoagulation and hospitalization. Although it is desirable to minimize fetal radiation exposure, the importance of making the correct diagnosis mandates that the appropriate diagnostic studies be performed. Although a negative D-dimer test can be helpful in patients with

a low pretest probability of PE, it is not helpful in patients whose pretest probability is estimated to be moderate or high. Because ultrasound poses no risk to the fetus, bilateral lower extremity ultrasound is considered by some authors to be the initial study of choice. If ultrasound is positive for DVT, PE is implied, and the patient should be treated accordingly with no further testing necessary. In pregnant patients being evaluated for PE without specific symptoms of DVT, however, ultrasound is rarely positive [66–68].

Many authorities advocate the use of V/Q scanning as the next step. During pregnancy, especially in patients without prior history of pulmonary disease, many scans are normal or near-normal in the absence of PE. The radiation exposures from V/Q scan and chest x-ray are well below the maximal recommended dose in pregnancy and can be decreased even further without compromising the study [62,64]. Although the use of helical CT historically has been discouraged, there is increasing evidence that next-generation CT scanners subject the patient to less radiation than does V/Q scanning [69,70]. This evidence has led to the preferential use of CT over V/Q scanning in pregnant patients at the authors' institution. If pulmonary angiography is required, the abdomen can be shielded in an attempt to reduce radiation exposure to the fetus. If PE is discovered, warfarin is contraindicated because it is a known teratogen [71], and the patient requires admission and daily administration of unfractionated heparin or low-molecular-weight heparin for the duration of pregnancy.

Elderly

Elderly patients are at an increased risk of developing PE, but it is unclear if this is because age is an independent risk factor or secondary to a higher prevalence of underlying disease and recent surgery in this patient population. The mean age of patients presenting with PE is approximately 60 years with a rate 10 times higher in patients older than 75 compared with patients younger than 40 [29,36]. Elderly patients with PE have higher mortality compared with younger patients. The reason is multifactorial and likely due to the fact that diagnosis is more difficult and the higher incidence of underlying disease in this patient population. In addition, the elderly have more bleeding complications from therapy with a resulting increased likelihood of having anticoagulants withheld [28].

The specificity of some diagnostic tests is decreased in the elderly. The specificity of D dimer was found to be 67% in patients younger than 40, but only 10% in patients age 80 and older. In addition, the number of non-diagnostic V/Q scans increased from 32% to 58% in these same age groups [72]. There is no single diagnostic test that is ideal for the diagnosis of PE in elderly patients. When a diagnosis of VTE is made in an elderly patient, the patient should be treated with anticoagulation unless he or she has a specific contraindication. Age should not preclude thrombolytic therapy when appropriate [73,74].

Comorbid diseases

Patients with multiple medical problems often present diagnostic challenges in the workup of PE. As previously discussed, symptoms of PE are notoriously nonspecific, and symptoms of a patient's underlying disease may be impossible to distinguish from that of PE. A coexisting illness may be assumed to be the cause of the patient's symptoms and the presence of PE may go undiagnosed in patients who can least tolerate it. Cardiopulmonary illnesses may present with similar symptoms and similar diagnostic and laboratory studies. To complicate matters further, many illnesses are independent risk factors for VTE, such as CHF, myocardial infarction, and cancer. Severe illness also leads to prolonged immobilization, an increased likelihood of surgery, and the use of central vascular access devices. Two examples of comorbid diseases that can complicate the diagnosis of PE are chronic obstructive pulmonary disease (COPD) and CHF.

Patients with COPD are at high risk for PE. These patients tend to be older smokers who also may have immobility, CHF, and lung malignancy. Autopsy studies reveal a rate of PE ranging from 28% to 51% in patients with COPD [75]. Differentiating the symptoms of a COPD exacerbation from PE can be extremely challenging given the similarity of symptoms. PE may precipitate an exacerbation of COPD causing additional diagnostic uncertainty with overlapping symptoms from both disorders. Patients with COPD and a pulmonary embolus found at autopsy were much less likely to have had the diagnosis made ante mortem compared with patients without COPD [6]. For these reasons, it is important to maintain a high index of suspicion in patients with COPD who present with shortness of breath that is acute in onset or differs from prior exacerbations.

