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Clinical Reviews

EMERGENCY EVALUATION FOR PULMONARY EMBOLISM, PART 2: DIAGNOSTIC APPROACH

Jeffrey A. Kline, MD* and Christopher Kabrhel, MD, MPH†

*Department of Emergency Medicine and Department of Cellular and Integrative Physiology, Indiana University School of Medicine, Indianapolis, Indiana and †Department of Emergency Medicine, Center for Vascular Emergencies, Massachusetts General Hospital and Department of Emergency Medicine, Harvard Medical School, Boston, Massachusetts

Reprint Address: Jeffrey A. Kline, MD, Department of Emergency Medicine and Department of Cellular and Integrative Physiology, Indiana University School of Medicine, 720 Eskanazi Avenue, Indianapolis, IN 46202

□ **Abstract—Background: In part 1 of this two-part review, we discussed which risk factors, historical features, and physical findings increase risk for pulmonary embolism (PE) in symptomatic emergency department (ED) patients. Objectives: Use published evidence to describe criteria that a reasonable and prudent clinician can use to initiate and guide the process of excluding and diagnosing PE. Discussion: The careful and diligent emergency physician can use clinical criteria to safely obviate a formal evaluation of PE, including the use of gestalt reasoning and the pulmonary embolism rule-out criteria (PERC rule, Table 2, part 1). We present published clinical and radiographic features of patients with PE who eluded diagnosis in the ED. D-dimer can be used to exclude PE in many patients, and employing age-based adjustments to the threshold to define an abnormal value can further reduce patient exposure to pulmonary vascular imaging. Moreover, we discuss benefits, limitations, and potential harms of computed tomographic pulmonary vascular imaging relevant to patients and the practice of emergency care. We present algorithms to guide exclusion and diagnosis of PE in patients with suspected PE, including those who are pregnant. Conclusions: Reasonable and prudent emergency clinicians can exclude PE in symptomatic ED patients on clinical grounds alone in many patients, and many more can have PE ruled out by use of the D-dimer. © 2015 Elsevier Inc.**

□ **Keywords—pulmonary embolism; medicolegal; defensive medicine; decision making; venous thromboembolism; pregnancy; diagnosis; pregnancy**

INTRODUCTION

This second part of a two-part review provides an in-depth analysis of issues critical to deciding when to initiate a formal diagnostic evaluation for pulmonary embolism (PE) in emergency department (ED) patients, and what diagnostic tests, if any, need to be ordered. We explore evidence-based options for excluding PE to a reasonable degree of diagnostic certainty but with minimal exposure to radiation and iodinated contrast material.

DISCUSSION

Decision to Initiate the Work-up and Empiric Treatment

Figure 1 presents an algorithm for the diagnostic evaluation of patients with possible PE. For PE to enter the active differential diagnosis list for any patient, he or she must have at least one possible physiologic manifestation of PE. The physiologic manifestation may be a symptom (e.g., dyspnea, pleuritic chest pain, or new fatigue) or a sign (e.g., heart rate > 100 beats/min or pulse oximetry < 95% near sea level) that is not explained by another cause. Other bedside physiological signs of PE include a low (<30 mm Hg) end-tidal CO_2, measured by capnography, or signs of pulmonary hypertension on 12-lead electrocardiography, including T-wave inversion

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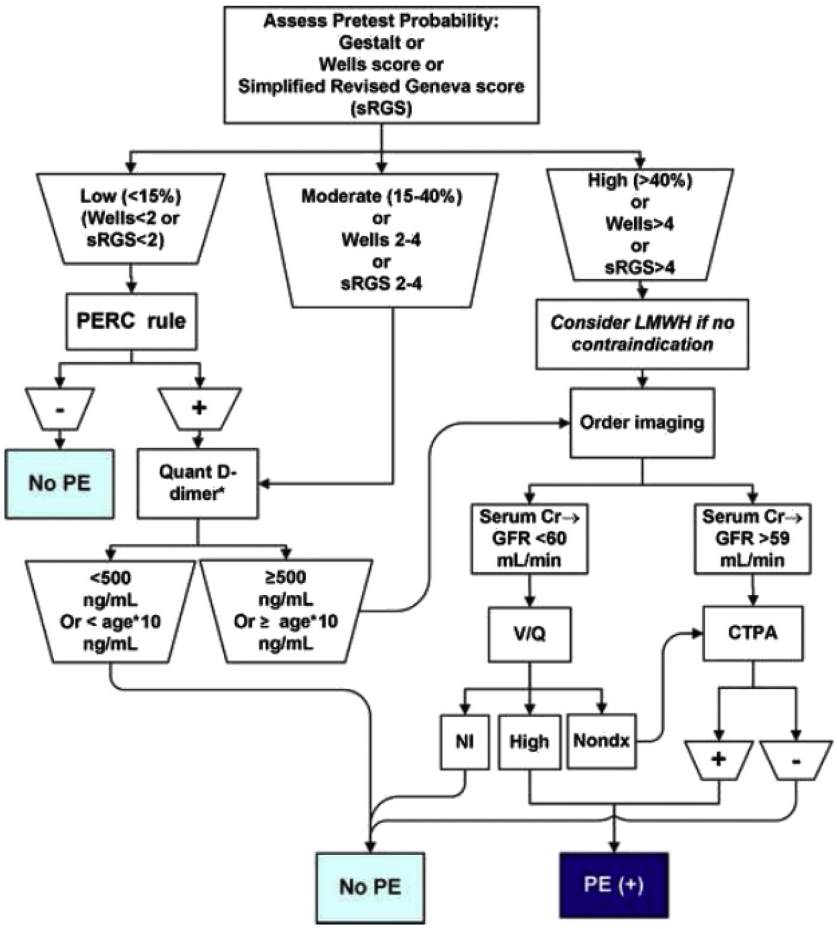

Figure 1. Diagnostic algorithm for pulmonary embolism (PE) in patients who prompt enough clinical suspicion to warrant the documented consideration of PE. *Assumes a cutoff for abnormal of ≥500 ng/mL. Nondiagnostic ventilation-perfusion (V/Q) scan findings require confirmation from results of another test, such as computed tomography pulmonary angiography (CTPA), if benefits outweigh risks. Abbreviations: + = positive for PE; – = negative for PE; Cr = creatinine; GFR = glomerular filtration rate; High = high probability scan findings; LMWH = low-molecular-weight heparin; NI = normal; Nondx = nondiagnostic (any reading other than normal or high probability); PERC = pulmonary embolism rule-out criteria; quant = quantitative, sRGS = simplified revised Geneva score.

in leads V_1 to V_4, incomplete or complete right bundle-branch block, and the S_1-Q_3-T_3 pattern (1,2).

