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# Diagnosis of pulmonary embolism: Following the evidence from suspicion to certainty



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*Abstract:* *Accurate, timely and cost-effective identification of pulmonary embolism remains a diagnostic challenge. This article reviews the pulmonary embolism diagnostic process with a focus on the best practice advice from the American College of Physicians. Benefits and risks of each diagnostic step are discussed. Emerging diagnostic tools, not included in the algorithm, are briefly reviewed.* (J Vasc Nurs 2018;37:28-42)

Pulmonary embolism (PE) is the third most common cardiovascular disease[1] with an estimated annual incidence between 60 and 79 cases per 100,000 persons.[2] Because up to a third of individuals with PE do not have any symptoms, these numbers likely underestimate the problem.[3] For example, one recent study found the prevalence of silent PE in patients with calf vein deep vein thrombosis (DVT) to be 13.1%.[4] Regardless of biological sex, DVT and PE incidence increase dramatically with age and obesity.[5] Moreover, the longitudinal community-based Framingham study found a venous thromboembolism (VTE) hazard ratio of 1.69 per every increase in age by 10 years and a VTE hazard ratio of 1.88 for those with a body mass index greater than 30 kg/m$^2$.[5] Given the obesity epidemic and growing aging population, PE prevalence is projected to increase.[5,6]

Survival after PE may lead to chronic health problems. Residual pulmonary vascular occlusion due to unresolved thrombus occurs in 20% of PE survivors.[7] Individuals with unresolved thrombus are at risk of developing chronic thromboembolic pulmonary hypertension (CTEPH), which occurs in 1–4% of people who survive the initial PE.[8,9] Current guidelines[10,11] do not address follow-up screening for CTEPH; thus, the exact percentage of CTEPH prevalence is unknown.[9] Prompt diagnosis and early initiation of evidence-based treatment is essential to help decrease PE-related morbidity and mortality.

Given that patients with PE can present with a wide variety of signs and symptoms ranging from asymptomatic to nonspecific to sudden death, a prompt, accurate diagnosis can be challenging.[10,12,13] Delay in treatment increases the chances of mortality, so timeliness is important.[11,13,14] Unfortunately, the PE diagnostic process carries risks from radiation and contrast dye exposure.[15–18] Also, once a PE is diagnosed, treatment creates bleeding risks from anticoagulation and/or thrombolytic therapy.[19–21] Indeed, untreated PE mortality can approach 25%, whereas PE mortality with therapy is 8%.[6,8] Accordingly, the goal for all patients is a quick, accurate diagnosis while minimizing risks. Thus, this article will review the current best evidence (Figure 1) for the PE diagnostic process and discuss emerging PE diagnostic tools.

## ETIOLOGY OF PE

Both PE and DVT comprise the same disease process known as VTE. A PE is the blockage of one or more branches of the pulmonary artery resulting in lack of perfusion to the alveoli.[22] The risk of developing a thrombus is often described with Virchow's triad, which includes venous stasis, endothelial injury, and hypercoagulability of the blood.[23] Venous stasis, pooling or slowing of venous blood flow, occurs with immobility, calf muscle weakness, and ankle/leg trauma. Endothelial injury arises from blood vessel injury, trauma, instrumentation, or the shear force associated with hypertension. Hypercoagulability is associated with cigarette smoking, hormone therapy, certain genetic conditions, cancer, obesity, and pregnancy.[10,24,25] Venous thrombi usually attach to the vessel at a site of injury and/or stasis and extend in the direction of blood flow.

When a thrombus dislodges, it embolizes to another location until it cannot pass any further, causing vessel occlusion. Most PEs arise from leg DVT.[13,26] Embolization risk is greater with proximal, above-the-knee DVT versus distal, below-the-knee DVT.[14,27] Nonthrombotic PE is rare and results from embolization of amniotic fluid, tumor or fat particles, gas, or foreign material.[28] Regardless of the etiology, a PE impairs perfusion of the pulmonary vascular bed.[22] As a result, alveolar

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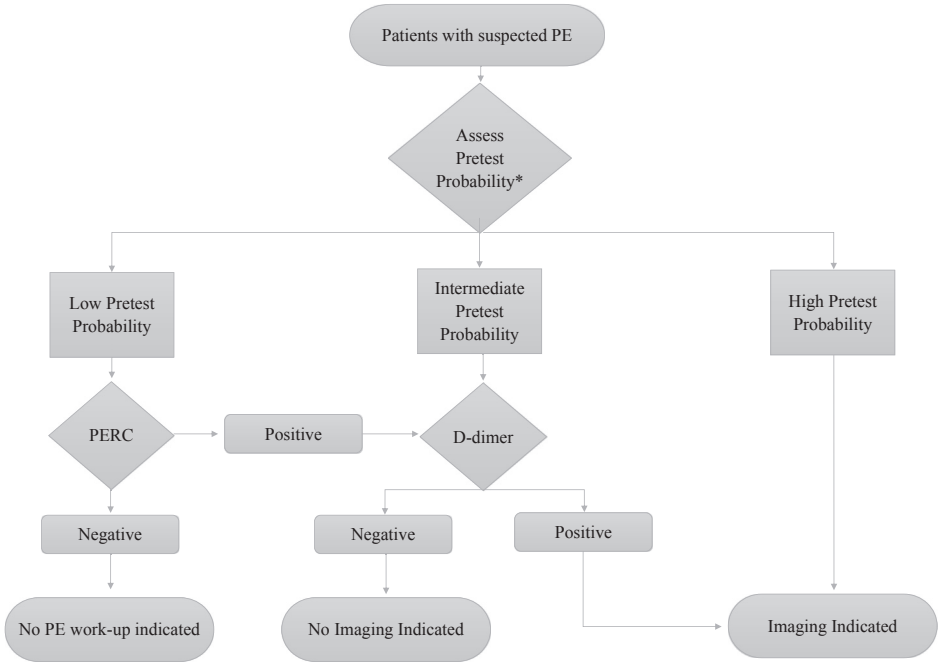


***Figure 1.*** *American college of physicians best practice advice. PE = pulmonary embolism; PERC = pulmonary embolism rule-out criteria. *Using either a clinical decision rule or clinician gestalt. Adapted and used with permission from the American College of Physicians Best Practice Advice (Raja, A. et al, 2015).*[11]

dead space (AVDS), an area of the lung ventilated without perfusion, increases (Figure 2).

## CLINICAL PRESENTATION OF PE

PE diagnosis is a stepwise process that begins with the healthcare provider's evaluation of the clinical presentation. Patients with PE may present with a variety of nonspecific signs and symptoms which overlap with multiple other conditions and range from very mild to devastating severe shock states.[10,11,14] The most common PE symptoms include pleuric and nonpleuric chest pain, sudden onset of dyspnea, leg pain, fatigue, anxiety, and hemoptysis.[10,11,14] Unfortunately, these symptoms are not unique to PE. For example, in a recent observational study of emergency department (ED) patients, Kelly et al.[29] (2017) found that although dyspnea is observed in 5.2% of all ED patients, only 1.2% of those patients were definitively diagnosed with a PE.

Clinical signs of PE may include electrocardiographic changes, leg swelling, low end-tidal carbon dioxide ($EtCO_2$), new onset atrial arrhythmias, hypotension, severe right-heart failure (sudden shortness of breath, pink sputum, atrial fibrillation, severe weakness/fatigue, tachycardia, low cardiac output), syncope, and/or tachypnea.[10,14,30] Likewise, these signs are not