The diagnostic workup in patients with COPD is complicated by an increased likelihood of obtaining nondiagnostic V/Q scans. In patients with COPD, less than 10% of scans are diagnostic (either normal/near-normal or high probability of PE) [75]. CT may be the study of choice in these patients with less associated risk compared with angiogram and greater likelihood of revealing a definitive answer compared with V/Q scan. CT has the advantage of revealing alternative diagnoses, and abnormalities from infectious and neoplastic processes commonly are present in patients with COPD.

As with COPD, the symptoms of PE can mimic the symptoms of CHF and can trigger CHF exacerbations. Because it is associated with a low-flow state, CHF predisposes patients to stasis and VTE. Because of the inherent activity limitation of CHF patients, they often are relatively immobile, which further increases their risk for PE. One must always consider PE in the differential diagnosis of patients with an exacerbation of CHF and should be extremely suspicious of symptoms that have an acute or new onset with no clear predisposing events, vary considerably from previous symptoms, or do not respond to conventional therapy. As with COPD, clinical and laboratory findings are rarely helpful, and V/Q scans only rarely give

definitive results. CT may help diagnose PE and alternative diagnoses, such as pericardial effusion.

Although human immunodeficiency virus (HIV) infection is considered by some to be a risk factor for PE secondary to the hypercoagulable state associated with the infection, VTE is actually uncommon in HIV-positive patients. Many HIV-positive patients present with symptoms due to respiratory infections that are difficult to distinguish from PE. The diagnosis of PE still should be considered in HIV-positive patients with presumed respiratory infections who do not respond to antimicrobial therapy [76].

Diagnostic approach

Given the lack of a single diagnostic test or clinical finding with adequate sensitivity and specificity, the diagnosis of PE generally involves interpretation of multiple data points in light of the emergency physician's assessment of an estimated pretest probability. The authors' current method of diagnosing PE relies heavily on subjective assessment of risk. In some cases, the diagnosis is made easily, but many more cases require the treating physician to make a diagnosis based on uncertain information.

The frustration of examiners was emphasized in a 1999 poll of 623 emergency physicians who identified the evaluation of PE as the clinical problem that would benefit most from a decision rule [77]. A nonvalidated decision rule was proposed in 1990 by the PIOPED investigators, who used the pretest assessment of risk combined with results from V/Q scanning. This rule allowed for the noninvasive diagnosis or exclusion of PE in only a few patients, however, with most requiring angiography [13]. Studies at academic and private hospitals have shown a poor compliance with the PIOPED approach [24,78,79].

The PIOPED recommendations require interpretation of the V/Q result in terms of pretest probability. Accurately assigning pretest probability can be difficult, however. No scoring system was devised initially, and clinical estimates of pretest probability have been met with considerable interobserver variability [80,81]. Siegel et al [81] reported instances in which the same patient was assigned a low pretest probability of PE by one examiner and high probability by another. Several algorithms have been devised to address this problem. Two of the most popular scoring systems are the Wells and Geneva criteria (Table 2) [82–84].

Validation studies of these decision rules reveal that they are predictive of which patients have PE [84,85]. They do not give definitive results, however, or obviate the need for further diagnostic tests, and they have not been proved to be superior to implicit clinical judgment. The prevalence of PE in the population to which these rules are applied affects the success of these scoring systems [84]. These decision rules are best suited for risk stratifying patients to estimate a pretest likelihood of PE before diagnostic studies.