Reasonable and prudent emergency care does not dictate that all patients with a sign or symptom of PE must be tested for PE. Nor does it dictate that a patient with one or more risk factors for PE must undergo testing for PE in the absence of a sign or symptom of PE. However, the authors believe that clinicians should consider PE for patients with a sign or symptom of PE and a known risk factor for PE (see Table 1, in part 1), and at least mentally formulate an explanation why a work-up was not pursued in the event that the patient had PE. If a reasonable alternative disease explains the patient's presentation, testing specifically directed at diagnosing PE need not be ordered. The value of an alternative diagnosis to obviate an evaluation for PE must be decided on a case-by-case basis, and is often a nuanced decision-making process. For example, if an emergency physician cares for a patient with long-standing dyspnea and tachycardia with a known lung cancer and a large pleural effusion, this does not mandate a computed tomographic pulmonary angiogram (CTPA). However, if the clinician was aware that lung mass and effusion were radiographically unchanged, but the patient recently developed new severe dyspnea and tachycardia, this patient may warrant further testing for PE.

The next step is to assess the pretest probability using either gestalt or a validated scoring method, such as the Wells score, or the revised Geneva score (RGS) or the simplified RGS (Tables 3 and 4, part 1) (3–5). Gestalt has the advantage of not requiring any memory aid, and has similar diagnostic performance characteristics and interobserver reliability as the Wells score and RGS (3,6). If a patient has a high pretest probability (from

any method), the clinician should consider immediately administering heparin or low-molecular-weight heparin for patients with low bleeding risk. However, the benefits of "empiric" anticoagulation remain unproven. One review suggested that the benefit of empiric systemic anticoagulation for 24 h exceeds the risks (bleeding and heparin-induced thrombocytopenia) for any patient with a pretest probability of PE of >20% (7). Several studies have suggested that delay in administration of heparin to patients with PE can increase mortality, but no study has found that heparin administered prior to imaging improves morbidity or mortality (8–10).

Three studies have provided data on patients who passed through the ED and were soon after diagnosed with PE (8,11–13). These patients can be categorized as those admitted to the hospital and those discharged home. Compared with patients who were promptly diagnosed and treated for PE, patients admitted to the hospital who went on to have delayed recognition of PE tended to have a higher frequency of altered mental status (either new or at baseline dementia) and preexisting heart and lung disease (8,11–13). Only one study provided data on patients apparently discharged with PE, and those patients were more likely to not have dyspnea, have isolated pleuritic chest pain and hemoptysis together with a pulmonary infiltrate on imaging, and a lower D-dimer concentration with a small distal clot seen on pulmonary vascular imaging (12). Coincidentally, in an analysis of PE(+) but pulmonary embolism rule-out criteria (PERC)(−) patients (see Table 2 in part 1) in a large database, the presence of pleuritic chest pain emerged as a common feature (14). Thus, it seems that highly competent emergency physicians may miss distal lung clots that produce pulmonary infarction and a clinical picture of pneumonia. More evidence is needed to determine if patients with these small distal clots, in the absence of deep venous thrombosis (DVT), actually benefit from systemic anticoagulation.

Exclusion of PE at the Bedside

About two-thirds of patients who are considered for testing for PE in the United States have a low pretest probability, regardless of the method used, and the prevalence of PE in this group is <5% (15). Patients with a low gestalt pretest probability (defined as a global estimate that the patient has <15% probability of PE) are eligible to have PE ruled out with the PERC rule (see Table 2 in part 1).

The authors suggest that ruling out PE requires a combination of pretest probability and diagnostic test results that predict an outcome rate, or false negative rate <2.0% for any one patient. This false negative rate, synonymous with posttest probability, equals the product of the likelihood ratio (LR) for a negative diagnostic test result (LR^- = [1 − sensitivity]/specificity) times the pretest odds (odds = probability/[1 − probability]) (note that odds are always higher than probability), which is then converted from an odds value back to probability. Thus, for a low-risk population—for example, one with an underlying prevalence of venous thromboembolism (VTE) of 4–5% defined by gestalt low clinical probability—the PERC rule, functioning as a diagnostic test, has an LR^- of about 0.2 or less, and therefore clearly can rule out VTE, based upon a predefined posttest threshold of 2.0% (3,16,17):

Pretest probability = 4%.

Pretest odds = 0.04 (1−0.04) = 0.04/0.96 = 0.042.

Post-test odds = LR^- * pretest odds = 0.2 * 0.042 = 0.0084.

Post-test probability = odds/(1 + odds) = 0.0084/1.0084 = 0.0083 or 0.8%.

Here we refer to "posttest" under the assumption that clinical criteria, namely the PERC rule, can function as the diagnostic test. Importantly, a population of patients, each with a pretest probability <2%, collectively has a lower false negative rate. The combination of a low clinical gestalt impression plus a negative PERC rule reliably predicts a probability of PE below 1% even in European populations (16–20). Use of the PERC rule after a low pretest probability using other methods of pretest probability assessment besides gestalt assessment has not been validated (21). At a pretest probability <2%, the risk of further testing outweighs the low probability of failing to diagnose PE (22,23). Therefore, if all criteria of the PERC rule are met in the setting of a gestalt-based low pretest probability, not only is further testing unnecessary, but it should be avoided if possible.