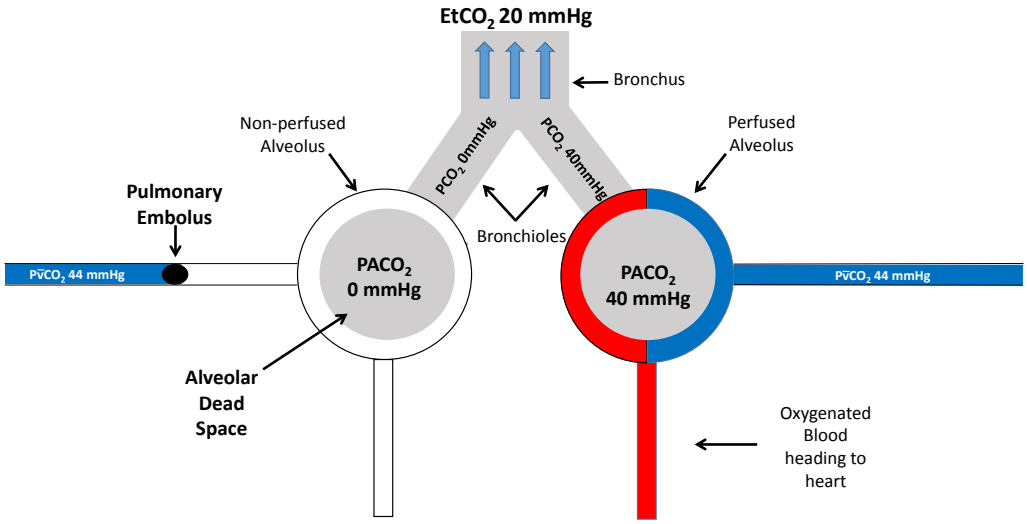


***Figure 2.*** *Pulmonary embolism alters alveolar dead space and end-tidal carbon dioxide. $EtCO_2$ = end-tidal carbon dioxide; $PACO_2$ = partial pressure of alveolar carbon dioxide; $PvCO_2$ = partial pressure mixed venous carbon dioxide.*

**TABLE 1**

**CLINICAL DECISION RULES (CDR) FOR THE DIAGNOSIS OF PULMONARY EMBOLISM (PE)**

| *Positive Indicators* | *Wells/ Canadian[36] (Point Value)* | *Modified Wells[37] (Point Value)* | *Simplified Wells[37] (Point Value)* | *Geneva[38] (Point Value)* | *Revised Geneva[39] (Point Value)* | *Simplified Revised Geneva[9] (Point Value)* | *PERC/Charlotte[40] (Indicators)* |
|---|---|---|---|---|---|---|---|
| VTE history | DVT or PE (1.5 points) | DVT or PE (1 point) | DVT or PE (1 point) | DVT or PE (2 points) | DVT or PE (3 points) | DVT or PE (1 point) | DVT or PE (presence) |
| Recent immobilization, surgery, or trauma | Immobilization ≥3 days or surgery ≤ 4 weeks (1.5 points) | Immobilization ≥ 3 days or surgery ≤ 4 weeks (1 point) | Immobilization ≥ 3 days or surgery ≤ 4 weeks (1 point) | Surgery ≤ 4 weeks (3 points) | Surgery or LE fracture ≤ 1 month (2 points) | Surgery or LE fracture ≤ 1 month (1 point) | Recent surgery or trauma ≤ 1 month (presence) |
| Heart rate | >100 (1.5 points) | >100 (1 point) | >100 (1 point) | >100 (1 point) | 75–94 (3 points) ≥95 (5 points) | 75–94 (1 point) ≥95 (1 point) | >100 (presence) |
| DVT clinical signs and symptoms | Minimum of leg swelling and pain with palpation of deep veins (3 points) | Minimum of leg swelling and pain with palpation of deep veins (2 points) | Minimum of leg swelling and pain with palpation of deep veins (1 point) | Not assessed | Unilateral LE pain (3 points); pain on limb palpation[40] unilateral edema (4 points) | Unilateral LE pain (1 point); pain on limb palpation[40] unilateral edema (1 point) | Unilateral leg swelling (presence) |
| Age in years | Not assessed | Not assessed | Not assessed | 60–79 (1 point) ≥80 (2 points) | ≥65 (1 point) | ≥65 (1 point) | ≥50 (presence) |
| Hemoptysis | Hemoptysis (1 point) | Hemoptysis (1 point) | Hemoptysis (1 point) | Not assessed | Hemoptysis (2 points) | Hemoptysis (1 point) | Hemoptysis (presence) |
| Malignancy | Treated malignancy ≤ 6 months or palliative (1 point) | Treated malignancy ≤ 6 months or palliative (1 point) | Treated malignancy ≤ 6 months or palliative (1 point) | Not assessed | Active malignancy or cured < 1 year (2 points) | Active malignancy or cured < 1 year (1 point) | Not assessed |
| Oxygenation | Not assessed | Not assessed | Not assessed | $PaO_2$ by RA ABG <49 (4 points); 49–59 (3 points); 60–71 (2 points); 72–82 (1 point) | Not assessed | Not assessed | SaO2 < 95% (on room air) (presence) |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ventilation | Not assessed | Not assessed | Not assessed | $PaCO_2$ by RA ABG <36 (2 points), 36–39 (1 point) | Not assessed | Not assessed | Not assessed |
| PE clinical suspicion | Alternative diagnosis less likely than PE (3 points) | Alternative diagnosis less likely than PE (2 points) | Alternative diagnosis less likely than PE (1 point) | Not assessed | Not assessed | Not assessed | Not assessed |
| Diagnostic testing | Not assessed | Not assessed | Not assessed | Chest X-ray; plate-like atelectasis (1 point); elevated hemidiaphragm (1 point) | Not assessed | Not assessed | Not assessed |
| Medications | Not assessed | Not assessed | Not assessed | Not assessed | Not assessed | Not assessed | Hormone use (presence) |
| Range of scores and interpretation of clinical probability | Range: 0–12.5; 3 level (original) scoring > 6 is high; 2–6 is moderate; <2 is low; 2 level (Wells 4) scoring > 4 PE likely ≤ 4 PE unlikely | Range: 0–9; >2 PE likely; ≤2 PE unlikely | Range: 0–7; >1 PE likely; ≤1 PE unlikely | Range: 0–16; ≥9 high; 5–8 intermediate; 0–4 low | Range: 0–22; ≥11 high; 4–10 intermediate; 0–3 low | Range: 0–9; 3 level scoring: ≥5 high; 2–4 intermediate; 0–1 low. 2-level scoring: 3 ≥ PE likely; 0–2 PE unlikely | No score calculated. Absence of all indicators rules out PE in a low-probability group |

ABG = arterial blood gas; DVT = deep vein thrombosis; LE = lower extremity; PE = pulmonary embolism; PERC = Pulmonary Embolism Rule-Out Criteria; RA = room air; VTE = venous thromboembolism.**Table modified and adapted from *Wells et al, 2000; **Gibson et al, 2008; #Wicki et al, 2001; ##LeGal et al, 2006; ###Klok et al, 2008; †Kline et al, 2004.**[40]

exclusive to PE. For instance, although syncope is associated with acute submassive PE,[30,31] syncope is only observed in about 12.3% of acute PE patients.[30,31] Indeed, no PE sign or symptom viewed in isolation has the ability to diagnose or exclude PE.[10,11,14] Nonetheless, clinical presentation, while nonspecific, is the foundation for determining the need for further diagnostic testing.

## PE PROBABILITY DETERMINATION

Current clinical guidelines[10,11] recommend using a validated clinical decision rule (CDR) to assist with the PE diagnostic process. Without a PE CDR to assess probability, the clinician would use their gestalt or best guess based on prior experience to determine PE likelihood. Although accuracy of an experienced clinician's gestalt may be similar to that of a CDR,[14,32] a CDR provides a standardized approach for less experienced clinicians or those who infrequently evaluate patients for suspected PE.[11] Specifically, a PE CDR quantifies signs and symptoms to determine PE probability and need for further testing.[11,33] Ultimately, the PE CDR provides a numerical score that categorizes the patient's PE likelihood. A patient with an intermediate- or high-probability CDR score will require further diagnostic testing.[10,11]

Multiple PE CDRs have been developed; some have been revised, modified, and/or simplified, and some are referred to by more than one name. Clinicians should note that Wells created two CDRs—a DVT CDR[34] and a PE CDR.[35] For this article, we only address PE CDRs. Table 1 provides an in-depth comparison of the indicators, scoring, and probability interpretation of the most commonly used PE CDRs.

