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Full Length Article

Diagnosis and Exclusion of Pulmonary Embolism☆

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ABSTRACT

Background: Failure to test for pulmonary embolism (PE) can be a lethal mistake, but PE and produces symptoms similar to many other diseases. Overtesting for PE has negative consequences.
Objectives: Use published evidence to create a rationale and safe diagnostic approach for ambulatory and emergency patients with suspected PE in 2017.
Findings: Pulmonary embolism need not be pursued in patients with no symptoms of PE in the present or recent history (dyspnea, chest pain, cough or syncope), and always normal vital signs. When clinicians have a low clinical suspicion for PE or a Wells score < 2, they can reasonably exclude PE with the Pulmonary Embolism Rule out Criteria (PERC rule). For patients with a "PE-unlikely" pretest probability (Wells or simplified revised Geneva score < 5), PE can be ruled out with a normal or age-adjusted D-dimer concentrations. Other patients should undergo pulmonary vascular imaging, and the choices are discussed, including computerized tomographic pulmonary angiography, planar and single-photon emission computed tomography (SPECT).
Conclusions: A thoughtful algorithm for PE exclusion and diagnosis requires pretest probability assessment in all patients, followed by selective use of clinical criteria, the quantitative D-dimer, and pulmonary vascular imaging.

1. Overview

This review concerns the approach to excluding and diagnosing PE in an undifferentiated patient. A key construct originates from the fact that PE produces a wide range of clinical severity, ranging from asymptomatic to sudden death. Signs and symptoms of PE overlap those of many other diseases, and even emotional states. Accordingly, no single approach fits all patients equally well, and recommendations herein are based upon published evidence and to some extent, the opinion of the author.

2. Approach to the patient before imaging

2.1. Hypothesis generation of PE in the undifferentiated patient

Initiation of diagnostic testing for PE requires the patient to have at least one symptom or sign that is referable to the chest, either dyspnea, discomfort, or loss of consciousness suggesting low cardiac output. A present history of unexplained dyspnea—not explained by a known cardiopulmonary problem–should prompt a consideration of PE [1,2]. Dyspnea from PE originates from ventilation perfusion abnormalities caused by mechanical obstruction and diversion of blood flow within the lung. It would seem intuitive that the larger the PE, the worse the dyspnea, however the size of PE on radiographic testing correlates poorly with patient report of perceived dyspnea severity [2]. Clinicians should also be wary that diagnosed PE generally manifests as the result of repeated embolic events, which individually may be barely noticed by the patient, until they accumulate to point that frustrates the patient with progressive fatigue and dyspnea on exertion [3]. Although Miniati et al. found "sudden onset of dyspnea" to significantly increase probability of PE, more generally, Courtney et al. found sudden onset of the chief complaint (dyspnea or chest pain) did not increase the risk of PE diagnosis (odds ratio 0.88, 95% CI: 0.75–1.07) [1,4,5]. Whereas substernal chest pain has no positive predictive value for PE, pleuritic chest pain (lateral or posterior thoracic pain between the costal margin and clavicles that increases with breathing) was found in several studies to significantly increase the probability of PE [2,5,6]. Presence of wheezing increases the likelihood of an alternative diagnosis of bronchospasm and the finding of symmetrical leg edema points toward left ventricular heart failure [7,8]. Unilateral leg swelling (assessed by raising the patient's legs from the heels and observing for asymmetry of the calves), or tenderness along the deep venous system, which also includes calf tenderness all significantly increase the probability of PE diagnosis. [9,10,11,12] At least one-third of patients with DVT have concomitant PE, even when the patient lacks symptoms of PE [13]. However, only about 40% of ambulatory ED patients with PE have concomitant DVT that can be found on standard compression ultrasonography [14,15].

