Management of Suspected Acute Pulmonary Embolism in the Era of CT Angiography: A Statement from the Fleischner Society[1]

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During the past decade, the contribution of computed tomographic (CT) angiography in the diagnosis of pulmonary embolism (PE) has dramatically increased as a consequence of major advances in CT technology. The question now no longer concerns demonstrating its clinical value but optimizing its use in various categories of patients. Since the introduction of multidetector CT with high spatial and temporal resolution, CT angiography has become the method of choice for imaging the pulmonary vasculature when PE is suspected in routine clinical practice.

This change in the imaging algorithm has had numerous practical consequences. The widespread availability of a noninvasive and accurate means of evaluating the pulmonary circulation has led to the recognition that acute PE has a lower prevalence than it was thought to have in the past among patients clinically suspected of having the disease. Because CT images contain additional diagnostic information in the majority of patients who are suspected of having acute PE and may therefore lead to diagnosis of alternative causes for the patient's symptoms, the increased use of CT has improved patient care by minimizing diagnostic delays that may be incurred when alternative imaging tests are used. The current possibility of performing electrocardiographically (ECG)-gated examinations of the entire thorax has further reinforced the role of CT angiography in this clinical setting, adding coronary artery disease to the list of alternative diagnoses detectable with the aid of this tool and enabling the use of CT angiography to provide prognostic information from the same data set as that used to help diagnose acute PE.

However, the increasingly frequent use of CT has raised concerns about the overall radiation exposure to the population scanned and has imposed on the radiology community a need to optimize scanning protocols. This, in turn, makes it necessary to stratify more precisely the population being scanned according to the likelihood of PE being present (pretest probability), with the aim of reducing the number of unnecessary CT pulmonary angiograms being obtained in patients who are unlikely to have PE. Furthermore, although the number of indeterminate studies has dramatically decreased over time because of improved CT technology, clinicians may still face diagnostic dilemmas when the CT angiographic results are either inconclusive or discordant with the pretest probability. Because of changes in strategy over the past few years and the numerous issues still being debated, the Fleischner Society has deemed it useful to propose a consensus update on the role of CT angiography in the diagnostic approach to PE in 2007.

Influence of Multidetector CT in Diagnosis of Acute PE

Can Multidetector CT Replace Pulmonary Angiography as the Reference for Diagnosis of Acute PE?

Multidetector CT offers better diagnostic performance than single-detector helical CT, as confirmed by study results that compared CT angiography with conventional pulmonary angiography. For single-detector helical CT, sensitivity and specificity in the detection of PE have been reported to vary from 53% to 91% and from 78% to 97%, respectively (1). With chest multidetector CT, the sensitivity and specificity vary between 83% and

100% and 89% and 97%, respectively (2–4). The better diagnostic accuracy of multidetector CT is directly linked to the dramatic improvement in image quality made possible by substantial advances in CT technology over the past decade (5–11). The improvements in spatial and temporal resolution, as well as in the overall quality of arterial opacification, have allowed the routine analysis of pulmonary arteries down to the subsegmental level (5,10,12). The majority of scans are now free of motion-related pitfalls, which reduces indeterminate results and improves interobserver agreement. These technical advances have improved image quality not only in outpatients (7,13) but also in dyspneic patients (eg, patients in the intensive care unit and those with underlying respiratory disease) (14,15).

What is the clinical validity of a negative multidetector CT scan? In a recent meta-analysis of 15 studies that used contrast material–enhanced chest CT to rule out the diagnosis of acute PE in a total of 3500 patients with a minimum of 3 months follow-up, Quiroz et al (16) reported that the clinical validity of using a CT scan to rule out PE is similar to that reported for conventional pulmonary angiography, namely 1.0%–2.8% for CT (including single-section, multidetector, and electron-beam CT) versus 1.1%–2.9% for conventional pulmonary angiography.

In addition to the direct visualization of clots on positive CT angiograms, the considerable advantage of CT over pulmonary angiography is that it can provide diagnostic information that is suggestive of either an alternative or an additional diagnosis. In 2007, multidetector CT angiography has fulfilled the conditions to replace pulmonary angiography as the reference standard for diagnosis of acute PE.

Can Multidetector CT Modify the Diagnostic Strategy for Acute PE?