Both the Wells and Geneva PE CDRs are considered valid tools for determining pretest probability[11]; however, neither is considered "better" at PE risk stratification.[32,41] Indeed, Douma et al[41] determined that when the PE CDR results were combined with a normal highly sensitive d-dimer test, accuracy indices (sensitivity [all were 99.5%], specificity [range: 29–31%], and negative predictive values (NPVs) [range: 99.4–99.5%]) were quite similar. Furthermore, simplified versions of the Wells and Geneva CDRs improved usage as clinicians could easily calculate the simplified CDRs from memory.[41]

The Pulmonary Embolism Rule-Out Criteria (PERC), the newest CDR, is unique in that it was purposefully created to assist with identifying patients at very low PE risk and excluding them from a PE diagnosis.[40] A patient is determined to have a low clinical probability of PE if all nine of the PERC (Table 1) are absent; thus, a PE diagnosis is excluded, and further diagnostic testing is avoided.[14,42] A meta-analysis of 12 studies involving 14,844 patients from seven countries confirmed the safety of the PERC for use in a clinically low-risk population, showing that the risk of missed PE was only 0.3% with a pooled sensitivity of 97% and a pooled specificity of 22%.[43] Of note, the PERC has not been validated in hospitalized patients[33] and should only be used for patients considered to have very low risk as determined by clinician gestalt or a validated CDR.[10,11]

To provide an accurate and reliable assessment, a CDR must be completed correctly. For example, one study evaluated the interrater reliability of the PERC and Wells PE CDR and found that clinician disagreement occurred with the following PE indicators: unexplained hypoxia, immobilization, and alternative diagnosis less likely than PE.[44] Although the CDR provides a valuable first step in the diagnosis of PE, CDR use adherence has not been methodically evaluated.[33] Factors leading to CDR nonadherence may be lack of education about CDRs, resistance to "cookbook" approaches to differential diagnosis, and lack of electronic medical record (EMR) support.[33] To facilitate CDR adherence, health-care agencies need to select a single CDR to be used to provide education to the medical and nursing staff on correct usage and interpretation of the CDR and incorporate the CDR into the EMR.[11,33]

Although the CDRs provide a valuable first step in the PE diagnostic process, they also have limitations. Validity testing is limited within certain populations. Specifically, CDRs need more validation in elderly, hospitalized, and pregnant patient populations.[10,45]

## D-DIMER

Current clinical guidelines[10,11] recommend using d-dimer testing in patients who do not meet all the PERC and those with an intermediate PE probability score from a Wells or Geneva CDR. D-dimer is a fibrin degradation product, a fragment released into the circulation during fibrinolysis. The quantitative method for measuring d-dimer is more accurate than a qualitative laboratory analysis.[46] The quantitative analysis d-dimer will be positive if the value is ≥500 nanograms per milliliter (ng/mL) and negative if the value is ≤499 ng/mL.[46]

D-dimer is elevated (i.e., positive d-dimer) in many normal and pathologic conditions where a thrombus is present, such as acute myocardial infarction, acute thromboembolic stroke, disseminated intravascular coagulation, DVT, PE, after surgery, and after trauma.[46,47] Additional nonthrombotic conditions that can lead to a positive d-dimer include acute kidney injury, advanced age (>50 years), cancer, heart failure, hemodialysis, high rheumatoid factor, inflammation, pregnancy and postpartum, sepsis, and severe liver disease.[48] Owing to the large number of false-positive results, d-dimer use is limited to patients who do not have a clinical condition that will stimulate the fibrinolytic system.[10,11,46,48] Although a positive d-dimer can be useful in the PE diagnostic process, it is not sufficient of itself to diagnose a PE. Consequently, patients with an intermediate CDR score and a positive d-dimer will require further testing to definitively determine PE presence or absence.[10,11]

In contrast, a negative d-dimer is very sensitive for absence of a blood clot.[46] A false-negative d-dimer occurs in <1% of patients but may be seen if the blood sample is drawn too soon after a clot has formed (<12 hours), too long after clot formation (>1 week), after the initiation of anticoagulation, or in patients with chronic PE.[14,25,49] A Cochrane review, several investigative teams, and the current clinical guidelines have all concluded that a low PE probability score on a validated CDR when used in combination with a negative, high-sensitivity d-dimer test can safely exclude PE with a NPV of 95%.[11,32,41,46,47,50,51] That said, recent research suggests that clinicians often order expensive and unnecessary radiologic tests such as computed tomography pulmonary angiography (CTPA) even in the presence of a negative d-dimer.[52–55]

Limitations of d-dimer testing need to be acknowledged. D-dimer requires a venous blood sample from the patient and laboratory analysis, which both add time to the diagnostic process. In addition, 24-hour laboratory testing may not be available at all locations or with all prehospital evaluations. Recent technological advances have made d-dimer point-of-care testing available. The recent development of point-of-care testing may assist with increasing d-dimer testing availability and decreasing the time to obtain results.[46] Since d-dimer levels increase with age, normal value ranges must be adjusted according to age (≥50 years). Age-adjusting d-dimer improves the number of older adults who can be safely excluded as having a PE; however, many false-positives still remain, especially among those over the age of 65 years.[10,50,56–58] Furthermore, d-dimer use has not been evaluated in pregnant or immediate postpartum patient populations.[59]

## RADIOLOGIC IMAGING

When indicated, radiologic imaging provides the most accurate and reliable PE diagnosis. According to the American College of Physicians and European guidelines, radiologic imaging is indicated for patients who do not meet all the PERC, have an intermediate PE clinical probability plus a positive d-dimer, or have a high PE clinical probability[10,11] (Figure 1). Radiologic imaging for definitive PE diagnosis can include CTPA, pulmonary angiography, and/or ventilation to perfusion (V/Q) scanning.

### *Computed tomography pulmonary angiography*

The CTPA has now replaced the pulmonary angiogram as the accepted gold standard for PE diagnosis.[10,11,60,61] CTPA is fast, reliable, and easily accessible in most hospital settings. The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study determined the CTPA to be 83% sensitive and 96% specific with a 96% positive predictive value (PPV) in patients with a high or low clinical probability and 92% PPV in patients with an intermediate-probability Wells score.[62] Improved technology has made the multidetector CTPA both sensitive and specific for PE diagnosis, and when used in conjunction with other clinical predictors (CDR and d-dimer), only 5% of CTPAs are inconclusive.[53,63] Thus, the clinician can be confident in both the negative and positive CPTA results. It should be noted, however, that obesity and severe tachypnea increase the rate of inconclusive examinations to 10%.[14] Another useful aspect of this imaging study is that CTPA can provide the clinician with an alternative diagnosis when the scan is negative for PE. For example, in a study by van Es,[64] the CTPA provided an alternative diagnosis for the presenting symptoms in roughly 50% of the PE-negative patients.

*CTPA overuse.* The downside to CTPA accessibility is overuse of the technology.[10,11] CTPA overuse leads to unnecessary exposure to imaging-related risks and increased health-care costs. Nationally, only about 10% of CTPA scans are positive for PE, indicating a large number of negative results and potential to eliminate unnecessary examinations.[53] For example, Parikh et al[53] found that CTPA was being used on patients with a negative d-dimer, which is contrary to current PE guidelines. CTPA overuse also has been noted in settings where clinicians do not routinely use a PE CDR or when errors are made in the calculation of the CDR related to education or infrequent use.[65] Indeed, in one single-center study where d-dimer and PE CDRs were not regularly used, 55% of patients received an unnecessary CTPA.[66] Moreover, CTPA also is being overused in older adult and female patients being evaluated for PE.[67,68] Adherence to PE practice guidelines has been shown to increase the diagnostic yield of CTPA.[69] For example, the use of a computerized diagnostic decision support system resulted in a 25% decrease in CTPA testing, indicating it may be an effective strategy to help eliminate CTPA overuse.[70]

*CTPA risks.* Although CTPA provides a definitive diagnosis, it also carries significant risks including radiation exposure, allergic reaction to intravenous (IV) contrast, and contrast-induced nephropathy (CIN). A CTPA exposes the patient to a significant amount of ionizing radiation that typically ranges between 10 to 20 millisieverts (mSv) with some reports as high as 70 mSv.[14,51] The current industry standard for occupational radiation exposure is 50 mSv/year.[71] The proposed 2018 International Commission on Radiologic Protection guideline suggests lowering occupational exposure to <10 mSv/year with an attempt to keep the yearly dose to 2–4 mSv or less. Exposure to 100 mSv has a 1% increased risk of developing cancer in a lifetime.[71]

Medical imaging is the primary source of radiation exposure in the United States.[71,72] Exposure to >10 mSv is thought to be carcinogenic, leading to an increased risk of leukemia, thyroid cancer, and breast cancer.[73] The risk of radiation exposure varies by tissue and organs. Breast tissue is one of the more sensitive with only 13 mSv of radiation needed to increase the risk of breast cancer.[74] Compared with a 2-view mammography, the CTPA exposes women to a 10- to 20-fold increase in radiation.[74,75] Younger age at exposure, along with genetic factors, may increase the risk of radiation injury.[73,76] Critically ill patients have an even greater risk of exposure as they often undergo repeated computed tomography scans.[71] Avoiding unnecessary CTPA is an important strategy to decreased radiation risks.

