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Pulmonary Embolism: A Clinician's Perspective

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Recent advances in the management of patients with suspected pulmonary embolism (PE) have both improved diagnostic accuracy as well as made management algorithms safer and more accessible. Physicians need to more frequently consider PE in patients with chest pain or dyspnea and should be aware of the proper diagnostic approach. Diagnostic strategies should include pretest clinical probability, D-dimer assays, and imaging tests. Although it has been proven that the use of algorithms result in better outcomes, there are patient-specific issues that must be considered. Approaches that use computed tomographic pulmonary angiography or ventilation-perfusion (V/Q) scanning appear equally safe, but each approach has advantages and disadvantages that should be appreciated to provide the best care. Ongoing clinical trials are evaluating whether these diagnostic processes can be made even easier and less expensive. Importantly, patients at low risk with a negative D-dimer can avoid imaging tests and those at moderate risk with a negative high sensitivity D-dimer can have venous thromboembolism excluded without the need for imaging. However, these patients also represent those most likely to have false-positive tests and clinically irrelevant PE. V/Q scanning may be more appropriate in premenopausal women, in those with renal dysfunction or diabetes, in those with known contrast allergies, and perhaps in patients with known family history of breast cancer. As with any illness, there is room for improvement in the management of PE, but it remains unknown whether preventive measures, diagnosis, treatment modalities, or physician or patient education should be the focus.

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Venous thromboembolism (VTE), manifesting as deep-vein thrombosis (DVT) or pulmonary embolism (PE), is one of the most common cardiovascular disorders in industrialized countries, affecting approximately 5% of people in their lifetime.[1] Left untreated, PE has a high rate of mortality and accounts for 5% to 10% of all in hospital deaths.[2-6] PE is highly fatal and, in 22% of cases, it is not diagnosed before causing death.[7,8] PE is clearly a serious public health issue, but details on why or how these deaths occur are lacking. Indeed, despite this seriousness, high-risk mismanagement is not infrequent,[9] at least in part because of the limitations of diagnostic tests, but also because of the fact that signs and symptoms are nonspecific. Many patients presenting with leg pain or swelling or chest pain or dyspnea are investigated but do not have DVT or PE and, conversely, many are not investigated when VTE should have been suspected may be even more common.[10] Furthermore, many clinical practitioners fail to realize the limitations of imaging tests. The evidence suggests that patients with suspected VTE are best managed with a diagnostic workup that includes clinical pretest probability assessment and D-dimer testing in combination with imaging. In fact, we are currently observing an encouraging decrease in mortality from PE, which may reflect both more accurate diagnosis and the use of diagnostic algorithms,[11-13] but at least one study questions this and suggests that despite a doubling in the number of diagnoses since the advent of computed tomographic pulmonary angiography (CTPA), there has been no change in risk of death. This finding suggests a problem of overdiagnosis with CTPA.

In this article, I will explore the main diagnostic issues from the perspective of a practitioner evaluating a patient for suspected PE, concentrating on how implementation may vary depending on patient issues that cannot always be elucidated in publications on diagnostic studies. First, I want an accurate diagnostic approach; I will summarize the literature on clinical probability assessment, D-dimer, and imaging tests and how they should be integrated but with an emphasis on the operational and the practicing physician perspective; next, I consider the safety issues. Third, I consider conve-

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Table 1 Variables Used to Determine Patient Pretest Probability for PE*

Clinical Variable	Score
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3
PE as or more likely than an alternative diagnosis	3
Heart rate greater than 100	1.5
Immobilization or surgery in the previous four weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy (on treatment, treated in the last 6 months or palliative)	1

*Scoring method: A score of >4 indicates the probability of PE is "likely"; ≤4 indicates the probability for PE is "unlikely." Alternatively, a score of <2 is low probability, moderate if score is 2 to 6, and high if score is >6.

nience and comfort for the patient. Finally, I consider the cost for the health care system. As will become evident, there is no one approach that is ideal in all cases.