A change in strategy for the diagnosis of thromboembolic disease has recently been proposed as a direct consequence of the improved image quality offered by multidetector CT. Using four- and 16-section CT scanners, Perrier et al (17) showed that the percentage of patients (all outpatients) with deep venous thrombosis (DVT) despite negative multidetector CT findings was less than 1% and that ruling out PE with the use of D-dimer measurement and multidetector CT would entail a 3-month thromboembolic risk of around 1.5%. These results have raised the possibility that PE might be safely ruled out without the use of lower limb venous ultrasonography (US), at least in outpatients without a high probability of PE.

A similar approach was investigated in the Christopher Study (18). The strategy consisted of an algorithm with a dichotomized decision rule, D-dimer testing, and CT (single-section and multidetector), in which PE was considered excluded in patients with an unlikely clinical probability score and a normal D-dimer test result, while CT was used in all other patients as the sole imaging method to help make management decisions. The large study cohort of 3306 consecutive patients (82% outpatients) clinically suspected of having PE demonstrated that the diagnostic strategy guided treatment decisions with a low risk for subsequent PE. In the one-third of their patients who had an unlikely clinical probability score in combination with a normal D-dimer test result, the 3-month incidence of a venous thromboembolic (VTE) event was only 0.5%. This indicates that CT can be safely omitted in this group of patients. CT results effectively ruled out PE in all other patients without the need to use other imaging tests (3-month incidence of VTE, 1.3%). The authors concluded that the algorithm was pragmatic in that it could be completed in 98.5% of eligible patients and allowed a management decision in 97.9%.

The Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) II study also evaluated the diagnostic performance of multidetector CT angiography in outpatients and inpatients (4). In this study with 824 patients, a composite reference standard was used to help diagnose or rule out PE. The PIOPED II data support the value of multidetector CT angiography for suspected PE but not as a stand-alone imaging technique (4,19).

Emerging Issues in Multidetector CT of PE

Reassessment of Isolated Subsegmental PE

The advent of multidetector CT scanners has improved the visualization of the segmental and subsegmental arteries, with subsequent improvement in the depiction of peripheral PE (5–11). This situation has raised concerns about overdiagnosis of peripheral PE with multidetector CT technology, in particular diagnosis of isolated subsegmental PE (ISSPE). Recent published experience (7,11,17,20) with four-, eight- and 16-section CT scanners does not uphold this concern, with reported frequencies of ISSPE ranging from 1.0% to 5.4% in study populations of patients suspected of having PE. These percentages are similar to the results from prior angiographic studies (21–23), in which rates of ISSPE in the range of 4%–6% were reported in patients suspected of having acute PE.

The clinical relevance of small peripheral pulmonary emboli and the need to administer anticoagulants in such cases remain a subject of debate. As recently emphasized (24), there are three clinical scenarios in which most would agree that even a small embolus requires treatment: *(a)* in patients with small embolus and inadequate cardiopulmonary reserve; *(b)* in patients who have a small embolus and coexisting acute DVT, and *(c)* in patients who have recurrent small embolus possibly due to thrombophilia, to prevent chronic PE and pulmonary artery hypertension.

There appear to be subsets of patients with a small pulmonary embolus and no DVT in whom the risks associated with anticoagulation outweigh the benefits. The rationale for withholding anticoagulation in such cases relies on the intrinsic fibrinolytic activity of the lungs, which allows small emboli to resolve spontaneously. Eyer et al (20) recently investigated clinician response and patient outcome in cases of ISSPE

detected by using multidetector CT. In their series, patients with ISSPE more commonly than not received anticoagulants. However, in the patients who did not receive anticoagulants, no recurrent pulmonary emboli were identified at follow-up. These authors suggest that, in certain circumstances, patients who receive a CT diagnosis of ISSPE (ie, good cardiopulmonary reserve, self-limited risk factors) may not need anticoagulation. Because ISSPE may herald subsequent PE from deep veins, negative findings on a lower extremity study are mandatory before deciding to withhold anticoagulation.

ECG-gated CT Angiography of the Chest: Is It Useful in the Diagnosis of Acute PE?