The PERC rule (Table 2, part 1) does not have 100% sensitivity, and will be negative in the presence of small PE at a rate of about 1 in 100 patients considered, and even more rarely in the presence of larger PE (14,24). In most cases, in a patient suspected of having PE if any one of the eight criteria is not met, or the doctor simply thinks a test is indicated, the patient should undergo a diagnostic test for PE. Not all patients who "fail" the PERC rule need an objective test for PE ordered; the PERC rule provides only one set of criteria to rule out PE, and other sets likely exist.

D-dimer Testing

Assuming PE cannot be ruled out with the PERC rule, the next step is to determine which specific diagnostic test makes sense in view of the patient's pretest probability. If the ED clinician has access to a quantitative D-dimer assay, it should be strongly considered as a first diagnostic test in patients for whom clinical suspicion is low or moderate based on either gestalt estimation, a Wells score of

≤4, or an RGS ≤4 (see Tables 3 and 4 in part 1) (25,26). Available data from the United States suggest that a quantitative D-dimer at standard threshold produces a false negative rate <1% even with a Wells score up to 6 (15). Most commercially available, automated, quantitative D-dimer assays that employ either immunoturbidimetric latex agglutination or enzyme-linked immunoabsorbance colorimetry as the detection method have an LR^- of <0.15 (27,28). Different D-dimer assays have variable thresholds for normal due to different capture antibodies and optical methods of detection. Some laboratories report results in D-dimer mass concentration (e.g., nanograms per milliliter or micrograms per milliliter) and others report fibrinogen equivalent units, which are twice the mass concentration. The D-dimer has a half-life in plasma of approximately 8 h, and extrapolating from humans and animal models of autologous PE, the D-dimer level probably remains abnormally high for at least 3 days after symptomatic PE (29–32). However, as D-dimer may be continuously shed by unstable clot, it is difficult to know exactly how long after an acute PE a D-dimer assay will remain positive.

The most common causes of false positive and false negative D-dimer results are listed in Table 1 (29–31,33,34). Almost all risk factors for PE also elevate the D-dimer concentration. The fact that D-dimer increases with age has prompted numerous researchers to test if the D-dimer can be adjusted upward for age and maintain adequate exclusionary ability, mainly for suspected PE. The most common formula studied is age * 10 ng/mL, where a patient aged 80 years would have an age-adjusted threshold for abnormal at 800 ng/mL (35–37). In a large multicenter management study, this approach, when used in conjunction with a Wells score ≤4 or a simplified revised Geneva score ≤4, was associated with a very low rate (0.3%) of PE diagnosis on 3-month follow-up (see Tables 3 and 4, part 1) (37). Age adjustment of D-dimer is also supported by previous meta-analyses of other studies, as well as recent studies not yet aggregated into a systematic review. It is our opinion that it is reasonable to use age-adjusted D-dimer values to rule out PE in patients with low or moderate pretest probability (36).

All patients with a positive D-dimer result that cannot be explained by another finding must undergo imaging directed at discovering clots, and the choice of the next test must be determined by a mix of patient and facility factors. As the physician becomes aware of new information, PE may move up, down, or off the differential diagnosis list even after a D-dimer test result is found to be positive. Removing VTE from the differential must be justified by the presence of a condition that obviously explains the elevated D-dimer (e.g., one of the causes listed in Table 1) together with a plausible explanation for the patient's symptoms that is unlikely to coexist with PE (e.g., pneumothorax) (34). In particular, clinicians should not assume that an elevated troponin decreases the probability of PE (e.g., in favor of cardiac ischemia), as troponin elevation occurs in about 20% of patients with PE and is associated with worse outcomes (38–40). Similarly, emergency physicians must be aware that about 45% of patients with PE have an elevated brain natriuretic peptide concentration (39,40). Clinicians should be aware that normalization of initially abnormal vital signs has not been found to reduce the probability of PE and should not be used to justify cancelling a previously ordered test for PE (41).

Table 1. Factors that Cause Errors in D-dimer Measurements (33–37))

False Positives	False Negatives*
Patient factors: • Increasing age: (60–69 years [OR 2.6], 70–79 years [OR 4.5], ≥80 years [OR 10.5]) • Cocaine use (OR 2.0) • Immobility: general (OR 2.3), limb (OR 2.8), or neurologic (OR 3.0) • Hemoptysis (OR 2.0) • Hemodialysis (OR 2.2) • Malignancy, active (OR 2.6) • Rheumatoid arthritis (OR 2.8) • Systemic lupus erythematosus (OR 2.1) • Sickle cell disease (OR 24.2) • Pregnancy and postpartum state: (2nd trimester [OR 7.3], 3rd trimester [OR 51.3], postpartum [OR 4.2]) • Surgery (<4 weeks prior): abdominal (OR 3.5), chest (OR 2.7), orthopedic (OR 2.2), other surgery (OR 3.2)	Patient factors: • Concomitant anticoagulation† • Symptoms lasting more than 5 days • Subsegmental PE • Isolated pulmonary infarction • Chronic PE System and machine issues: • Wrong sample • Severe lipemia or hemolysis • Protein degradation by proteolysis that can occur with prolonged time from sample draw to analysis

OR = odds ratio; PE = pulmonary embolism.
* Derived from case reports, experience and manufacturer's information.
† Theoretically, risk is greatest with vitamin K antagonists and dabigatran, as both inhibit active thrombin generation and therefore reduce factor XIII generation, which could allow for non-cross-linked but insoluble clots. More likely, most PE diagnosed in patients on anticoagulation are simply chronic and thus liberate small amounts of D-dimer.