Table 2
Prediction rules for suspected pulmonary embolism

Geneva score [13]	Points	Wells' score [14]	Points
Previous pulmonary embolism or deep vein thrombosis	+2	Previous pulmonary embolism or deep vein thrombosis	+1.5
Heart rate >100 beats p/min	+1	Heart rate >100 beats p/min	+1.5
Recent surgery	+3	Recent surgery or immobilization	+1.5
Age (y)		Clinical signs of deep vein thrombosis	+3
60–79	+1	Alternative diagnosis less likely than pulmonary embolism	+3
≥80	+2	Hemoptysis	+1
		Cancer	+1
$Paco_2$			
<4.8 pKa (36 mm Hg)	+2		
4.8–5.19 pKa (36–38.9 mm Hg)	+1		
Pao_2			
<6.5 pKa (48.7 mm Hg)	+4		
6.5–7.99 pKa (48.7–59.9 mm Hg)	+3		
8–9.49 pKa (60–71.2 mm Hg)	+2		
9.5–10.99 pKa (71.3–82.4 mm Hg)	+1		
Atelectasis	+1		
Elevated hemidiaphragm	+1		
Clinical probability		Clinical probability	
Low	0–4	Low	0–1
Intermediate	5–8	Intermediate	2–6
High	≥–9	High	≥7

Abbreviations: Pao_2, partial pressure of oxygen, arterial; $Paco_2$, partial pressure of carbon dioxide, arterial.

From Chagnon I, Bounameaux H, Aujesky D, et al. Comparison of two clinical prediction rules and implicit assessment among patients with suspected pulmonary embolism. Am J Med 2002;113:270; with permission.

If one follows the PIOPED recommendations, most patients being evaluated for PE require angiography. The rate of pulmonary angiography performed in these patients is typically less than 12%, however, with most physicians unwilling or unable to obtain angiography routinely in the workup of PE [24,78,79,86,87]. Some authors believe that failure to obtain angiography in all cases that have nondiagnostic studies is unacceptable due to the likelihood of missed pulmonary emboli. Follow-up studies have shown, however, that PE is unlikely in patients discharged after a low-probability V/Q scan [26]. Wolfe and Hartsell [24] argued that an outcome-based approach is more important than diagnosis of all PE cases. They pointed out that in patients with adequate cardiopulmonary reserve, occult VTE not diagnosed by noninvasive testing does not seem to affect outcome [24,25,82,88,89]. This situation has led to the formation of an alternative algorithmic approach, which attempts to reduce the number of recommended angiography studies (Fig. 2) [24]. Although currently lacking