Contrast is given to enhance the quality of the imaging. Life-threatening reactions to IV contrast occur in 0.1% of the population, with an unexpected death rate from the allergic reaction being 1 in 75,000.[77] The incidence and severity of allergic reaction in ED patients is low (0.2%) with 70% described as mild and 30% as moderate. The most common allergic reactions are skin or mucosal (92%) ones followed by respiratory reactions (22%), with gastrointestinal allergic reactions being the lowest (4%). Allergic symptoms typically occur within 5 minutes of contrast injection and include urticaria (61%), sneezing/rhinorrhea (32%), and shortness of breath (22%).[78] Patients with a history of allergic reactions can be pretreated with steroids and antihistamines to mitigate the development of a reaction; however, pretreatment usually occurs over several hours. In emergency situations or when allergy history is unknown, clinicians need to be prepared to treat allergic reactions.[78]

CIN is defined as an increase in serum creatinine by 25% over baseline which occurs 48 to 72 hours after contrast administration. Risk factors for CIN include diabetes mellitus, chronic kidney injury, heart failure, and nephrotoxic medications.[79] Administration of normal saline before the IV contrast appears to decrease CIN risk in patients with one or more CIN risk factors.[18] Recent studies suggest that the CIN risk may have been

**TABLE 2**

**SUMMARY OF TESTING OPTIONS FOR PULMONARY EMBOLISM (PE) DIAGNOSIS**

| *Tests* | *Advantages* | *Disadvantages* |
|---|---|---|
| **Preliminary testing: Used early in diagnostic process to determine if further testing is necessary** | | |
| PE clinical diagnostic rules (CDR) | • Guide clinician as to low, moderate, or high probability for PE<br>• Easy<br>• Quick<br>• Can eliminate unnecessary tests<br>• Requires minimal education<br>• Best results obtained with CDR standardization and integration into EMR | • Pisa CDR requires dedicated website for calculation and interpretation.<br>• Wells DVT CDR may be confused with Wells PE CDR.<br>• PERC not validated for inpatient use.<br>• Inconsistent use leads to less reliable results. |
| D-dimer | • Highly sensitive for the presence of clot<br>• Negative result can help rule out PE<br>• Widely available in hospitals<br>• May be available as a point-of-care test (POCT)<br>• Use with CDR may help determine need for further testing | • Requires venipuncture<br>• Time delay for results, if not POCT<br>• May not be available in all prehospital settings<br>• Low specificity<br>• Positive result not specific for PE<br>• May not be useful in hospitalized patient population |
| **Definitive testing: used for final diagnosis** | | |
| Computed tomography pulmonary angiogram (CTPA) | • Preferred test for definitive PE diagnosis<br>• Widely available in hospital setting<br>• Quick results (~10 minutes for to complete test)<br>• May identify other causes of patient signs and symptoms<br>• Lower fetal radiation exposure | • Requires clinician skilled in performing and interpreting results<br>• 5% of results are indeterminate<br>• Not available in prehospital settings<br>• Not available as a bedside procedure<br>• Requires IV accessable to withstand a power injection (5–10 mL/second)<br>• Moderate radiation (10–20 millisiverts [mSv])<br>• High breast radiation exposure<br>• Potential for renal injury and/or allergic reaction from IV contrast exposure |
| Ventilation to perfusion Scan | • Able to determine the presence of PE (high-probability scan) or absence of PE (normal scan)<br>• Good option if CPTA is contraindicated<br>• Widely available in hospital setting<br>• Able to be completed at the bedside<br>• No contrast risk<br>• Lower radiation exposure to breast tissue | • Requires a trained clinician to perform procedure and interpret results<br>• Not available in prehospital settings<br>• Requires IV access<br>• Longer time to complete testing (~90 minutes)<br>• Minimal radiation exposure (0.28–0.9 mSv)<br>• Higher fetal radiation exposure than CTPA<br>• Harder to interpret results with underlying lung pathology<br>• Most scans categorized as low or intermediate probability preventing definitive diagnosis |

(*Continued*)

**TABLE 2**

**CONTINUED**

| *Tests* | *Advantages* | *Disadvantages* |
|---|---|---|
| Catheter pulmonary angiography | • Definitive diagnosis<br>• Can provide therapeutic intervention (catheter-directed thrombolysis or thrombectomy) along with diagnostic testing | • Requires a physician and team skilled in performing test<br>• Not available at all hospitals<br>• Not available as a bedside procedure<br>• Not available in prehospital settings<br>• Delay in obtaining procedure, especially during off-hour shifts<br>• Invasive procedure<br>• Risk of infection, bleeding, nerve, and blood vessel damage<br>• Moderated radiation (6 mSv)<br>• Potential for renal injury and/or allergic reaction from IV contrast exposure |
| **Adjunct testing: adds information to help interpret results of other tests and further refines risk assessment** | | |
| Electrocardiogram | • Easy to obtain<br>• Noninvasive<br>• Can be completed at the bedside<br>• Immediate results<br>• Widely available including prehospital settings<br>• Can detect right ventricular (RV) strain<br>• May provide alternative explanation for signs and symptoms | • Not specific for PE |
| Transthoracic echocardiogram | • Noninvasive<br>• Can be completed at the bedside<br>• Immediate results<br>• May be available in prehospital settings<br>• Can determine the presence and severity of RV strain<br>• May provide alternative explanation for signs and symptoms | • Requires a trained clinician to perform and interpret results<br>• Imaging capability limited in morbidly obese individuals<br>• Not specific for PE |
| Chest X-ray | • Noninvasive<br>• Can be completed at the bedside<br>• Results immediately available<br>• Widely available including prehospital settings<br>• Can determine if pulmonary infarct is present<br>• May provide alternative explanation for signs and symptoms | • Requires a trained clinician to perform and interpret results<br>• May not be available in some prehospital settings<br>• Exposure to minimum radiation (0.1 mSv)<br>• Potential delay related to interpretation by radiologist<br>• Not specific for PE |
| Compression ultrasonography | • Noninvasive<br>• Can be completed at the bedside<br>• Results immediately available<br>• Widely available in hospital setting and some prehospital settings<br>• Able to determine the presence and location of venous thrombus, if present | • Requires a trained clinician to perform and interpret results<br>• Delay in interpretation<br>• May not be available in prehospital settings<br>• Imaging capability limited in morbidly obese individuals<br>• Not specific for PE<br>• May not be able to distinguish new from preexisting thrombus |

(*Continued*)

**TABLE 2**

**CONTINUED**

| *Tests* | *Advantages* | *Disadvantages* |
|---|---|---|
| **Emerging diagnostic tools** | | |
| End-tidal carbon dioxide ($EtCO_2$) (Capnography) | • Easy to perform<br>• Immediate results for absolute $EtCO_2$<br>• Widely available in hospital and prehospital settings<br>• Can determine the presence or absence of alveolar dead space (AVDS)<br>• May be used with other assessments to guide further testing (positive D-dimer)<br>• Potential to eliminate unnecessary CTPA in some patients | • Increased AVDS not specific for PE<br>• Some capnography methods require an ABG and mathematical calculations (alveolar dead space calculation and $EtCO_2$ gradient)<br>• Delay in results if ABG is needed<br>• Lack of established cutoff value for PE exclusion |
| Goal-directed point-of-care ultrasound | • Improves accuracy of CDR by providing objective measurements of DVT and/or other diagnosis likely<br>• Potentially available in all settings including prehospital<br>• Multiple-organ testing increases accuracy | • Lack of trained clinicians<br>• Lack of specific protocols<br>• May not be specific for PE |

ABG = arterial blood gas; DVT = deep vein thrombosis; EMR = electronic medical record; IV = intravenous; PERC = Pulmonary Embolism Rule-Out Criteria.

over estimated and is actually lower than what is previously thought.[17,80] Depending on the baseline glomerular filtration rate, the incidence of CIN ranges from a low of 1% to a high of 14%.[17,80,81] Fortunately, research suggests that only 0.06% of patients require renal replacement therapy after a computed tomography examination. Although the incidence of CIN is low, unnecessary exposure to IV contrast should, nonetheless, be avoided.