IMAGING

CT Pulmonary Angiography (CTPA)

A good quality computed tomography (CT) scan, which requires about 200 Hounsfield units of contrast opacification in the main pulmonary artery, rules out PE at all pretest probabilities on the day of examination (42,43). Chest CT does not rule out the possibility of future PE from undiagnosed DVT. Chest CT angiography only identifies filling defects in contrast-enhanced pulmonary arteries. Most scanning protocols require the patient to lie supine and hold his or her breath for a few seconds. CT scanning requires injection of approximately 120 mL of contrast by a computer-controlled injection device. The patient must have a peripheral intravenous (i.v.) catheter (20 gauge or larger) or an approved indwelling line to allow injection of the contrast. Equipment with multiple detector heads (e.g., 64-head scanners) allows better resolution so that filling defects can be observed even in subsegmental pulmonary arteries (44). The diagnostic sensitivity and specificity of a technically adequate CT scan, performed on a multidetector CT scanner in an ED population independently of pretest probability, are both about 90% (43). Interobserver agreement in identifying segmental or larger filling defects has been consistently demonstrated to be very good, but interobserver agreement for subsegmental clots is poor (45). Benefits of CT scanning include a binary positive or negative result and the ability to detect evidence supporting a clinically significant alternative diagnosis (where pneumonia is most common, found in 8–22% of cases) (33,46–50).

Radiologists indicate presence of suboptimal image quality in about 10% of their formal interpretations of CTPA scans (45,51). Figure 2 (A and B) shows examples of high-quality scan images and a degraded image. Image quality is most commonly degraded by low arterial opacification, or motion artifact (e.g., from severe tachypnea) (52). Obesity increases risk of inadequate CTPA imaging (53,54). Radiologists probably cannot detect filling defects with <150 Hounsfield units of opacification (42,52). In real practice, approximately 10% of CT scans yield technically inadequate images secondary to motion artifact or poor pulmonary artery opacification, most commonly in obese or very tachypneic patients (53,54). Many diagnostic studies of CTPA scanning exclude these scans from analysis, but in the PIOPED II study, 11/51 patients with indeterminate CTPA scans had PE on reference testing (51). Patients with indeterminate CTPA results and moderate or high pretest probability may need bridging anticoagulation until a PE can be ruled out. This can be done with a follow-up Ventilation Perfusion (V/Q) scan that has homogeneous perfusion. Because the outcome rate of PE after a negative quantitative D-dimer is <1%, even in high pretest probability patients, the quantitative D-dimer, if negative (age adjustment allowed), provides strong evidence to rule out PE in the setting of a degraded image CTPA. However, as about 80–90% of high pretest probability patients will have a positive D-dimer, the usefulness of this approach is limited (15,34). Alternatively, standard care also includes bilateral lower-extremity venous ultrasonography, performed in the ED and again within 3–7 days (55–58). If results of this repeat examination are negative, VTE can be ruled out in high-risk patients after indeterminate CTPA scanning (27,37,51,59–61).

The CT scan, despite its remarkable value as a diagnostic tool, poses risks to patients that emergency physicians must know. First among these is a 6–10% false positive rate in low-risk populations, possibly leading to over-diagnosis and unnecessary anticoagulation (44,45,51,62). CTPA imparts approximately 10 to 20 mSv of radiation, with an estimated increased lifetime risk of fatal cancer of at least 1 in 500 per chest CT (63,64). This risk may be higher in young women due to radiation to the breast (65). Furthermore, within 5 years afterward, more than one-third of patients who have one CT angiography to rule out PE can be expected to undergo subsequent CT pulmonary angiography, incurring a second dose of radiation (66). Acute life-threatening complications from CT scanning include anaphylactoid reaction to contrast and pulmonary edema. Other complications from CT scanning include contrast extravasation into a limb that causes pain, or in severe cases, compartment syndrome. Fortunately, extravasation is rare, occurring in <1 in 500 patients (67).

For patients who report a history of previous immediate reaction to iodinated contrast (itching, urticarial, wheezing, or full anaphylactoid reaction), their recurrence rate is approximately 6–15% with re-exposure, compared to 1% for patients with no prior contrast reaction (67,68). The risk of breakthrough hypersensitivity seems to be reduced by one-half with pretreatment with parenteral corticosteroids (e.g., hydrocortisone, 200 mg, i.v.) and antihistamines (e.g., chlorpheniramine 4 mg i.v. or diphenhydramine 25 mg i.v.) (69–73). In general, patients with prior allergic diathesis (e.g., any allergy, asthma or general atopy) have a 3–10-fold increased risk of immediate contrast reaction, but data are mixed as to whether a shellfish allergy increases a patient's risk of immediate contrast media reaction (74,75).

About 15% of patients undergoing contrast-enhanced chest CT scanning go on to develop contrast nephropathy, which, according to its minimal definition, comprises a 25% increase in the serum creatinine concentration, measured within 2–7 days of the examination (76).