The predictive value of syncope as sole symptom of PE is controversial, and may be population specific. For example, one US registry found that only 4% of ED patients with PE had syncope, significantly less than an Italian study in which 22% of patients with PE had syncope

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[6,16]. In a highly selected subset of Italian patients with syncope admitted from the emergency department, Prandoni and colleagues found that an astounding 17% of patients had PE [17]. In a systematic review, West et al. found syncope to be highly predictive of the diagnosis of PE with a likelihood ratio positive of 2.6 (95% CI 1.5–3.8) [18]. However, less than 1% of patients with pre-syncope and less than 3% of patients with syncope have the diagnosis of PE, perhaps explaining why syncope does not appear as a risk factor for PE in any validated clinical prediction rule for PE (Tables 2–3) [19,20]. Patients with PE who present with syncope do tend to have larger and more dangerous PE [21,22]. In the experience of the author reviewing over 100 medicolegal cases alleging negligence from failure to diagnose PE that ultimately was fatal, about 30% of cases had a history of syncope. Thus, a reasonable and prudent approach is to say that syncope associated with dyspnea or respiratory distress, a low pulse oximetry reading or elevated heart rate, or strong risk factors, warrants diagnostic testing for PE, but patients with syncope with a reasonable other explanatory cause for loss of consciousness in a patient without risk factors for PE does not indicate the automatic need for a workup for PE.

2.2. What does a patient with PE "look like" on physical examination?

All clinicians use gestalt or system I processing to some extent in their diagnostic hypothesis generation [23,24]. Few studies have examined simple non-verbal cues that might increase or decrease probability of PE, such as facial affect, tone of voice, body posture, head position, or attentiveness. Generally speaking, among patients tested for PE, when clinicians perceive the patient as having an appearance of distress, the probability of PE increases. One small study found that patients undergoing CTPA who had a treatable and significant cardiopulmonary diagnosis (including a minority with PE), had less facial affect variability than patients without a significant diagnosis [25]. However, contrary to their a priori hypothesis, Kline et al. found that among patients undergoing CPTA for PE, that clinicians recalled a smile more commonly among patients who ultimately had PE [26]. Thus, available data are inadequate to allow generalizations as to whether the patients' overall appearance of comfort can help with decision making. Fortunately, the vital signs are more helpful. Vital sign abnormalities that clearly increase probability of PE include an elevated heart rate (>100 beats/min), a reduced pulse oximetry reading (<95% with the patient breathing room air near sea level) (Table 2) [9–12]. The normalization of vital signs with treatment or time does not change the likelihood that a patient will be diagnosed with PE [27]. Studies are inconsistent on the significance of an elevated respiratory rate, and the definition of tachypnea varies. Two studies, one using a definition of >20 breaths/min and the other >24 breaths/min, found tachypnea significantly associated with PE [2,5]. Approximately 10% of patients with PE have an oral temperature of >38 °C (100.4 °F), though <2% of patients with PE have a temperature of >39.2 °C (102.5 °F), and one decision rule found high fever a negative predictor [1,28]. Many patients with chest pain and/or dyspnea immediately receive a 12-lead electrocardiogram (ECG). An ECG that shows signs of acute pulmonary hypertension increases the probability of PE. Signs of pulmonary hypertension on ECG include heart rate over 100 beats/min (LR + 1.8; 95% CI 1.5 to 2.2), the S1Q3T3 pattern in leads I and II, (LR + 3.7; 95% CI 2.5 to 5.4); T wave inversion in V1 to V4, (LR + 3.7; 95% CI 2.4 to 5.5); incomplete right bundle branch block, (LR + 1.7; 95% CI 1.0 to 2.7); and non-sinus rhythm (LR + 1.4; 95% CI 1.2 to 1.7) [29]. Fig. 1 shows an ECG that was used by an emergency physician to decide to order a D-dimer on a patient sent for psychiatric clearance. The D-dimer was positive and the CT scan showed a large PE (Fig. 2B).