Accurate Diagnosis

Clinical diagnosis of PE can be difficult on the basis of individual clinical predictors, but several explicit clinical models have been described that are reasonably accurate for the determination of pretest probability categories. Physicians should always take a careful history and physical and, in many cases, perform an electrocardiogram and chest x-ray before using these clinical probability tools.[14-17] Our model has been used in at least 12 studies, and more than 10,000 patients have been evaluated, including 5 studies with a total of more than 5800 patients in which the authors used the dichotomous scoring system of PE unlikely (score ≤4) or PE likely (score of >4)[15,18-22] (Table 1). In addition, the revised Geneva model is now supported by a large clinical trial,[23] along with other tools.[24-26]

Although many physicians advocate gestalt over these tools, and the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) investigators and others have demonstrated that the clinicians' overall diagnostic impression could be useful in management.[27-29] In general, it can be said that most of data on gestalt have come from centers that also use predefined clinical decision tools; therefore, it is not clear whether empiric assessment is generalizable. In addition, with empiric assessment, (1) clinicians often disagree (even for broad categories) on the pretest probability of pulmonary embolism,[30] (2) the clinician's experience level appears to influence assessment,[31] (3) gestalt probability estimates tend to follow a middle road, categorizing fewer into the more useful low- or high-probability groups, and (4)the exact methods used by each clinician to estimate pretest probably are difficult to measure or reproduce.[32]

At least 3 studies have demonstrated moderate-to-substantial interrater agreement and reproducibility of the Wells and coworkers model,[20,33,34] but one study noted only moderate agreement.[29] The latter study reported a higher interobserver agreement for the Charlotte rule, but that rule is limited by having only safe and unsafe categories. To my knowledge, no other prediction rule has evaluated interrater agreement and reproducibility. Why then is gestalt still relied on? This speaks to the issue of knowledge translation and limitations of the existing models. All these rules have limitations, predominantly the fact that they have several variables and complex scoring systems. Efforts to simplify the rules are ongoing. The Wells and coworkers model used in the Christopher Study was reevaluated by Gibson and coworkers[35] with the intent of developing an easier model. The simplified model assigns one point to all the variables in the model and, if any point is present, imaging is indicated. This new model appears to work well in this dataset, but further validation will be necessary and whether these changes will be sufficient to increase use remain to be seen. Posting these rules in clinic areas, access to them by computer or palm device, and tying their use to agreement to perform imaging tests all may increase use, but studies are lacking. Simply posting the rule in the clinic area has proven useful in our center.

Approach to Patients With Suspected PE

My recommended approach is to first perform clinical probability assessment. Subsequently, if patients are younger then 80 years of age and are not in the intensive care unit,[36] then a

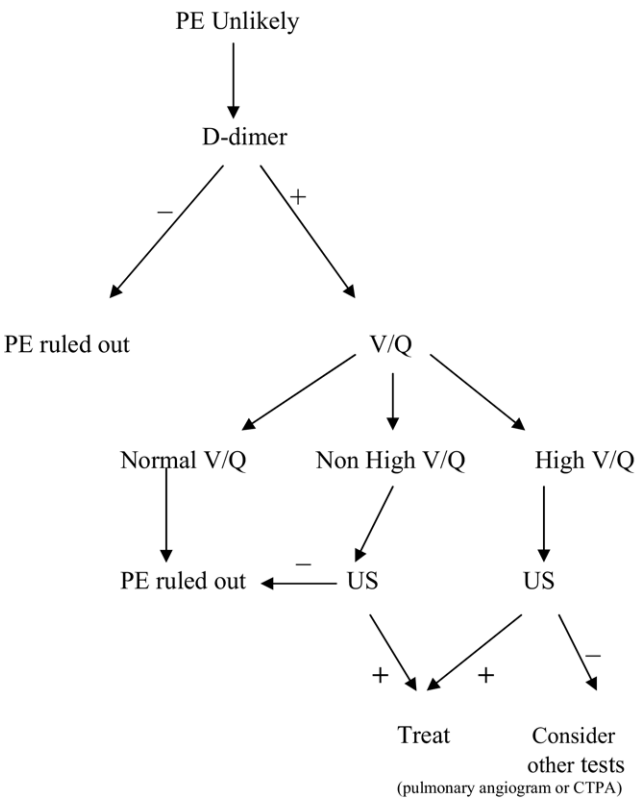

Figure 1 Strategy for diagnosing PE with the use of V/Q in patients who are PE unlikely.