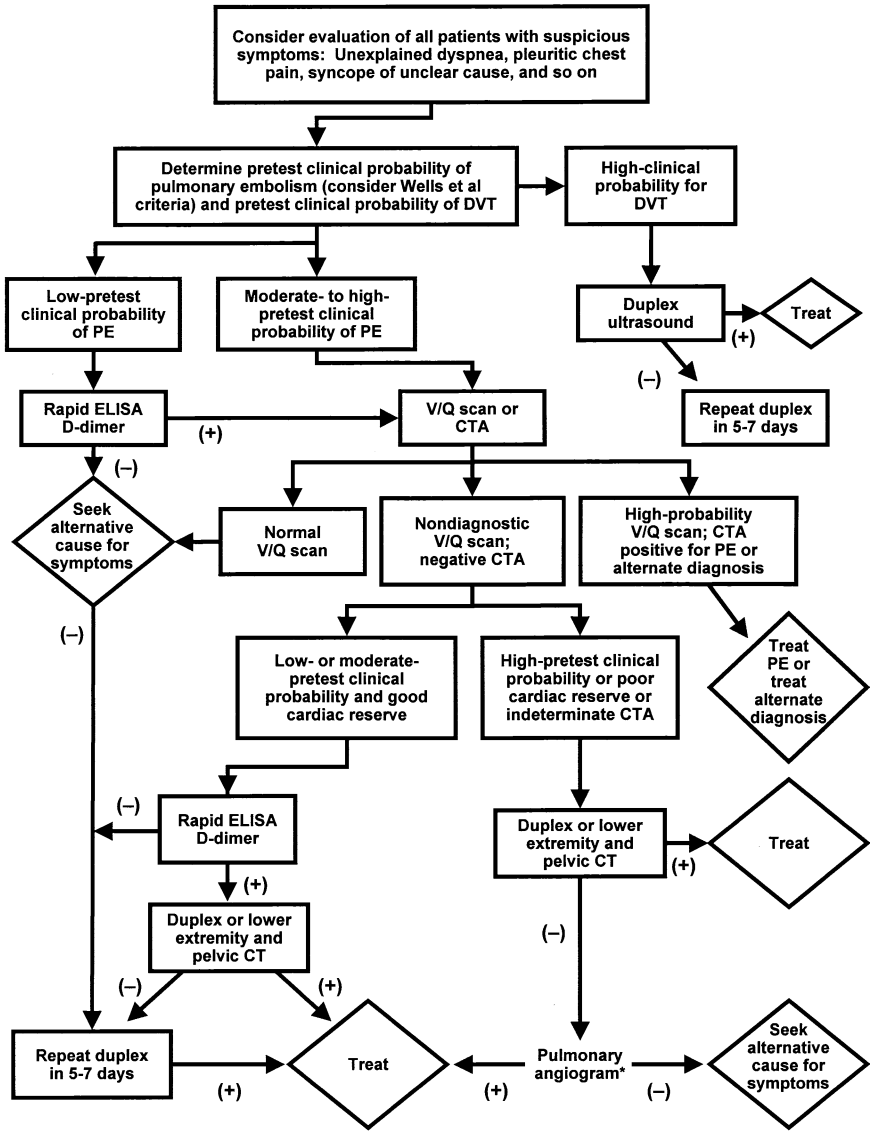

Fig. 2. Proposed diagnostic algorithm for the evaluation of suspected pulmonary embolism (PE). CTA, computed tomography angiography; DVT, deep venous thrombosis; ELISA, enzyme-linked immunosorbent assay; V/Q, ventilation-perfusion. (*Adapted from* Wolfe TR, Hartsell SC. Pulmonary embolism: making sense of the diagnostic evaluation. Ann Emerg Med 2001;37:509; with permission.)

prospective validation, such an algorithm better fits current practice and avoids the need for angiograms in most patients.

Diagnostic tests

Electrocardiogram, arterial blood gas, chest radiography

Electrocardiogram, arterial blood gas analysis, and chest radiography all have a limited role in the evaluation of PE. The primary utility of the electrocardiogram is its ability to point to an alternate diagnosis, such as acute coronary syndrome or pericarditis. Classic findings, such as $S_1Q_3T_3$, lack sensitivity and specificity (54% and 62%), whereas the most common electrocardiogram abnormality, found in 68%, is T-wave inversion in the precordial leads [90]. Chest radiography similarly has its primary utility in detecting alternative diagnoses, such as pneumothorax, CHF, and pneumonia. Chest x-ray findings can be misleading, however, and must be interpreted carefully because findings suggesting CHF or pneumonia may coexist with a pulmonary embolus. In a study of patients ultimately diagnosed with PE, 76% of chest x-rays were abnormal, but the noted abnormalities tended to be nonspecific [91]. Arterial blood gas analysis has a limited role in the evaluation of PE. It is a relatively invasive procedure that lacks the sensitivity or specificity to rule in or out disease [92].

D dimer

D-dimer testing has been proposed by some authorities as a convenient, noninvasive way to exclude or to increase suspicion for VTE. Specificity is known to be low secondary to false-positive results from numerous causes, such as trauma, postoperative state, sepsis, and myocardial infarction [30]. It also is less likely to be helpful in elderly patients and patients with significant comorbid disease. The role of D dimer generally has been reserved for ruling out disease in low-risk patients. Wells et al [93] found that patients with a low clinical probability of VTE and a negative D-dimer assay could be discharged safely with only 0.4% found to have VTE on follow-up examination. However, The numerous different assays available and institutional variability in terms of the assays used have led to confusion and precluded the universal adoption of D-dimer assays as screening tests for PE. Readers are referred to a review by Sadosty et al [94] for a more in-depth analysis of D-dimer assays and to a meta-analysis by Brown et al [95] regarding enzyme-linked immunosorbent assay D-dimer testing.