2.2.1. Medical and population risk factors for PE in ambulatory patients

Predictors that increase risk of PE figure prominently into pretest probability assessment for PE. The following discussion and Table 1 includes risk factors which have been proven with a high degree of certainty to increase the odds of a patient by at least two-fold, independently of other clinical factors. Their presentation is ordered in terms of the author's perceived clinical importance with consideration of their frequency and intensity of risk. Most guidelines and authors categorize VTE as either provoked (synonymous with secondary) or unprovoked (synonymous with primary or idiopathic) [30]. Provoked VTE refers to clots associated with certain acquired conditions which are all risk factors for VTE that are reversible, generally including surgery requiring endotracheal intubation or epidural anesthesia within the previous 30 days, major trauma requiring hospitalization, new immobility the post-partum condition, cancer, new use of estrogen. Unprovoked PE, refers to patients with no provoking factor and about two-thirds patients diagnosed with PE in the ambulatory setting have unprovoked, or idiopathic, or primary PE [16].

1. *Surgery*: One of the most powerful risk factors for DVT and PE is recent surgery that required endotracheal intubation or epidural anesthesia. Over one-half of postoperative PE occurs after hospital discharge with a peak incidence at around the 10th postoperative day [31]. The highest-risk surgeries include abdominal surgery to remove cancer, joint replacement surgery, and surgery on the brain or spinal cord in the setting of neurologic deficits [32].
2. *New Immobility*: Patients who are newly immobilized for >72 h, those with new limb immobility from neurological disease, and those with joint fixation by splints, casting or external fixators have a two to three fold increase in probability of PE compared with equally symptomatic and age matched patients without immobility [33]. Case-control data show that immobilization of the ankle alone confers at least an 8-fold increase in risk of VTE, and the risk increases for patients with trauma and inherited thrombophilia [34]. Prolonged travel within the previous 72 h increases risk of thrombosis in a dose-dependent fashion; the risk becomes significant at about 6 h of continuous seated position [35]. However, the absolute risk of long-haul travelers in the ED is small. In one study, travel per se did not increase the risk of being diagnosed with PE in symptomatic patients with suspected PE in the ED [33]. Travel is not part of any published clinical decision rule to assess probability of PE in ED patients.
3. *Prior VTE* increases probability of PE diagnosis in symptomatic patients by two–three fold. For this reason, all published pretest probability assessment systems include prior VTE as a positive predictor. Some useful facts about prior VTE include the fact that most recurrences occur within 6 months of discontinuing anticoagulation, and that compared with provoked VTE, unprovoked onset increases the risk of recurrence from about 3–4% per year to 7–8% per year, and males have about twice the risk of VTE recurrence as females [36–39].
4. *Estrogen*: Administration of exogenous estrogen by oral, transvaginal or transcutaneous delivery, increases a woman's risk for PE by two to threefold in the general population and in the emergency department [5,40]. The risk of VTE is greatest in the first few months after starting an estrogen regimen [41,42]. The third-generation oral contraceptives containing desogestrel or gestodene as the progestin component confer significantly (1.5–3 fold) higher risk for VTE than preparations containing levonorgestrel [43]. The risk of drospirenone remains controversial [44]. Progestegen-only contraception, including certain subcutaneous implantables and intrauterine devices (e.g., Implanon® [etogestrel] and Mirena® [levonorgestrel]) and long-acting injections of progestins (e.g., Depo-Provera®) do not appear to increase risk [45].
5. *Active cancer*: Patients with active cancer do have an increased risk. Cancer can be considered active if the patient is under treatment or the cancer is metastatic. Active cancer is included in the Wells and Geneva clinical probability rules. Highest risk cancers include adenocarcinomas (e.g., pancreatic, colon, ovary, stomach, and renal cell), glioblastoma, metastatic melanoma, lymphoma and multiple myeloma [46]. Other highest risk cancers include acute lymphocytic leukemia treated with L-asparaginase, and acute promyelocytic leukemias treated with all-trans-retinoic acid [47]. Approximately 15–25% of