D-dimer is performed with a D-dimer test that has been evaluated in VTE patients to have a negative likelihood ratio of ≤0.20. Patients who are PE unlikely or low probability can have PE excluded with a negative D-dimer. The likelihood ratio of 0.06 to 0.09 with high sensitivity D-dimer test enables PE to be excluded with moderate pretest probability (≤22%) when the D-dimer is negative (Figs. 1 and 2). However, the high sensitivity D-dimers are limited by very low specificity in the elderly and hospitalized patients and are of little use in these groups. The authors of 7 studies who used our model reported follow-up data on patients in whom PE was ruled out on the basis of clinical probability (low probability or PE unlikely) and negative D-dimer testing.[15,19,21,22,37-39] The VTE event rates in follow-up were less than 0.5%. Studies in which authors use similar strategies but with other clinical assessment tools also reported very low rates of follow-up events.[40,41] Thus, the D-dimer assay can be the first objective test used after clinical assessment with the goal of determining which patients require diagnostic imaging.

If patients have a high pretest probability or are PE likely, or if they have a positive D-dimer, then imaging (ventilation-perfusion [V/Q] scan or CTPA) is required. If the imaging test is a V/Q scan, then lower-extremity venous ultrasound is also recommended when the V/Q is nondiagnostic (ie, neither normal nor high probability; Figs. 1 and 3). If low-pretest probability patients have a high-probability V/Q scan, it is important to verify the diagnosis with an ultrasound study, pulmonary angiogram, or CTPA.[14,42]

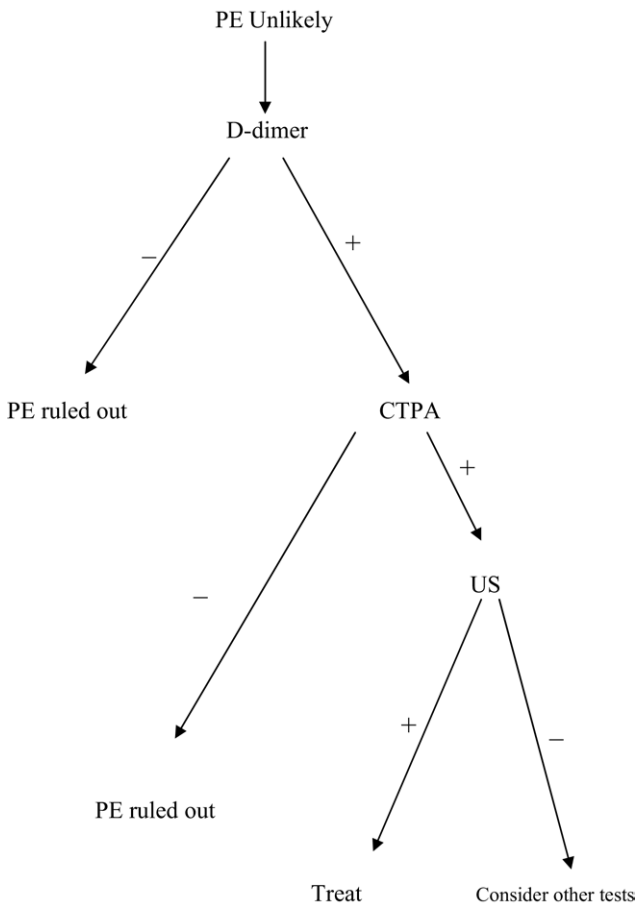

Figure 2 Strategy for diagnosing PE with the use of CTPA in patients who are PE unlikely.