The rationale for considering ECG-gated CT in the clinical context of acute PE is two-fold. First, the prognosis and optimal therapy in patients with PE are strongly influenced by the presence or absence of hemodynamic compromise. Recent evidence indicates that the presence of right ventricular dysfunction identifies a subgroup of normotensive patients with a much more guarded prognosis than that in patients without right ventricular impairment, who may benefit from intensive therapy with thrombolytic agents (25) or surgery (embolectomy) (26). Consequently, an objective assessment of right ventricular function could help stratify these patients and guide certain therapeutic decisions. Second, the clinical presentation of patients suspected of having acute PE is nonspecific, and it is well established that clinical signs and symptoms of PE and myocardial infarction overlap. Therefore, the possibility of using ECG-gated CT angiography for assessment of coronary artery disease as a potential cause for chest pain or dyspnea could improve patient evaluation and triage, especially in the emergency department.

The ideal scanning protocol would be one that enabled the radiologist to evaluate both morphology and function from a single imaging data set, an objective that is achievable with both 16- and 64-section CT technology. With regard to assessment of cardiac function, several studies have investigated the accuracy of CT angiography in comparison with magnetic resonance (MR) imaging (27,28), radionuclide ventriculography (29–31), and echocardiography (32). In the specific clinical context of chronic respiratory impairment, these studies have demonstrated that multidetector CT was an accurate and reliable noninvasive technique for evaluating right ventricular function and offered certain advantages over other imaging modalities. Recently, promising results have been obtained with the use of multidetector CT in the evaluation of the coronary arteries from whole-chest ECG-gated CT examinations performed with 16- and 64-section CT scanners (33,34). It has been noted that this approach does not require the systematic administration of β-blockers (34,35) and that such studies can be obtained without excessive radiation exposure to the patient (36).

Two current limiting factors for ECG-gated acquisitions—namely longer scanning times compared with those for non–ECG-gated acquisitions and image quality degradation due to irregular and/or high cardiac rhythms—are expected to be overcome with the newly introduced dual-source CT technology, which should allow radiologists to provide clinicians with cardiac functional information in routine clinical practice.

Is There a Role for Postprocessing in Acute PE?

Before the introduction of multidetector CT technology, investigators had suggested that additional two-dimensional image reconstructions might be of diagnostic value because they can compensate for the adverse consequences of partial volume effects on the detection of endoluminal clots. Since the introduction of thin-collimation multidetector CT and its subsequent advantages in terms of image quality, there has been an increasing consensus that image postprocessing is generally unnecessary for detecting acute PE in routine clinical practice. Nevertheless, two areas of research in the field of postprocessing for acute PE are worth considering, one dealing with the detection of perfusion defects as an adjunct to transverse CT scans for the detection of peripheral PE and one focusing on the automatic detection of endoluminal clots.

The integration of perfusion imaging with diagnostic anatomic CT imaging could help improve the diagnostic accuracy of CT angiography for PE, particularly at the subsegmental level and in more distal vessels. At these levels, the combined display of CT angiographic and perfusion scans might help observers in their search for small emboli and increase their confidence when low-attenuation filling defects are found. As previously reported from experimental and clinical studies (37–39), detection of perfusion defects is not practical with routine contrast-enhanced CT scans. Until now, two approaches have been investigated for the detection of perfusion abnormalities: In one approach, authors used color-coded maps of lung attenuation in humans (40), while other authors have investigated a subtraction technique using precontrast and postcontrast conventional CT images in experimental animal studies (41,42). Although both approaches have demonstrated the detectability of perfusion defects with CT, the feasibility of this approach in clinical practice currently has substantial limitations pertaining to scanning times and levels of radiation exposure to the patient.

Computed-aided diagnosis of acute PE is another area of active research, driven by the recognition that detection of acute PE, especially in small peripheral arteries, requires meticulous analysis of a large number of vessels. However, the use of automated tools requires the generation of images of the pulmonary circulation that are devoid of artifacts to allow reliable recognition of endoluminal clots. To date, there has been a dramatic improvement in the level of vascular enhancement of pulmonary arteries, with resultant suppression of flow artifacts in pulmonary arteries. However, other artifacts due to respiratory and cardiac motion may still lead to diagnostic problems, namely by mimicking endoluminal clots at the level of segmental and subsegmental arteries.

A marked reduction in their frequency can be achieved by selecting the shortest rotation time, as recently demonstrated by Bruzzi et al (43) on 16-section CT angiograms of the pulmonary circulation. Virtually complete suppression of cardiac pulsation artifacts can be achieved with ECG-gated 64-section CT (44).