### *Ventilation to perfusion scan*

The V/Q scan has largely been replaced by the more accurate CTPA; however, there remains a role for V/Q scans in patients at increased risk for radiation exposure (pregnancy), contrast allergy, and contrast exposure (renal injury).[10,11,27,59,75,82] Although the patient is exposed to radiation with the V/Q scan (range: 0.28 to 0.9 mSv), the dose is considerably lower than that received from a CTPA.[60,75] Another advantage of the V/Q scan is that it can be performed at bedside if a patient is too hemodynamically unstable to travel to the diagnostic imaging suite. The V/Q scan requires the patient to breathe radioactive gas, followed by the IV injection of a radioactive material which allows the comparison of the areas in the lung that are ventilated to the areas in the lung that have perfusion. A normal V/Q scan can rule out a PE (NPV near 100%), and a high-probability V/Q scan can diagnosis a PE (97% specific).[19,82–84] Unfortunately, nearly 50% of the V/Q scans will fall in the gray area of low- and intermediate-probability scans which are less useful to the clinician.[63,84] The low-probability V/Q scan has less than 20% likelihood of the patient having a PE, and the intermediate-probability V/Q has 20 to 80% likelihood.[84]

Limitations of the V/Q scan include availability, length of the test, imprecision of the test, and exposure to radiation and IV contrast. The V/Q scan can take up to 90 minutes to complete, thereby slowing the diagnosis of PE. Lack of availability of 24/7 radiology staff who can perform and interpret the examination limits the availability at some health-care facilities. The clinician may have to supplement the less precise (low and intermediate probability) V/Q scan results with the other clinical information (eg, transthoracic echocardiogram (TTE), compression ultrasound) to help determine PE likelihood. In addition, the V/Q scan is not available in the prehospital setting.

### *Pulmonary angiogram*

Pulmonary angiogram was long considered the gold standard for PE diagnosis; however, it also has been replaced by CTPA. Although excellent for PE diagnosis, the pulmonary angiogram is an invasive procedure that carries significant risks such as central venous cannulation (vessel injury, infection, bleeding) and IV contrast exposure (allergic reactions, nephrotoxicity).[14,60] The pulmonary angiogram can be difficult to obtain after business hours as it requires a specialist trained in performing the procedure. In addition, although the fluoroscopy system adjusts the radiation dose to body size, on average, the radiation exposure is approximately 6 mSv.[85]

The pulmonary angiogram may be used if treatment such as catheter-directed thrombolysis or thrombectomy is planned.[10] Catheter-directed thrombolysis increases the risk of bleeding

complications associated with the procedure[10]; however, there are lower bleeding risks than systemic thrombolysis in a high-risk population.[20] Pulmonary thromboembolectomy is mainly reserved for the patient with CTEPH versus the acute PE.[20] Many health-care facilities will not have the skilled team required for catheter-directed procedures and therapies.[20]

## ADDITIONAL DIAGNOSTIC STUDIES

### *Chest X-ray*

The chest X-ray (CXR) is neither sensitive nor specific for PE but can be useful when excluding other causes of chest pain and dyspnea with findings such as pneumonia or pneumothorax.[84,86] The optimum CXR study for the PE diagnostic process includes posterior and lateral chest views.[86] In about 10% of PE-positive patients, the CXR will have a wedge-shaped opacity (Hampton Hump) indicative of a pulmonary infarction.[51,87] Additional CXR findings that might suggest PE presence include atelectasis, cardiomegaly, elevated hemidiaphragm, enlarged major pulmonary artery (Fleischner sign), focal hypovolemia with collapse of vessels (Westermark sign), pleural effusion, and/or pulmonary infiltrates.[86] Research suggests that senior (≥10 years of experience) and junior radiologists (≤4 years of experience) only have fair interrater agreement (k = 0.24; confidence interval [CI]: 0.19–0.29) for determining PE presence or absence based on CXR.[86] Advantages of the CXR are that it can be performed at the bedside, can determine the cause of pulmonary symptoms, and direct further radiologic testing. Limitations of the CXR include its low specificity for PE diagnosis and lack of availability in all health-care settings, particularly in the prehospital arena. In addition, CXR does expose the patient to a low dose of radiation (~0.01 mSv).[76]

### *Electrocardiogram*

Because the electrocardiogram (ECG) cannot definitively diagnose PE, an ECG may be ordered in an effort to evaluate nonspecific symptoms such as chest pain or dyspnea. For example, the ECG is often used to rule out acute cardiac ischemia as the cause of dyspnea and/or chest pain.[14] Advantages of the ECG is that it is noninvasive, easy to perform, easy to interpret, and readily available in multiple health-care settings.

In most cases of PE, the ECG will be completely normal, especially in patients aged <60 years.[88] The ECG of a person with a PE may show nonspecific changes such as sinus tachycardia, atrial arrhythmias, right axis deviation, and a right bundle branch block.[88] Although classic ECG signs of right ventricular (RV) strain such as an S-wave in lead I, a Q-wave in lead III, and an inverted T-wave in lead III (S1Q3T3) can be seen,[89] research suggests that only 3% of PE-positive patients have the classic S1Q3T3 findings.[88] Indeed, the most common ECG abnormalities were T-wave inversion (34.4%), T-wave flattening (29.5), and sinus tachycardia (27.3%).[88] The increased availability of the ECG stored in the EMR allows the clinician to compare current and prior ECGs and more easily identify new ECG changes. That said, the ECG cannot be a primary diagnostic tool for PE due to the nonspecific nature of any ECG changes.

### *Compression ultrasonography*

Because a proximal DVT carries the greatest risk of PE,[90] a compression ultrasonography (CUS) can be used to identify the presence and location of a DVT.[10] When a DVT is present, the vein will not compress at the location of the thrombus. CUS has a sensitivity of 90% and a specificity of about 95% for symptomatic DVT.[10] If a patient has had a DVT in the last 12 months, remaining thrombus remnants may limit CUS accuracy in identifying new thrombus.[79,91] If prior CUS images are available, the accuracy of identifying new thrombus is improved.[79] Advantages of CUS are that it is an inexpensive, noninvasive option that does not involve exposure to IV contrast or radiation for DVT diagnosis; however, it is not currently available in the prehospital setting.

Although DVT presence is most certainly a risk factor for PE, it is not diagnostic for a PE. Salaun[90] found that 50% of the patients positive for a proximal DVT were also positive for PE. That said, the presence of a proximal DVT can guide the clinician to order further testing. For example, CUS can be used in conjunction with CTPA. If the CTPA is negative for PE and the CUS is positive for DVT, patients would qualify for anticoagulation which may prevent a future PE.[10,20,92] It should be noted, however, that the absence of a DVT cannot completely eliminate the possibility of a PE.

### *Transthoracic echocardiogram*

PE will rarely be diagnosed by a TTE.[93] Similar to the ECG, the usefulness of the TTE is in the identification of RV strain that may be the result of a PE.[10] TTE can assess for the classic McConnell's sign, regional RV dysfunction with akinesis of the mid-free wall with normal apical wall motion.[94,95] The original study found that the McConnell's sign was 77% sensitive and 94% specific for the diagnosis of acute PE, with a positive predictive value of 71% and an NPV of 96%.[94] Caution must be exercised, however, because clinical conditions other than PE may cause a McConnell's sign such as intracardiac shunts, pulmonary regurgitation, tricuspid regurgitation, and/or tricuspid stenosis.[95,96]

A systematic review and meta-analysis of 24 studies determined that signs of right-heart strain yielded a positive likelihood ratio (PLR) of 3.12 compared with a lack of signs for right-heart strain having a negative likelihood ratio (NLR) of 0.57.[97] The meta-analysis pooled signs used for right-heart stain including 10 discrete assessments (60/60 sign, RV hypokinesis, McConnell's sign, pulmonary arterial hypertension, visualization of a right-heart thrombus, RV to left ventricle ratio, RV end-diastolic diameter, abnormal or paradoxical septal motion, tricuspid regurgitation, tricuspid annular plane systolic excursion, and RV systolic pressure).[97] Individual analysis of the signs indicated that right-heart thrombus was not statistically significant for sensitivity or specificity, whereas both the 60/60 sign and the tricuspid annular plane systolic excursion were only significant for specificity.[97] Although TTE can be useful to further evaluate a clinician's suspicion of PE, clinicians cannot exclude PE based on a normal TTE because not all PE will cause RV strain.[97–99] Furthermore, in the situation of a PE, the TTE can help the clinician to quantify the hemodynamic consequences of a PE, to classify the severity of PE and guide therapy.[95] For

example, a patient with RV strain and also has a systolic BP < 90 mmHg is considered to have a massive PE and meets the criteria for treatment with thrombolytic therapy.[10,20,21,51] The TTE also can be used in conjunction with CUS in the critically ill patient who is too unstable to transfer for further diagnostic testing.