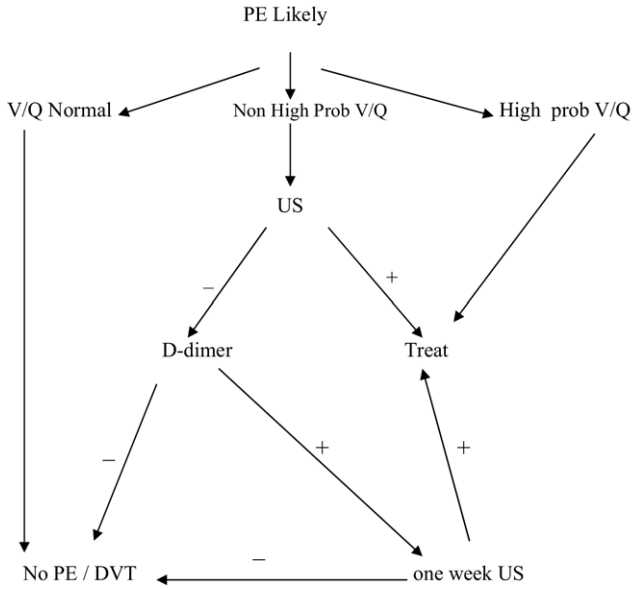

Figure 3 Strategy for diagnosing PE with the use of V/Q in patients who are PE likely.

We now have convincing data that lower-extremity venous ultrasonography is not needed when multirow detector CTPA is negative for PE. Three large prospective studies that combined CTPA and clinical probability, including one randomized trial in which most or all patients underwent multidetector row CTPA and no ultrasound was performed in patients with a negative CTPA, determined only 0.3% to 1.4% of patients with a negative CTPA will develop VTE events during follow-up.[19,23,41] Despite these data, as a clinician it is not unreasonable to perform ultrasound if clinical suspicion remains high despite a normal CTPA, provided the patient has leg symptoms (indeed, ultrasound could be performed first because of its high positive predictive value and thereby spare radiation exposure),[43] that single detector row CTPA is used, or that the patient is in the early postoperative period. In the latter case, there are many reasons for pulmonary symptoms; therefore, a negative CTPA should not necessary decrease the suspicion for DVT (Fig. 4).

Underdiagnosing PE

It could be argued that an accurate diagnostic approach should result in 100% sensitivity with no missed cases, but the reality is this is not possible. The approach most physicians believe reasonable is one that is as accurate as the putative gold standard of contrast pulmonary angiography, an invasive, expensive, rarely performed procedure that requires a skilled radiologist and a cooperative patient.[44,45] With a negative result, 1.6% of patients developed PE during the 1-year follow-up, most in the first month[27,46] and, as such, the accuracy figure strived for in management strategies should be in this range. Trying to achieve an even lower PE

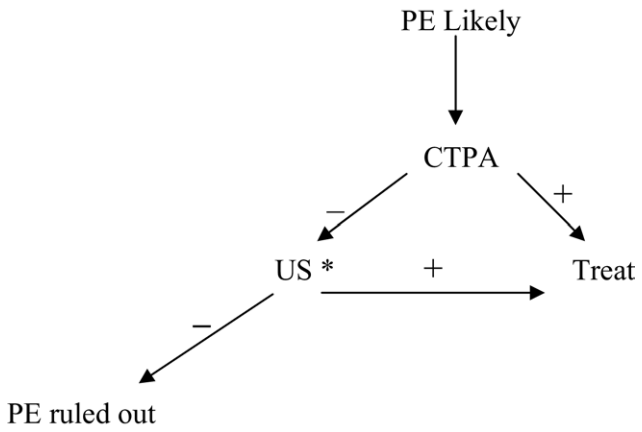

Figure 4 Strategy for diagnosing PE with the use of single-row detector CTPA in patients who are PE likely.

follow-up rate when the diagnosis is initially ruled out seems unrealistic. Finally, a cut-off <1% would lead to an unacceptable trade-off in increased imaging and increased false-positive diagnoses of PE.