Assessment of PE Severity

The prognosis and optimal therapy in patients with PE are strongly influenced by the presence of hemodynamic events. Recent evidence indicates that the presence of right ventricular dysfunction identifies a subgroup of normotensive patients with much more guarded prognosis who may benefit from intensive therapy with thrombolytic agents (25) or surgery (26). Until now, CT angiography has been shown to be a useful tool for assessment of the severity of acute PE on the basis of morphologic criteria. The two main approaches that were investigated were quantification of the obstruction of the pulmonary arterial bed (45–48) and recognition of signs indicating right-sided heart failure (49,50). The advent of multidetector CT technology has allowed the integration of morphology and function during CT examinations of the chest. Whereas several studies have demonstrated that multidetector CT was an accurate and reliable noninvasive technique for evaluating right ventricular function, its use in the clinical context of acute PE remains to be investigated.

CT Angiography Combined with CT Venography: How, When, and If?

An integral part of the diagnosis of VTE is evaluation of lower extremity DVT. Conventional venography has been replaced by compression and Doppler US. With venography as the reference standard, studies have shown that the sensitivity and specificity of US were greater than 95% for patients with symptomatic DVT but lower for patients who were asymptomatic or had nonocclusive DVT (51,52). In 1998, Loud et al (53) showed that CT scanning of the pelvis and leg veins 3–3½ minutes after intravenous injection of contrast material for CT pulmonary angiography was able to reliably demonstrate lower extremity venous thrombi. Numerous comparative studies have shown there is approximately 97% agreement between CT venography and US (54–58). CT venography and US have also been shown to be equivalent in patients in the intensive care unit (59). The recently completed PIOPED II study of 711 CT venograms showed 95% concordance between US and helical CT venography (4). CT surpasses US in the diagnosis of pelvic DVT and possibly in the diagnosis of nonobstructing DVT.

Where does lower extremity imaging fit in the diagnosis of PE? Is US or CT the preferred modality? After CT angiography, should CT venography be performed routinely to image the veins? Does the additional diagnostic yield justify the additional time, expense, and patient radiation? For these questions, the evidence remains contradictory, making evidence-based consensus difficult. Clearly, US is well accepted, has low cost, and does not expose the patient to radiation. In comparison, what are the pros and cons of CT venography?

CT Venography Pros

Several studies in which single-detector and multidetector CT angiography were used have shown that the addition of CT venography to the CT pulmonary angiography examination increases the percentage of patients requiring anticoagulation by 5%–27% (52,58,60–64). In PIOPED II (based predominantly on four-section CT scanners), 14 of 181 (8%) patients identified with VTE had DVT only. CT venography increased the sensitivity of VTE detection from 83% to 90% without affecting specificity (4). The increased VTE detection indicates either that small pulmonary emboli were missed or that the patient was at high risk for VTE and had a DVT but no PE. PIOPED II also found that variations in sensitivity for the diagnosis of PE among eight clinical centers were diminished when CT venography was added. This suggests that less experienced centers or centers with more difficult patients or older equipment benefited most from the addition of CT venography. PIOPED II concluded that CT angiography (sensitivity = 83%, specificity = 96%) was not adequate to exclude PE but that CT angiography with CT venography (sensitivity = 90%, specificity = 95%) was.

CT angiography with CT venography provides "one-stop shopping," which has proved popular with referring physicians, patients, and radiologists. In a busy practice or emergency room setting, the ease of scheduling, speed of diagnosis, reassurance that negative CT angiograms and venograms can be relied on, and demonstration of alternative diagnoses has made CT angiography or CT angiography with CT venography the study of choice, even before definitive scientific validation (65).

CT Venography Cons

Others argue that routine DVT studies are not required in light of the numerous clinical outcome studies that have shown that a negative CT angiogram or ventilation-perfusion scan has the same negative predictive value as a negative pulmonary angiogram (16,66–68). Fewer than 1.5% of patients with a negative CT angiogram or ventilation-perfusion scan who have not received anticoagulants develop clinical evidence of PE within the next 3 months and that fewer than 0.5% have fatal PE. Many of these CT angiographic studies also included lower extremity imaging of one type or another in a substantial minority of study patients. A recent study by Quiroz et al (16) showed that the type of CT scanner and the addition of lower extremity imaging had little influence on the results, and Perrier and Bounameaux (69) estimated the recurrence rate to be 1.5% after a negative CT angiogram, even if US results were discounted. Unlike many other investigators, Perrier et al (17) found that fewer than 1% of patients imaged with a four- or 16-section scanner had DVT alone at US. Although PIOPED II showed an 8% increase in VTE diagnosis, only 2% of the entire population benefited from CT venography (69). PIOPED II demonstrated that the use of Wells criteria, along with CT angiogra-

phy alone, raises sensitivity to that of CT angiography and CT venography in combination (4).