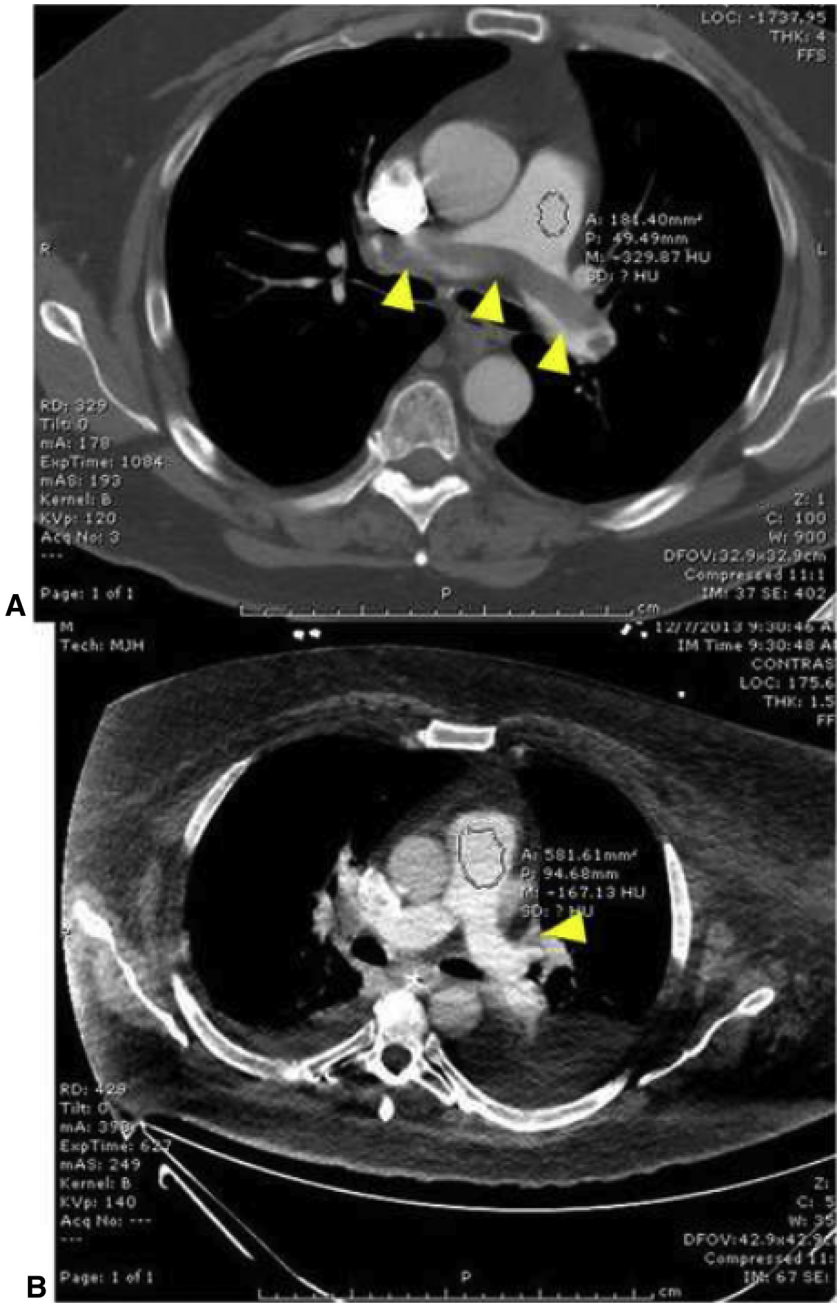

Figure 2. (A) Obvious saddle embolism (yellow arrowheads) in a main pulmonary artery with 329 Hounsfield units opacification density. (B) Questionable filling defect (yellow arrowhead) within a left lower lobar artery associated with only 167 Hounsfield units of opacification. Note that visual inspection of the quality contrast opacification can be misleading without on-screen region of interest measurement of the Hounsfield units. These images illustrate that computed tomography chest angiography can range from highly certain to ambiguous and underscore the importance of talking to the radiologist about image quality.

Whether or not this laboratory finding represents clinically important kidney injury remains controversial, but contrast nephropathy has been associated with worse outcomes (76–79). At present, no specific prophylactic measure beyond prehydration with intravenous saline has demonstrated any beneficial effect to reduce the incidence and significance of contrast nephropathy (80).

The increased resolution of multidetector-row CT scanning has led to an increase in the detection of isolated subsegmental PE. About one-quarter of all

contrast-enhanced chest CT scans read as positive for PE have isolated subsegmental PE (81–83). Isolated subsegmental PE refers to a filling defect seen in one small pulmonary artery, usually <3 mm in diameter, in the absence of DVT. The problem with this diagnosis is that when the same images are shown to a second blinded radiologist, in about half of all cases, the second radiologist finds no PE (45). This raises concern that subsegmental PE may be a radiographic artifact rather than a true disease. One survey found that most clinicians in Canada would opt not to treat these patients without further testing (84). However, another study found that the prognosis of patients with subsegmental PE was not different than patients with segmental or more proximal PE (85). No randomized trial has examined the safety of withholding anticoagulation for isolated subsegmental PE and perhaps as a result, one clinical guideline recommends standard course anticoagulation (86,87). In general, most experts agree that isolated subsegmental PE in patients with active cancer should be treated, even if discovered incidentally (84,88–92). For patients without cancer, a second international survey found that a majority thrombosis experts recommend anticoagulation for most isolated subsegmental PE (93). The authors recommend treatment of isolated subsegmental PE if the patient has PE symptoms, a prior history of PE, an ongoing risk of PE (e.g., indwelling catheter or immobility), or an elevated Ddimer (93). Patients with isolated subsegmental PE and a high risk of bleeding (e.g., Registro Informatizado de pacientes con Enfermedad TromboEmbólica [RIETE] bleeding score > 1) probably should not be treated (94). In these situations, and in any case where the risks and benefits of treatment are unclear, the patient should be informed of the situation and help make the decision about anticoagulation.

Ventilation Perfusion Scintillation (V/Q)

Ventilation-perfusion scintillation (V/Q) lung scanning requires peripheral intravenous access, and for the patient to sit upright during injection of a radioisotopic nuclide, usually ^{99}Tc macroaggregate, followed by positioning the patient in front of a gamma camera to capture the gamma emission from the radionuclide as it traverses the pulmonary vasculature. Use of a central line to inject isotope will often lead to inadequate images. If the perfusion lung scan shows a homogenous perfusion pattern (i.e., a "normal" perfusion scan; Figure 3A), this is associated with a likelihood ratio negative of 0.05, and essentially rules out PE (95,96). Patients without PE and with normal chest radiographs are far more likely to have normal V/Q scan than patients with intrinsic lung disease seen on chest radiograph. In patients with nonnormal perfusion, most U.S. radiology departments also perform the ventilation phase of the V/Q scan, which requires the patient to inhale an aerosol containing ^{99}mTc diethylenetriamine-pentaacetic acid or ^{133}Xe. Although starting with the perfusion scan may obviate the need for the ventilation scan, and thereby reduce radiation exposure, image quality is best if the ventilation phase is performed first because the background emission from the perfusion scan persists for hours. To diagnose PE, the perfusion scan must show two or more apex-central, wedge-shaped defects in perfusion pattern in a segmental or larger vascular distribution, together with evidence of normal ventilation in the same lung segments (Figure 3B). The primary technical limitations of V/Q scanning include the availability of personnel to perform and interpret them and the availability of isotope. Some emergency clinicians may not be aware that the availability of the ^{99}Tc isotope depends upon a cyclotron particle accelerator to manufacture each day. The primary clinical limitation of V/Q scanning is the fact that approximately two-thirds of scans are neither normal nor diagnostic of PE, which requires patients to undergo further testing.