V/Q lung scanning has been the imaging procedure of choice in patients with suspected PE. A normal scan essentially excludes the diagnosis of PE (1% VTE rate in follow-up), and a high-probability lung scan has an 85% to 90% predictive value for PE.[27,47] Unfortunately, most lung scans fit into a nondiagnostic category, in which the incidence of PE varies from 10% to 30% and further investigation is necessary. This is a real barrier for physicians and patients who are uncomfortable with uncertainty. This uncertainty may be the major reason why the first imaging test in many centers is now CTPA, despite excellent evidence supporting the accuracy of management strategies that use V/Q scanning.[14,15,38,48] However, physicians should be not fooled that CTPA is the holy grail because a recent meta-analysis suggests the sensitivity and the specificity of CTPA are 86% and 93.7%, respectively,[49] although a recent study suggests greater sensitivity with multidetector row CTPA.[40] However, the less-than-perfect sensitivity and specificity mandates a need for management studies with CTPA. As discussed, management studies have been done, and the initial fears that CT would miss many PE are unfounded and, indeed, with current multidetector row scanners, diagnostic sensitivity is such that false detection of PE, or detection of clinically irrelevant PE, is a now a pressing issue.

Overdiagnosing PE

In a recent randomized controlled trial in which we compared a V/Q strategy to a CTPA in patients with suspected PE, we detected VTE in 19.2% of the CT group versus 14.2% in the V/Q group.[37] An earlier study demonstrated patients with nondiagnostic V/Q subsequently had PE detected by CTPA in 35% of cases.[50] In our study crossover from the V/Q group to CTPA resulted in PE detection in 33% of patients with nondiagnostic V/Q scans. It seems apparent that multidetector row CTPA is a more sensitive test than suggested by initial investigations of accuracy and detects more PE than V/Q scans, indeed even more than with single-detector row CTPA.[51] However, in our randomized trial, this increased detection rate did not result in significantly fewer VTE events in the follow-up period in those in whom PE was initially excluded.[37] A significant reason for this may be an increase in detection of subsegmental PE by CTPA, which represents <4% of detectable PE with single-detector row CT but as many as 28% of PE detected with multidetector row CT.[51,52] Furthermore, if we consider Bayes Theorem, we can predict that using a (generous) sensitivity of 92% and a specificity of 94% for CTPA, patients who have low (5%) pretest probability for PE will have a false-positive rate on the order of 55% and 21% false-positive rate for moderate (20%) pretest probability.[53] It seems that the new CTPA technology has created 2 overlapping important clinical issues: (1) CT is overly sensitive to the point of detecting clinically irrelevant PE and (2) the use of CTPA results in false positives. No studies exist to deal with these issues but we can explore options.

Clinically Irrelevant PE

It is quite likely that small PE may be of lower or even no clinical significance if such emboli are not accompanied by DVT on lower-extremity imaging. The concept of clinically irrelevant pulmonary emboli is not new. The first major study to suggest that there may be clinically irrelevant PE demonstrated that it was safe to withhold anticoagulant therapy in patients with "nonhigh" or nondiagnostic ventilation perfusion scan results provided their deep venous system remained free of thrombus based on serial impedance plethysmography.[54] Overall, the PE rate in these patients with nonhigh V/Q scans was 10%, far less than was suggested by the original PIOPED study. The original PIOPED study, which was a comparison of pulmonary angiograms with V/Q lung scan results, demonstrated that 21% of patients with neither normal/near-normal V/Qs or high-probability V/Q results (ie, nonhigh V/Q results) had pulmonary embolism.[27] Clearly, Hull and colleagues[47] diagnosed and treated far fewer then 21% of patients; despite this, follow-up event rates were only 2.7%. This study suggested that small PE, if accompanied by no evidence of lower-extremity DVT, can safely go untreated.

Similar results were obtained by our group. We demonstrated only 8.4% of patients with nonhigh V/Q scans had PE and only 0.5% of patients negative with serial ultrasound developed VTE in follow-up.[14] In patients with a low or moderate clinical probability and a nondiagnostic (or nonhigh) V/Q lung scan result, only 5% of patients had PE requiring therapy. In a second study, we detected PE/DVT in only 6.6% of patients with nonhigh V/Q scans.[15] These rates are far less than would be expected from the PIOPED study, which performed angiography. Furthermore, as mentioned earlier, in our randomized trial, we detected 5% more PE by CTPA but follow-up events rates in patients with PE ruled out were not significantly different between the V/Q and CTPA strategies. Finally, it is clear that CTPA detects PE incidentally, and management of these cases remains unclear. In 581 CTPAs performed for non-PE indications, Storto and colleagues[55] reported a 3.4% PE rate with half of these isolates subseg-