Ventilation-perfusion scintigraphy

V/Q is a two-part study involving a ventilation and a perfusion phase. A radioisotope is injected, and areas of pulmonary perfusion are identified using a gamma camera. A radiopharmaceutical is inhaled to identify areas

of ventilation. The areas of perfusion and ventilation are compared to identify foci of mismatch. Areas with ventilation but without perfusion increase the suspicion for PE because thrombus obstruction of a pulmonary artery would cause hypoperfusion to the affected lung segment without affecting ventilation. The test must be interpreted in light of the patient's pretest probability. It is most helpful when there is concordance between the pretest probability and the scan results (ie, a low pretest probability and a normal/near-normal scan or a high pretest probability with a high probability study (Table 3) [96]. Interpreting the study without factoring in the pretest probability would lead to overdiagnosis and underdiagnosis of PE: Of patients who have a high-probability V/Q scan but a low pretest probability, 44% would have angiograms negative for PE, whereas in patients with a low-probability scan but a high pretest probability, 40% would be found to have PE on angiogram (see Table 3) [13,96]. Because of these interpretive factors and because patients with preexisting lung disease often have abnormal studies, V/Q scan provides a definitive answer regarding whether or not a patient should be started on anticoagulation therapy in only 25% to 40% of cases [12].

Spiral computed tomography

CT is becoming increasingly accepted in the evaluation of PE. Fig. 3 shows a large proximal pulmonary embolus in the pulmonary artery. CT is rapid, noninvasive, and widely available. It is more likely to be diagnostic than V/Q scanning and is less expensive than V/Q scanning, magnetic resonance angiography, and pulmonary angiography. CT also has the advantage of being able to elucidate alternative diagnoses, such as infectious or neoplastic processes. Its primary limitations relate to the need for potentially nephrotoxic intravenous contrast material, which is contraindicated in patients with a contrast allergy or renal failure. Many investigators have questioned whether the sensitivity of CT is sufficient to

Table 3
Clinical assessment and ventilation-perfusion scan probability in PIOPED*

Ventilation-perfusion scan (probability)	Clinical probability		
	High likely (80–100%)	Uncertain (20–79%)	Unlikely (0–19%)
High	28/29† (96%)	70/80 (88%)	5/9 (56%)
Intermediate	27/41 (66%)	66/236 (28%)	11/68 (16%)
Low	6/15 (40%)	30/191 (16%)	4/90 (4%)
Near-normal/normal	0/5 (0%)	4/62 (6%)	1/61 (2%)
Total	61/90 (68%)	170/569 (30%)	21/228 (9%)

* PIOPED = Prospective Investigation of Pulmonary Embolism Diagnosis.

† Number of patients with proven pulmonary embolism per number of patients with the specific scan result.

From American Thoracic Society. The diagnostic approach to acute venous thromboembolism: clinical practice guideline. Am J Respir Crit Care Med 1999;160:1055; with permission.

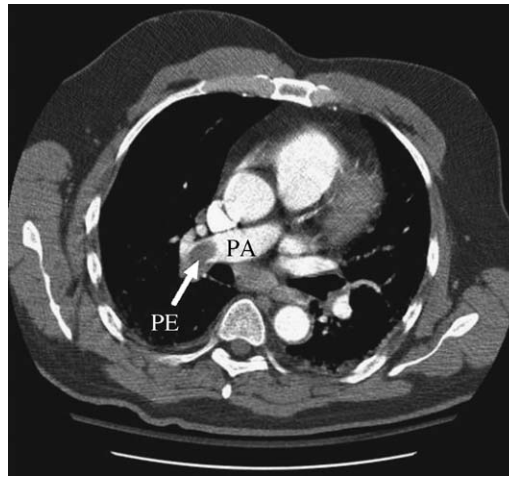

Fig. 3. Pulmonary embolus (PE) located in the proximal pulmonary artery (PA) as seen on spiral CT.

rule out definitively the possibility of PE [97]. Perrier et al [12] found the sensitivity and specificity to be only 70% and 91%, whereas others have reported sensitivities of 88% to 100% with negative predictive values of 89% to 95% [98–100].

Despite its potential promise, the role of CT in the diagnosis of PE is not clear. Isolated subsegmental emboli and horizontal vessels are not visualized well on CT, and lymph nodes may be misinterpreted as emboli with false-positive results [24,30,69]. Subsegmental emboli are not visualized well on angiogram either [24,101]. Newer thin-collimation multislice CT scanners have increased speed and allow improved visualization with less motion artifact [68]. The clinical significance of isolated subsegmental emboli is uncertain and has been questioned [102]. If these emboli are not clinically important, failed diagnosis would be beneficial because unnecessary anticoagulation therapy could be avoided. However, If subsegmental emboli are clinically relevant, false-negative results could lead to poor outcomes or possible untoward future events.