## EMERGING DIAGNOSTIC TOOLS

### *Point-of-care ultrasound*

Point-of-care ultrasound (POCUS) is becoming more available. Nazerian et al performed an observational study using a POCUS of the legs and lungs to modify the Wells CDR for either presence or absence of DVT and whether an alternative diagnosis is less likely than PE.[100] The results showed that integrating the POCUS for determining the Wells score improved the sensitivity to 69.6% and specificity to 88.2% from 57.6% and 68.2%, respectively, without the POCUS.[100] Both the presence of DVT and alternative diagnosis aspects of the Wells are subjective. The POCUS added an objective measure, thereby improving the Wells score.[100]

Assessment of multiple organs with POCUS improves the use over a single-organ assessment.[93,101] Skilled clinicians can assess lung, heart, and extremity veins to evaluate multiple physiologic effects that may be expected from a PE.[93,101] In a study of ED patients who met criteria based on CDR and d-dimer for intermediate probability for PE, they were evaluated with multiple-organ POCUS. Seventy-four percent of patients who were positive for PE were correctly identified with POCUS; however, 5% of patients with PE were missed.[93] Of note, the accuracy of residents (80%; 95% CI: 74.2 to 85.8%) was lower than that of senior physicians (85%, 95% CI: 80.7 to 89.3%). The use of goal-orientated multiorgan POCUS in conjunction with CDR may increase the pretest probability of PE and improve the use of CTPA to further eliminate unnecessary testing.[101] The goal-directed multiorgan POCUS that does not show any abnormality has an NPV of 95% for excluding PE.[101] An additional role for goal-directed multiorgan POCUS can be facilitating further diagnostic testing of the hemodynamically unstable patient who is too ill to be transported.[101] Limitation of POCUS is related to availability of equipment and trained personnel. Although availability of POCUS is improving, it may not be available in all health-care settings.

### *End-tidal carbon dioxide (capnography)*

Another noninvasive tool that has been investigated for its use in the exclusion of a PE diagnosis is a measurement of end-tidal (exhaled) carbon dioxide ($EtCO_2$), also known as capnography. As discussed earlier, the primary physiologic effect of PE is an increase in AVDS. Increased AVDS impairs $CO_2$ elimination (Figure 2). As AVDS increases, alveolar gas from nonperfused alveoli ($CO_2$-free gas) mixes with alveolar gas from perfused alveoli (normal concentration of $CO_2$ gas), thereby lowering $EtCO_2$. In the case of PE, $EtCO_2$ is disproportionally low as compared with arterial $CO_2$ ($PaCO_2$). $EtCO_2$ measurements are useful to assess AVDS changes. Based on the pathophysiology of PE, patients with normal AVDS can be excluded from a PE diagnosis.[22] A meta-analysis was completed on $EtCO_2$ studies published between 1990 through 2010. All methods of AVDS assessments with capnography were included, but outcomes were not differentiated by AVDS assessment type.[102] The 14 pooled studies indicated the sensitivity of an $EtCO_2$ assessment for PE to be 80% (95% CI: 76–83%), specificity of 49% (95% CI: 45–51%), an NLR of 0.32 (95% CI: 0.23–0.45), and a PLR of 2.43 (95% CI: 1.70–3.46). The NLR in this study shows a stronger likelihood of identifying patients without PE than the PLR that would identify patients with PE.[103] The meta-analysis suggests that $EtCO_2$ may be a good additional assessment to use in the PE diagnostic process to help identify low-risk patients (pretest probability less than 10%) who do not have PE.[102]

Of the methods for estimating AVDS with $EtCO_2$, using the absolute $EtCO_2$ value is the easiest, fastest, and the only completely noninvasive method. Five recent studies have used absolute $EtCO_2$ measurements in the PE diagnostic process.[104–108] Four of the five studies found a statistically significant difference between the absolute $EtCO_2$ of patients with and without PE.[105–108] Specifically, patients without PE had a significantly higher $EtCO_2$ than patients with PE. Unfortunately, to date, there is no agreed-upon $EtCO_2$ cutoff value that can be used to exclude a patient from the diagnosis of PE. Until additional research has established a consistent cutoff score for $EtCO_2$, it is unlikely to be implemented widely.

## CONCLUSION

Patients with PE may present with a variety of nonspecific signs and symptoms which overlap with multiple other conditions. PE signs and symptoms range from very mild to devastating severe shock states.[14] In addition, occasionally, the patient may be asymptomatic or present with sudden death.[10] Unfortunately, no individual sign or symptom viewed in isolation has the ability to diagnose or exclude PE.[10] Thus, making a prompt accurate diagnosis of PE often is a clinical challenge. For hemodynamically unstable patients suspected of PE, the diagnostic plan is straightforward; they should forgo any other testing and proceed directly to CTPA, if available.[10,11] For all others, the American College of Physicians[11] and the European Society of Cardiology[10] provide guidelines and suggest best practices for a stepwise approach in the diagnosis of PE. Specifically, the stepwise approach for the hemodynamically stable patient includes probability determination, D-dimer testing, and imaging with CTPA.[10,11] It is the responsibility of the clinician to guide patients appropriately along the diagnostic algorithm weighing the risk and benefits of each diagnostic test. Limited research indicates a lack of adherence to the PE diagnostic guidelines. Even with adherence to clinical guidelines, there is still a preponderance of negative CTPAs. Additional research is needed to help identify other diagnostic strategies that can be incorporated into the current PE diagnostic guidelines to further eliminate the need for unnecessary, costly radiology imaging (Table 2).

## REFERENCES

1. LaMori JC, Shoheiber O, Mody SH, et al. Inpatient resource use and cost burden of deep vein thrombosis and pulmonary embolism in the United States. Clin Ther 2015;37(1):62-70.