mental PE. In another study of 785 patients incidental PE was detected in 1.5%, with 30% of these subsegmental PEs.[56] Intuitively, physicians are questioning the importance of these small PEs. Eyer and coworkers[52] evaluated physician response to subsegmental PE on CTPA. In 37% of cases no treatment was given and none of these 25 patients had events on follow-up.

False-Positive CT Results

In Hayashino and colleague's meta-analysis, the post-test probability of PE with a positive CTPA was 30% (70% false positive) in low pretest probability patients and 84% in patients with moderate pretest probability.[49] A recent study of 322 patients with suspected PE, assessed the influence of clinical probability on the false-positive rates for CTPA.[57] Among the patients with a positive CTPA who were treated for PE, 58% and 10%, respectively, of the low and moderate pretest patients, were actually false positives. Overall, up to 25% of all patients with a diagnosis of PE may have been treated inappropriately because of a false-positive result. This mathematical fact is supported by a large accuracy study of CTPA (PIOPED II) that reported the positive predictive values for PE detected by CTPA in the lobar, segmental, and subsegmental vessels were 97%, 68%, and 25%, respectively.[58] Stein and coworkers[59] demonstrated that intraobserver disagreement with pulmonary angiography was greatest in subsegmental vessels, again raising doubt on the diagnosis if this is the CTPA result. Indeed, the Kappa value for interobserver agreement for segmental vessels was only 0.47 (moderate agreement) with 3 mm collimation CTPA.[60] A recent comparative study of a multidetector row CT to digital subtraction pulmonary angiography demonstrated a false-positive CT rate of 30%, with most false CT results incorrectly detecting PE in isolated segmental or subsegmental vessels.[61] Therefore, although only limited data are available, it is logical to assume that most of the false-positive diagnostic results will be in patients who have PE detected in subsegmental vessels and a significant proportion will be in those who have isolated segmental PE.

The implications are that the practicing physician can consider high-probability V/Q scans or positive results on CTPA as diagnostic of PE if pretest probability is high or PE likely (Figs. 3 and 4) but not when the pretest clinical probability is low or unlikely (Figs. 1 and 2). In this latter case, the results should be reviewed with the radiologist with consideration of a false-positive result. Confirmatory ultrasound or conventional pulmonary angiography should be considered or withholding treatment and performing serial lower extremity ultrasound. Further research is needed to validate these approaches.

Safety of the Diagnostic Approach

The increased risk of breast cancer from the radiation exposure with CTPA has become a controversial issue. It is probable that premenopausal women represent a very significant segment of the population that is evaluated for PE. However, dose calculation is very complex because absorption is variable from patient to patient and risk data are extrapolated from studies of individuals exposed to large amounts of radiation (Hiroshima atomic bomb survivors).[62] The linear-no-threshold relationship between dose and cancer risk is theoretical and not uniformly decided. Breast radiation estimates made with 4-slice CT vary from 20 to 60 mSv whereas those from V/Q vary approximately 0.28 to 0.9 mSv.[63-66] A recent report by Einstein and coworkers[67] estimated that 64-slice CTA delivers a dose of 50 to 80 mSv to the breast.[67] These reports indicate an enormous difference between CTPA and V/Q scans. The estimated radiation exposure from CTPA suggests that a non-negligible increase in lifetime attributable risk of cancer exists, particularly to the breasts of young women (1 in 143 for a 20-year-old woman and 1 in 284 in a 40-year-old woman, with risk further decreasing with increasing age).[67,68] It is estimated that 0.4% of all cancers in the United States are attributable to the radiation from CT studies (not just CTPA, of course), but proper large-scale population-based studies are lacking.