Bilateral Ultrasonography

Performing lower-extremity venous ultrasonography is sensible due to its lack of ionizing radiation and the fact that diagnosing DVT is tantamount to diagnosing PE from the standpoint of the decision to administer heparin anticoagulation in the ED. In fact, studies suggest that a combination of D-dimer testing and lower-extremity ultrasound may be the most cost-effective approach to the initial evaluation of PE (22,97). However, in the absence of physical findings that suggest DVT, bilateral ultrasonography is of limited usefulness for excluding PE in the ED. Data from the largest study that simultaneously performed bilateral leg ultrasonography and performed pulmonary vascular imaging indicate that a negative bilateral proximal lower-extremity venous ultrasound has a sensitivity of 30% and a specificity of 57% (LR for a negative test = 1.22) for PE (98). Other studies have yielded similar results, so all patients suspected of having PE for whom ultrasound findings are negative require pulmonary vascular imaging (51,99). Nonetheless, following the logic that discovery of DVT is tantamount to diagnosis of PE in terms of treatment action in the ED, pursuing DVT first makes sense for patients with a positive D-dimer and for patients who object to pulmonary vascular imaging.

Follow-up bilateral venous ultrasound is also the best option to rule out PE in patients with high pretest probability, a positive D-dimer, and a negative CTPA scan with any radiologist comment about degraded image quality.

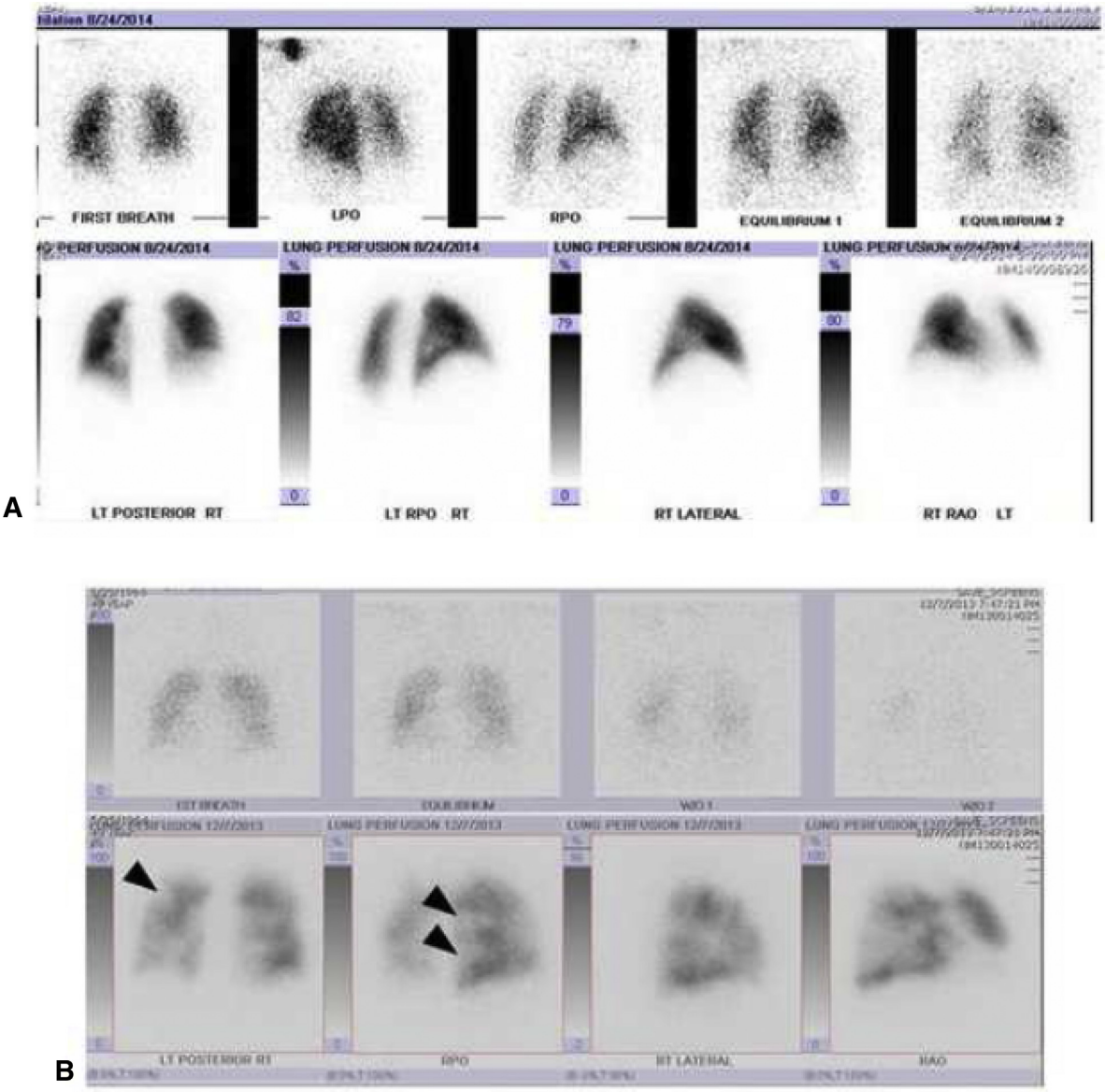

Figure 3. (A) Normal ventilation-perfusion (V/Q) scan showing homogenous ventilation (top) and perfusion (bottom) images. These images rule out pulmonary embolism. (B) V/Q lung scan series consistent with a high probability of acute pulmonary embolism using standard criteria. The top row of each panel shows the ventilation phase, conducted with ^{133}Xe, which produces only one planar image. The images labeled "equilibrium" or "w/o" represent washout images taken later. The second row of each panel demonstrates perfusion phases of the examination, obtained with ^{99}Tc macroaggregate. The black arrowheads point to wedge-shaped defects in the perfusion images. Scans are read by looking for defects in the perfusion phase where the corresponding ventilation view shows relatively homogeneous scintillation activity in the anatomic segments that lack perfusion.