Three studies have concluded that withholding anticoagulant therapy on the basis of a negative helical CT scan is safe [100,102,103]. Swensen et al [99] and Donato et al [102] found that only 8 of 993 and 4 of 239 patients developed VTE within 3 months of a negative CT scan. In patients with CT results negative for PE, there were 189 deaths (118, 33, and 38 deaths in the Swenson et al [100], Donato et al [102], and van Strijen et al [102] studies), with only 5 of these deaths thought to be secondary to PE. Whether occult PE played a role in the remaining 184 deaths is unknown but could affect significantly the data interpretation. These studies used superior CT technology and experienced radiologic interpretation that may not be available

at all centers. Given all the variables affecting the quality of CT evaluation, the practitioner is left to determine whether or not CT is a reliable means of detecting PE at his or her institution.

Pulmonary angiography

Although pulmonary angiography is considered the gold standard in the diagnosis of PE, it has numerous disadvantages. It is expensive, it requires the use of potentially nephrotoxic intravenous contrast material, and it is invasive with complications occurring in 6.5% and death in 0.5% [102,104]. It also is time-consuming and requires transport of the patient away from the emergency department to the angiography department. Additionally, angiography may not be readily available at many centers. These limitations may explain the reluctance of clinicians to follow through with angiography despite other nondiagnostic testing. Patients can undergo pulmonary angiography safely even after receiving intravenous contrast material for a CT scan [24].

Magnetic resonance angiography

Magnetic resonance angiography is expensive (although less so than pulmonary angiography), is time-consuming, and has limited availability. Access to the patient is limited, which makes it impractical for potentially unstable patients. Contraindications include implanted metallic objects, morbid obesity, and claustrophobia [30]. Magnetic resonance angiography has the advantage of using a safer contrast agent and does not expose the patient to ionizing radiation. A study by Oudkerk et al [105] comparing magnetic resonance angiography with CT reported similar results between the two modalities. Given the many disadvantages, however, the role of magnetic resonance angiography remains limited.

Alveolar dead space measurements

When alveoli are ventilated but not perfused secondary to the presence of a pulmonary embolus, blood flow is obstructed, while ventilation continues resulting in dead space. Under normal conditions, there is no alveolar dead space. Alveolar dead space measurements may play a future role in the diagnosis of PE, especially in conjunction with other testing. Although studies have shown that indices of alveolar dead space volume are predictive of the presence of PE [106], further study and better availability of these bedside tests are needed before measurement of alveolar dead space obtains more widespread use [3,30].

Summary

The presentation of PE is often subtle and may mimic other diseases. Many pulmonary emboli invariably preclude diagnosis by their occult

nature or by leading to rapid death from cardiopulmonary arrest. In patients who do manifest symptoms from PE, accurate diagnosis is essential. Often it is difficult to distinguish the vague symptoms of PE from other diagnoses, such as acute coronary syndrome, pneumonia, COPD, CHF, aortic dissection, myocarditis or pericarditis, pneumothorax, and musculoskeletal or gastrointestinal causes. Regardless of the presentation, the most fundamental step in making the diagnosis of PE is first to consider it. Historical clues and risk factors should raise the clinician's suspicion.

PE is an unsuspected killer with a nebulous presentation and high mortality. In all likelihood, PE will remain an elusive diagnosis despite advances in technology and a wealth of research. A high index of suspicion is required, but no amount of suspicion would eliminate all missed cases. Patients with significant underlying cardiopulmonary disease seem to be the most challenging. Patients with significant comorbidity have poor reserve and are likely to have poor outcomes, especially if the diagnosis is not made and anticoagulation is not initiated early.

Controversy exists over the best diagnostic approach to PE. A battery of diagnostic studies is available, with few providing definitive answers. Studies such as CT may be helpful at some institutions but offer poor predictive value at others. Other diagnostic tests are not universally available. It is hoped that further research and improvements in current diagnostic modalities will clear some of the current confusion and controversy of this ubiquitous and deadly disease.

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