These radiation risks are concerning, and we are obliged to address them. The American College of Radiology white paper strongly emphasizes that it is the responsibility of the imaging physician to be fully educated concerning the radiation risks associated with each procedure and, in turn, educate the clinician requesting the procedure. This is difficult given the gaps in knowledge and because the risks are theoretically derived. Nonetheless, providing diagnostically equivalent options is part of this educational process. Brenner[68] suggests 3 ways to decrease the radiation dose from CT in the population and I will expand on these: (1) we should aim to reduce the dose through automatic exposure-control options available on newer CT scanners, with the use of bismuth radioprotection devices to shield the breast and thyroid (which decrease dose by approximately 60%), by x-ray tube modulation and the use of more-sensitive detectors (such as the 320-slice CT now available), setting the inferior limit of the scan at a higher level, reducing the field of view, and decreasing the peak values for kilovolt peak and milliampere seconds.[69] (2) We should use other options first (eg, use ultrasound first, especially if the patient presents with leg symptoms, or V/Q, especially if the probability is low and there is no obvious lung pathology on chest x-ray).[70] (3) We should decrease the number of CTPAs performed (which argues for an increase in the use of V/Q scanning).

The issue becomes more complicated in pregnant patients. A practice survey suggests CTPA is used more frequently then V/Q in this situation.[71] From the perspective of the fetus, this may be appropriate because radiation exposure to the fetus may be greater with the use of V/Q.[72,73] Radiation concerns also require evaluation of CT venography for detection of DVT. Thankfully, this is less controversial because it appears there is little is to be gained by extending CT imaging to the pelvis or lower extremities because isolated pelvic DVT are very rare and ultrasound is very accurate for lower extremity DVT.[74-77] If DVT imaging is required, ultrasonography is the test of choice.

Contrast-induced nephropathy is the other safety issue. This is an issue yet to be evaluated in randomized trials. A

meta-analysis suggests the risk is halved with the low-osmolality contrast agents currently in use and, in PIOPED II, only 1 of 824 patients experienced renal failure.[58] This patient had diabetes, 2 contrast injections in 24 hours, and the renal dysfunction was transient. However, PIOPED II excluded patients with "abnormal creatinine." Data suggest an increased odds for contrast medium-induced nephropathy in preexisting renal dysfunction, with the odds ratio almost 13 if the serum creatinine pre-exposure is >265 μmol/L (3.0 mg/dL).[78] In patients presenting to the emergency with suspected PE, contrast nephropathy (an increase of creatinine of 45 μmol/L [0.5 mg/dL] or a >25% increase, within 7 days of CTPA) developed in 4% of patients in one study.[79] To prevent renal dysfunction in low-risk patients, saline hydration appears to be of benefit. There are conflicting data on the use of *N*-acetylcysteine, but it is recommended in high-risk patients. In the later group (those with preexisting significant dysfunction and diabetics), saline and *N*-acetylcysteine should be used but, ideally, a V/Q scan would be performed in these patients. Allergy to contrast is also an issue. If the patient's allergy is mild, ultrasound can be done first, then premedication with steroids has been recommended if the ultrasound is negative and CTPA is performed. However, in most of these cases I recommend V/Q scan first, reserving CTPA for select cases.

Convenience and Comfort for the Patient

These issues are a matter of personal preference in many cases. CTPA is faster, but some patients are claustrophobic, even in the relatively open CT scanners is use today. CTPA is often more convenient because it is now more widely available, especially on weekends and after usual working hours. The latter is not an issue in our practice since we inject patients with low molecular weight heparin and perform imaging within 24 hours, which allows us to choose either CTPA or V/Q scan.[80]

Cost-Effectiveness

As always, cost is a complicated issue, exhibiting remarkable variation between country and health care systems. Evidence suggests a strategy that uses clinical probability and D-dimer will be most cost-effective.[81] The savings diminish with patients older than 80 years.[82] However, comparative analyses of CTPA and V/Q are lacking. We have performed a comparative analysis from our randomized study.[37] Although more effective at preventing overall mortality, the CTPA strategy has an incremental cost of more than $27,000 per life year saved compared with V/Q scanning. This study is not yet published. To my knowledge, there has not been a "willingness-to-pay" analysis or analysis from societal perspective.

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