Management protocols using this approach find that 5% of these high-risk patients will have a DVT at 3–7 days follow-up (55–58).

Pregnant Women

Figure 4 proposes an algorithm to rule out and diagnose PE in pregnant patients. The algorithm starts with bilateral lower-extremity venous ultrasound. If the bilateral ultrasound is positive, then treatment can be started. Otherwise, the next step is determined by pretest probability assessment. To our knowledge, no pretest probability rules have been validated in pregnant patients. It is clear that over one-half of all VTEs diagnosed in pregnancy occur in the third trimester (100). In the authors' experience (JAK and CK) and based on available patient-level data

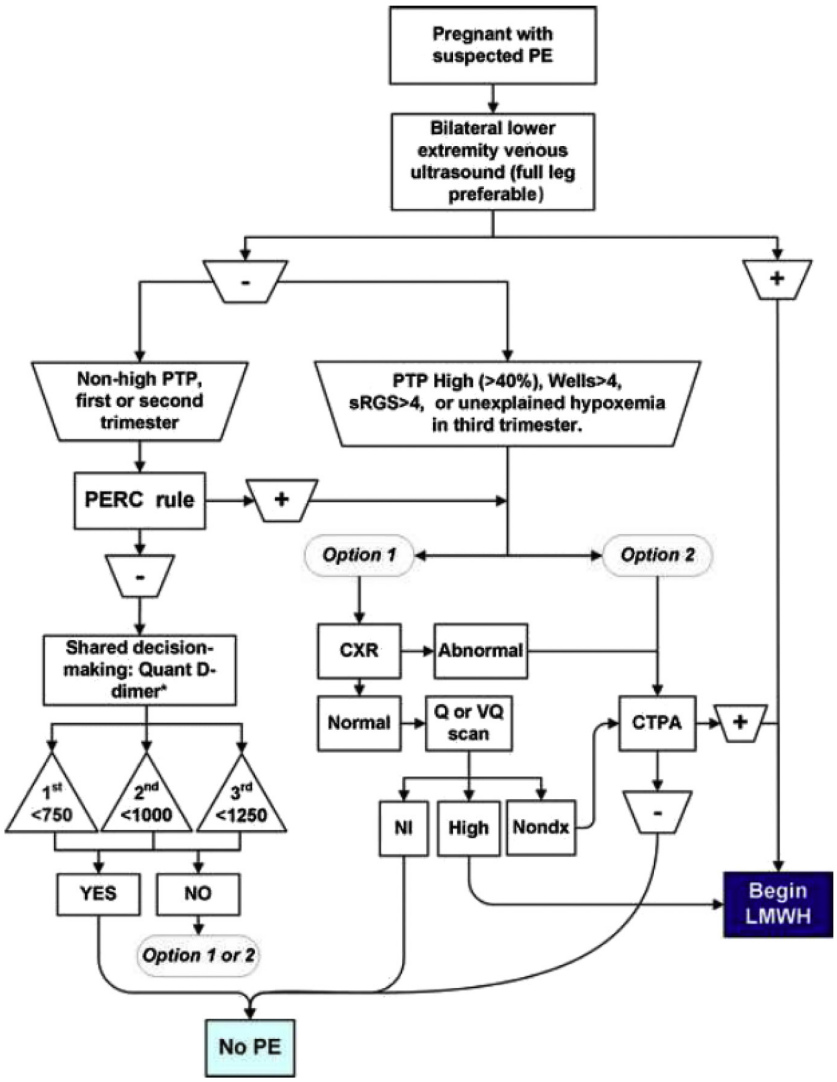

Figure 4. Proposed algorithm for the exclusion and diagnosis of pulmonary embolism in pregnant patients with suspected pulmonary embolism (PE) in the emergency department setting. This algorithm has not been formally tested. Shared decision-making refers to discussion of the diagnostic options with the patient, including uncertain, but probably <5% risk of undiagnosed PE and the potential risks of computed tomographic pulmonary angiogram (CTPA) or V/Q scanning to the fetus. Nonhigh pretest probability (PTP) refers to absence of high PTP by gestalt, Wells or sRGS. See text for references. *D-dimer concentrations per trimester given in ng/mL assuming a standard D-dimer threshold for abnormal of 500 ng/mL. Abbreviations: CXR = chest radiograph; Q = perfusion lung scan; + = positive for PE; – = negative for PE; Cr = creatinine; High = high-probability scan findings; LMWH = low-molecular-weight heparin; NI = normal; Nondx = nondiagnostic (any reading other than normal or high probability); PERC = pulmonary embolism rule-out criteria; quant = quantitative, sRGS = simplified revised Geneva score; V/Q = ventilation perfusion.

from pregnant ED patients, high Wells and Geneva scores, the third trimester, or unexplained hypoxemia ($SaO_2 < 95\%$ breathing room air at sea level) predict a relatively higher pretest probability for PE (101).