2. Smith S, Geske J, McNamara D, et al. Pulmonary Embolism Trends From 1996 to 2010. Chest 2013;144(4):850A.
3. Stein PD, Matta F, Musani MH, et al. Silent pulmonary embolism in patients with deep venous thrombosis: a systematic review. Am J Med 2010;123(5):426-31.
4. Hughes MJ, Stein PD, Matta F. Silent pulmonary embolism in patients with distal deep venous thrombosis: systematic review. Thromb Res 2014;134(6):1182-5.
5. Puurunen MK, Gona PN, Larson MG, et al. Epidemiology of venous thromboembolism in the Framingham Heart Study. Thromb Res 2016;145:27-33.
6. Smith S, Geske JB, Kathuria P, et al. Analysis of national trends in admissions for pulmonary embolism. Chest 2016;150:35-45.
7. Planquette B, Ferré A, Peron J, et al. Residual pulmonary vascular obstruction and recurrence after acute pulmonary embolism. A single center cohort study. Thromb Res 2016;148:70-5.
8. Kahn SR, Houweling AH, Granton J, et al. Long-term outcomes after pulmonary embolism: current knowledge and future research. Blood Coagul Fibrinolysis 2014;25(5):407-15.
9. Klok FA, Dzikowska-Diduch O, Kostrubiec M, et al. Derivation of a clinical prediction score for chronic thromboembolic pulmonary hypertension after acute pulmonary embolism. J Thromb Haemost 2016;14(1):121-8.
10. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014;35(43):3033-80.
11. Raja AS, Greenberg JO, Qaseem A, et al. Evaluation of patients with suspected acute pulmonary embolism: best practice advice from the clinical guidelines committee of the american college of physicians. Ann Intern Med 2015;163(9):701.
12. Aschermann M, Widimský J. Comparison of ESC guidelines 2008 and 2014–diagnostic and treatment of acute pulmonary embolism. Cor et Vasa 2015;57(4):e270-4.
13. Lavorini F, Di Bello V, De Rimini ML, et al. Diagnosis and treatment of pulmonary embolism: a multidisciplinary approach. Multidiscip Respir Med 2013;8(1):1.
14. Kline JA, Kabrhel C. Emergency evaluation for pulmonary embolism, part 2: diagnostic approach. J Emerg Med 2015;49(1):104-17.
15. Brenner DJ. Radiation and chest ct scans. Chest 2012;142(3):549-50.
16. Le Roux P-Y, Palard X, Robin P, et al. Safety of ventilation/perfusion single photon emission computed tomography for pulmonary embolism diagnosis. Eur J Nucl Med Mol Imaging 2014;41(10):1957-64.
17. McDonald JS, McDonald RJ, Carter RE, et al. Risk of intravenous contrast material–mediated acute kidney injury: a propensity score–matched study stratified by baseline-estimated glomerular filtration rate. Radiology 2014;271(1):65-73.
18. Traub SJ, Mitchell AM, Jones AE, et al. N-acetylcysteine plus intravenous fluids versus intravenous fluids alone to prevent contrast-induced nephropathy in emergency computed tomography. Ann Emerg Med 2013;62(5):511-52025.
19. Fesmire FM, Brown MD, Espinosa JA, et al. Critical issues in the evaluation and management of adult patients presenting to the emergency department with suspected pulmonary embolism. Ann Emerg Med 2011;57(6):628-65275.
20. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease. Chest 2016;149(2):315-52.
21. Levin D, Seo JB, Kiely DG, et al. Triage for suspected acute pulmonary embolism: think before opening pandora's box. Eur J Radiol 2015;84(6):1202-11.
22. West JB, Luks A. West's Repiratory Physiology: The Essentials. 10th ed. Philadelphia: Wolter Kluwer; 2016.
23. Stone J, Hangge P, Albadawi H, et al. Deep vein thrombosis: pathogenesis, diagnosis, and medical management. Cardiovasc Diagn Ther 2017;7(S3):S276-84.
24. Dybowska M, Tomkowski WZ, Kuca P, et al. Analysis of the accuracy of the Wells scale in assessing the probability of lower limb deep vein thrombosis in primary care patients practice. Thromb J 2015;13(1):1-5.
25. Lippi G, Danese E, Favaloro E, et al. Diagnostics in venous thromboembolism: from origin to future prospects. Semin Thromb Hemost 2015;41(04):374-81.
26. Marshall PS, Mathews KS, Siegel MD. Diagnosis and management of life-threatening pulmonary embolism. J Intensive Care Med 2011;26(5):275-94.
27. Piovella F, Iosub DI. Acute pulmonary embolism: risk assessment, risk stratification and treatment options: Acute pulmonary embolism. Clin Respir J 2016;10(5):545-54.
28. Montagnana M, Cervellin G, Franchini M, et al. Pathophysiology, clinics and diagnostics of non-thrombotic pulmonary embolism. J Thromb Thrombolysis 2011;31(4):436-44.
29. Kelly AM, Keijers G, Klim S, et al. An observational study of dyspnea in emergency departments: the Asia, Australia, and New Zealand dyspnea in emergency department study (AANZDEM). Acad Emerg Med 2017;24:328-36.
30. Omar HR, Mirsaeidi M, Weinstock MB, et al. Syncope on presentation is a surrogate for submassive and massive acute pulmonary embolism. Am J Emerg Med 2017;36(2):297-300.
31. Oqab Z, Ganshorn H, Sheldon R. Prevalence of pulmonary embolism in patients presenting with syncope. A systematic review and meta-analysis. Am J Emerg Med 2017;36(4):551-5.
32. Lucassen W, Geersing G-J, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. Ann Intern Med 2011;155(7):448-60.
33. Sherk WM, Stojanovska J. Role of clinical decision tools in the diagnosis of pulmonary embolism. AJR Am J Roentgenol 2017;208(3):W60-70.
34. Wells P, Anderson D, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. Lancet 1997;350(9094):1795-8.
35. Wells P. Use of a clinical model for safe management of patients with suspected pulmonary embolism. Ann Intern Med 1998;129(12):997.

36. 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;83:416-20.
37. Gibson N, Sohne M, Kruip MJ, et al. Further validation and simplification of the Wells clinical decision rule in pulmonary embolism. Thromb Haemost 2008;99(1):229-34.
38. Wicki J, Perneger TV, Junod AF, et al. Assessing clinical probability of pulmonary embolism in the emergency ward. Arch Intern Med 2001;161:92-7.
39. Le Gal G, Righini M, Roy PM, et al. Prediction of pulmonary embolism in the emergency department: The revised geneva score. Ann Intern Med 2006;144:165-71.
40. Kline JA, Mitchell AM, Kabrhel C, et al. Clinical criteria to prevent unnecessary diagnostic testing in emergency department patients with suspected pulmonary embolism. J Thromb Haemost 2004;2(8):1247-55.
41. Douma RA, Mos IC, Erkens PM, et al. Performance of 4 clinical decision rules in the diagnostic management of acute pulmonary embolism: a prospective cohort study. Ann Intern Med 2011;154(11):709-18.
42. Kline JA, Peterson CE, Steuerwald MT. Prospective evaluation of real-time use of the pulmonary embolism rule-out criteria in an academic emergency department: perc. Acad Emerg Med 2010;17(9):1016-9.
43. Singh B, Mommer SK, Erwin PJ, et al. Pulmonary embolism rule-out criteria (PERC) in pulmonary embolism—revisited: A systematic review and meta-analysis. Emerg Med J 2013;30(9):701-6.
44. Nordenholz KE, Naviaux NW, Stegelmeier K, et al. Pulmonary embolism risk assessment screening tools: the interrater reliability of their criteria. Am J Emerg Med 2007; 25(3):285-90.
45. Tromeur C, van der Pol LM, Klok FA, et al. Pitfalls in the diagnostic management of pulmonary embolism in pregnancy. Thromb Res 2017;151:S86-91.
46. Riley RS, Gilbert AR, Dalton JB, et al. Widely used types and clinical applications of d-dimer assay. Lab Med 2016; 47(2):90-102.
47. Kline JA, Hogg MM, Courtney DM, et al. D-dimer threshold increase with pretest probability unlikely for pulmonary embolism to decrease unnecessary computerized tomographic pulmonary angiography: Elevated D-dimer threshold. J Thromb Haemost 2012;10(4):572-81.
48. Chopra N, Doddamreddy P, Grewal H, et al. An elevated D-dimer value: a burden on our patients and hospitals. Int J Gen Med 2012;5:87-92.
49. Youssf ARI, Ismail MFM, ElGhamry R, et al. Diagnostic accuracy of D-dimer assay in suspected pulmonary embolism patients. Egyptian J Chest Dis Tuberc 2014;63(2): 411-7.
50. Crawford F, Andras A, Welch K, et al. D-dimer test for excluding the diagnosis of pulmonary embolism. Cochrane Database Syst Rev 2016;8:CD010864.
51. Lapner ST, Kearon C. Diagnosis and management of pulmonary embolism. BMJ 2013;346:f757.
52. Chandra S, Sarkar PK, Chandra D, et al. Finding an alternative diagnosis does not justify increased use of CT-pulmonary angiography. BMC Pulm Med 2013;13(1):1-8.
53. Parikh N, Morris E, Babb J, et al. MDCT diagnosis of acute pulmonary embolism in the emergent setting. Emerg Radiol 2015;22(4):379-84.
54. Perelas A, Dimou A, Saenz A, et al. CT pulmonary angiography utilization in the emergency department: diagnostic yield and adherence to current guidelines. Am J Med Qual 2015;30(6):571-7.
55. Yin F, Wilson T, Della Fave A, et al. Inappropriate use of D-dimer assay and pulmonary CT angiography in the evaluation of suspected acute pulmonary embolism. Am J Med Qual 2012;27(1):74-9.
56. Righini M, Van Es J, Den Exter PL, et al. Age-adjusted d-dimer cutoff levels to rule out pulmonary embolism: the adjust-pe study. JAMA 2014;311(11):1117.
57. Schouten HJ, Geersing G-J, Oudega R, et al. Accuracy of the wells clinical prediction rule for pulmonary embolism in older ambulatory adults. J Am Geriatr Soc 2014; 62(11):2136-41.
58. Woller SC, Stevens SM, Adams DM, et al. Assessment of the safety and efficiency of using an age-adjusted d-dimer threshold to exclude suspected pulmonary embolism. Chest 2014;146(6):1444-51.
59. Solomon CG, Greer IA. Pregnancy complicated by venous thrombosis. N Engl J Med 2015;373(6):540-7.
60. Dogan H, de Roos A, Geleijins J, et al. The role of computed tomography in the diagnosis of acute and chronic pulmonary embolism. Diagn Interv Radiol 2015;21(4): 307-16.
61. Ma Y, Wang Y, Liu D, et al. A safe strategy to rule out pulmonary embolism: The combination of the Wells score and D-dimer test: One prospective study. Thromb Res 2017; 156:160-2.
62. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med 2006;354(22):2317-27.
63. van der Hulle T, Dronkers CEA, Klok FA, et al. Recent developments in the diagnosis and treatment of pulmonary embolism. J Intern Med 2016;279(1):16-29.
64. van Es J, Douma RA, Schreuder SM, et al. Clinical impact of findings supporting an alternative diagnosis on CT pulmonary angiography in patients with suspected pulmonary embolism. Chest 2013;144(6):1893-9.
65. Newnham M, Stone H, Summerfield R, et al. Performance of algorithms and pre-test probability scores is often overlooked in the diagnosis of pulmonary embolism. Br Med J 2013;346(2):f1557.
66. Perera M, Aggarwal L, Scott IA, et al. Underuse of risk assessment and overuse of CTPA in patients with suspected pulmonary thromboembolism: Overuse of CTPA in suspected PTE. Intern Med J 2017;47(10):1154-60.
67. Bickley D, Lindsey J, Saint-Hilaire R, et al. 678: an analysis of the use of ct pulmonary angiography in young women in an urban emergency department. Crit Care Med 2015;43: 171.