The evaluation of possible PE in pregnancy challenges clinicians, who must consider the epidemiological data showing increased risk of PE, the potential catastrophe of failing to protect the life of mother and child, and the potential for increased lifetime risks from unnecessary radiation and contrast exposure to the mother and the fetus. It is worth noting that most patients with pregnancy selected by emergency physicians for PE work-up have a low clinical probability (101). No firm guidelines exist to guide the work-up of pregnant patients with suspected PE (102,103). Efforts should be made to avoid fetal exposure to radiation and iodinated contrast (104,105). The proposed algorithm in Figure 4 draws from available literature and expert opinion, and has been used informally by one of the authors for over 8 years, but has not been formally tested (102). If the patient has a high

pretest probability by Wells or the revised Geneva score, or is in the third trimester, or has unexplained hypoxemia, then she should probably proceed to testing. Unfortunately, the D-dimer at standard threshold is not usually helpful because almost all women in the third trimester have a positive D-dimer when the standard positivity threshold is used, and pulmonary vascular imaging is frequently required (106). Because imaging with ionizing radiation may be required, the authors recommend discussing the diagnostic approach with the patient prior to initiating the work-up using a shared decision-making approach, similar to that described by Hess et al. for low-risk chest pain (107). When the risks and benefits of testing are explained, some mothers will opt to proceed, whereas others will choose to avoid imaging at all costs. To minimize radiation exposure, the authors propose a combined approach, where negative bilateral lower-extremity venous ultrasonography is supported by a negative PERC rule and a threshold-adjusted D-dimer assay. The exclusionary power of a single negative bilateral leg ultrasound for PE per se has not been tested in pregnancy, but seems to be similar to that of nonpregnant patients for excluding DVT (108,109). The D-dimer threshold can be adjusted according to the trimester of pregnancy, as follows: first trimester, 750 ng/mL; second trimester, 1000 ng/mL; third trimester, 1250 ng/mL (assuming a standard cutoff of 500 ng/mL) (106,110,111). If the patient has a non-high-pretest probability, has no high-risk features, is PERC negative, and the bilateral ultrasound is negative, and the D-dimer is below the trimester-adjusted values, PE can be ruled out to a reasonable degree of medical certainty. Note that this recommendation does not state that the PERC criteria can be used alone in pregnancy.

If the D-dimer is abnormal or the patient fails the PERC criteria, then a pulmonary vascular imaging study is warranted. The best choice of pulmonary vascular imaging is controversial and uncertain (102). Some evidence has suggested up to a 35% rate of inadequate pulmonary vascular opacification with CPTA, especially in the third trimester, resulting in a higher rate of nondiagnostic studies with CTPA than V/Q or Q-alone scanning (112,113). Other data indicate that either CT pulmonary angiography or V/Q scanning will produce adequate images to rule out and diagnose PE in a pregnant patient (103,114,115). The data used to estimate the risk of fetal exposure to radiation for CT scanning vs. V/Q scanning are both highly speculative. Shielding the abdomen with a lead or bismuth-antimony apron during CT scanning may reduce radiation based upon phantom modeling (116). When available, tube voltage modulating technology may also serve to lower fetal radiation exposure more than shielding (116). Magnetic resonance imaging has not been adequately tested in pregnancy to provide any basis for recommendation, but had too low a sensitivity (78%) to rule out PE in nonpregnant patients (117). As Figure 4 demonstrates, both CTPA and V/Q scanning are equally justifiable when imaging a pregnant patient is necessary. If a V/Q scan is chosen, the authors suggest first performing a plain film chest radiograph, and performing the V/Q scan only if the radiograph is normal. Then, we suggest performing a perfusion-only (Q) scan with half-dose ^{99}Tc macroaggregate. Because ^{99}Tc is excreted in the urine, prehydration with 1 L of intravenous saline and insertion of a Foley catheter seems a logical, but unproven, step to reduce fetal exposure to radiation. The risk of this approach is that if the perfusion lung scan is nonnormal, and CT scanning is ultimately required, the mother and fetus will be exposed to more radiation than if CTPA had been performed first. In patients with an abnormal chest radiograph, we suggest performing a CTPA rather than a V/Q scan.

CONCLUSION

Acute pulmonary embolism can be ruled out on clinical grounds without laboratory or radiographic imaging by the combined use of gestalt pretest probability estimation plus negative PERC rule. In the presence of non-high-pretest probability by any method, including gestalt assessment, a negative quantitative D-dimer rules out PE at standard or age-adjusted threshold. However, threshold adjustment is complicated by differing, manufacturer-specific thresholds to define the cutoff for an abnormal D-dimer. A good-quality CTPA scan rules out PE. Patients with high pretest probability and a negative CTPA but with degraded image quality, can have PE ruled out with a normal V/Q scan, a negative quantitative D-dimer, or negative bilateral lower-extremity venous ultrasound performed in the ED and again 3–7 days later. Exclusion of PE in pregnancy remains a controversial subject, but a shared decision-making model that prioritizes testing without fetal radiation exposure may offer the most effective and safe approach.

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ARTICLE SUMMARY

1. Why is this topic important?

Acute pulmonary embolism (PE) can cause sudden death, and failure to diagnose PE can lead to devastating patient outcomes and medicolegal allegations of negligence. However, overtesting and overdiagnosis for PE pose a major threat to public health.

2. What does this review attempt to show?

With awareness of medicolegal implications, and a rich literature base, this in-depth review considers current evidence to define a rational approach to the exclusion and diagnosis of PE in the emergency department (ED) setting that maximizes patient safety.

3. What are the key findings?

Not all patients with a sign, symptom, or risk factor for PE require a formal evaluation for PE. In gestalt low-risk patients, the pulmonary embolism rule-out criteria rule or a D-dimer can be used to rule out PE. Emergency physicians should know the difference between a high-quality and a low-quality computed tomographic pulmonary angiogram scan. Algorithms are presented to guide the process of evaluating possible PE in both nonpregnant and pregnant patients.

4. How is patient care impacted?

Specific test modalities can rule out PE without patient exposure to radiation and iodinated contrast material. Although the exclusion and diagnosis of PE in symptomatic pregnant women remains controversial, a protocol that includes a shared decision-making approach may be a rational approach.