68. Chen YA, Gray BG, Bandiera G, et al. Variation in the utilization and positivity rates of CT pulmonary angiography among emergency physicians at a tertiary academic emergency department. Emerg Radiol 2015;22(3):221-9.
69. Wang RC, Bent S, Weber E, et al. The impact of clinical decision rules on computed tomography use and yield for pulmonary embolism: a systematic review and meta-analysis. Ann Emerg Med 2016;67(6):693-7013.
70. Jiménez D, Resano S, Otero R, et al. Computerised clinical decision support for suspected PE: Table 1. Thorax 2015; 70(9):909-11.
71. Rohner DJ, Bennett S, Samaratunga C, et al. Cumulative total effective whole-body radiation dose in critically ill patients. Chest 2013;144(5):1481-6.
72. Dainiak N. Radiation dose and stochastic risk from exposure to medical imaging. Chest 2013;144(5):1431-3.
73. Huppmann MV, Johnson WB, Javitt MC. Radiation risks from exposure to chest computed tomography. Semin Ultrasound CT MRI 2010;31(1):14-28.
74. Alkhorayef M, Babikir E, Alrushoud A, et al. Patient radiation biological risk in computed tomography angiography procedure. Saudi J Biol Sci 2017;24(2):235-40.
75. Freeman LM. Don't bury the v/q scan: it's as good as multidetector ct angiograms with a lot less radiation exposure. J Nucl Med 2007;49(1):5-8.
76. Schembri GP, Miller AE, Smart R. Radiation dosimetry and safety issues in the investigation of pulmonary embolism. Semin Nucl Med 2010;40(6):442-54.
77. Jung J-W, Kang H-R, Kim M-H, et al. Immediate hypersensitivity reaction to gadolinium-based MRI contrast media. Radiology 2012;264(2):414-22.
78. Gottumukkala RV, Glover M, Yun BJ, et al. Allergic-like contrast reactions in the ED: incidence, management, and impact on patient disposition. Am J Emerg Med 2017; 36(5):825-8.
79. Huisman MV, Klok FA. Current challenges in diagnostic imaging of venous thromboembolism. Blood 2015; 126(21):2376-82.
80. Kooiman J, Pasha SM, Zondag W, et al. Meta-analysis: Serum creatinine changes following contrast enhanced CT imaging. Eur J Radiol 2012;81(10):2554-61.
81. Alhassan S, Sayf AA, Arsene C, et al. Suboptimal implementation of diagnostic algorithms and overuse of computed tomography-pulmonary angiography in patients with suspected pulmonary embolism. Ann Thorac Med 2016;11(4):254-60.
82. Hunsaker AR, Lu MT, Goldhaber SZ, et al. Imaging in acute pulmonary embolism with special clinical scenarios. Circ Cardiovasc Imaging 2010;3(4):491-500.
83. Moores LK. Current approach to the diagnosis of acute nonmassive pulmonary embolism. Chest 2011;140(2):509.
84. Worsley DF, Alavi A. Comprehensive analysis of the results of the pioped study. J Nucl Med 1995; 36(12):2380-7.
85. Zanzonico P, Rothenberg LN, Strauss HW. Radiation exposure of computed tomography and direct intracoronary angiography. J Am Coll Cardiol 2006;47(9):1846-9.
86. Sverzellati N, De Filippo M, Quintavalla M, et al. Interobserver reliability of the chest radiograph in pulmonary embolism. Clin Appl Thromb Hemost 2014;20(2):147-51.
87. Lankeit M, GÃŗmez V, Wagner C, et al. A strategy combining imaging and laboratory biomarkers in comparison with a simplified clinical score for risk stratification of patients with acute pulmonary embolism. Chest 2012; 141(4):916-22.
88. Co I, Eilbert W, Chiganos T. New electrocardiographic changes in patients diagnosed with pulmonary embolism. J Emerg Med 2017;52(3):280-5.
89. Hunt JM, Bull TM. Clinical review of pulmonary embolism: diagnosis, prognosis, and treatment. Med Clin North Am 2011;95(6):1203-22.
90. Salaun P-Y. Noninvasive diagnosis of pulmonary embolism. Chest 2011;139(6):1294.
91. Ageno W, Squizzato A, Wells PS, et al. The diagnosis of symptomatic recurrent pulmonary embolism and deep vein thrombosis: guidance from the SSC of the ISTH. J Thromb Haemost 2013;11(8):1597-602.
92. Beckman MG, Hooper WC, Critchley SE, et al. Venous thromboembolism: a public health concern. Am J Prev Med 2010;38(4 Suppl):S495-501.
93. Nazerian P, Vanni S, Volpicelli G, et al. Accuracy of point-of-care multiorgan ultrasonography for the diagnosis of pulmonary embolism. Chest 2014;145(5):950-7.
94. McConnell MV, Solomon SD, Rayan M, et al. Regional right ventricular dysfunction dectected by echocardiography in acute pulmonary embolism. Am J Cardiol 1996; 78:469-73.
95. Weekes AJ, Johnson AK, Troha D, et al. Prognostic value of right ventricular dysfunction markers for serious adverse events in acute normotensive pulmonary embolism. J Emerg Med 2017;52(2):137-50.
96. Walsh BM, Moore CL. McConnell's sign is not specific for pulmonary embolism: case report and review of the literature. J Emerg Med 2015;49(3):301-4.
97. Fields JM, Davis J, Girson L, et al. Transthoracic echocardiography for diagnosing pulmonary embolism: a systematic review and meta-analysis. J Am Soc Echocardiogr 2017;30(7):714-7234.
98. Ma Y, Yan S, Zhou L, et al. Competitive assessments of pulmonary embolism: Noninvasiveness versus the golden standard. Vascular 2016;24(2):217-24.
99. Reissig A, Copetti R, Kroegel C. Current role of emergency ultrasound of the chest. Crit Care Med 2011;39(4):839-45.
100. Nazerian P, Volpicelli G, Gigli C, et al., the Ultrasound Wells Study Group. Diagnostic performance of wells score combined with point-of-care lung and venous ultrasound in suspected pulmonary embolism. Acad Emerg Med 2017; 24(3):270-80.
101. Zhu R, Ma X-C. Clinical value of ultrasonography in diagnosis of pulmonary embolism in critically ill patients. J Transl Int Med 2017;5(4):200-4.
102. Manara A, D'hoore W, Thys F. Capnography as a diagnostic tool for pulmonary embolism: a meta-analysis. Ann Emerg Med 2013;62(6):584-91.

103. Sedighi I. Interpretation of diagnostic tests: Likelihood ratio vs predictive value. Iran J Pediatr 2013;23(6):717.
104. Fabius TM, Eijsvogel MM, van der Lee I, et al. Volumetric capnography in the exclusion of pulmonary embolism at the emergency department: a pilot study. J Breath Res 2016; 10(4):046016.
105. Hemnes AR, Newman AL, Rosenbaum B, et al. Bedside end-tidal CO2 tension as a screening tool to exclude pulmonary embolism. Eur Respir J 2010; 35(4):735-41.
106. Ramme AJ, Iturrate E, Dweck E, et al. End tidal carbon dioxide as a screening tool for computed tomography angiogram in postoperative orthopaedic patients suspected of pulmonary embolism. J Arthroplasty 2016;31(10):2348-52.
107. Riaz I, Jacob B. Pulmonary embolism in Bradford, UK: role of end-tidal CO2 as a screening tool. Clin Med 2014;14(2): 128-33.
108. Rumpf TH, Krizmaric M, Grmec S, et al. Capnometry in suspected pulmonary embolism with positive D-dimer in the field. Crit Care 2009;13(6):1-9.