The addition of CT venography also substantially increases the overall examination radiation exposure by greatly increasing pelvic radiation exposure. Estimates of pelvic radiation vary considerably according to the specific CT venography protocol used. In PIOPED II, patients were scanned continuously from the iliac crest to the tibial plateau in 7.5-mm intervals. The calculated radiation doses to the chest, pelvis, and thighs were 3.8, 6.0, and 3.2 mSv, respectively (CT scanner used: Sensation 16; Siemens Medical Solutions, Erlangen, Germany) (L.R.G., unpublished data, 2005). A study by Rademaker et al (70), who used a single-section CT scanner, calculated the radiation dose to be approximately 2.2 mSv for the chest and 2.5 mSv for the pelvis. Gonadal dose for CT venography was two or more orders of magnitude above those for CT angiography alone.

Strategies to Reduce CT Venography Radiation

PIOPED II found that CT venography depicted isolated clots in the inferior vena cava or iliac vessels in fewer than 3% of cases and that all of those patients had PE detected on CT angiograms (4). Katz et al (54) counted only two inferior vena cava and seven iliac vein clots among 146 (6%) lower extremity clots depicted on CT venograms but did not state how many were isolated to those areas or were cases of visible PE. Therefore, pelvic radiation can be decreased considerably by scanning from the acetabulum (femoral veins) rather than from the iliac crest (distal inferior vena cava).

There is still controversy over the need for continuous helical scanning versus discrete 5-mm transverse images every 2–4 cm. In 2005, Cham et al (58) in a study of 159 cases showed that 6% of clots were smaller than 2 cm and might have been missed with discontinuous scanning every 2 cm. Loud et al (57) used 5–10-mm-thick images every 5 cm and showed 97% sensitivity and 100% specificity, with US findings as the reference standard. A discontinuous imaging strategy starting at the acetabulum and using automated tube current modulation can reduce radiation by approximately 75% (71).

PIOPED II data also show that only 10% of patients had signs or symptoms of DVT and only 5% had a history of DVT. CT venograms were positive in 60% and 26%, respectively, of these patients. Conversely, without signs or symptoms or history of DVT, only 8% and 13%, respectively, had a positive CT venogram (L.R.G., unpublished data, 2005).

In general, we recommend the use of CT venography when emphasis must be placed on a complete vascular examination that can be accomplished expeditiously. When there are concerns about radiation exposure, we recommend substituting lower extremity US. When evaluation of the lower extremity veins is not important clinically, CT venography can be omitted.

Radiation Dose

Contrast-enhanced spiral CT has been enthusiastically embraced by the medical community as an excellent minimally invasive examination for the evaluation of PE. Consequently, it has been widely used in all categories of adult patients (inpatients, outpatients, emergency room patients). However, as a result of this wide application and the well-documented high radiation exposure associated with CT (72–74), there are serious concerns regarding radiation exposure (75,76). In support of this concern, it has been recently reported that nearly 70% of the medical radiation exposure in a tertiary academic referral hospital is delivered through CT examinations (77). In most protocols for spiral CT of PE, the effective dose is between 3 and 5 mSv, equivalent to 1–2 years of exposure to background radiation. The cancer risk associated with this exposure would be approximately 150 excess cancer deaths per million people exposed to a single spiral CT examination for PE (78).

It is important to recognize that this risk is calculated for a 30-year-old man. Children may be an order of magnitude more sensitive than adults to the risk of cancer induction from the same amount of ionizing radiation. This arises from the fact that they have more time to express the cancer and have more rapidly dividing cells than do adults. Women are also more sensitive to the radiation exposure of spiral CT for PE, owing to the presence of breast tissue in the radiated field. Radiation dose to the breast in chest CT has been calculated (79–81) and directly measured (82,83), with a wide variation in reported average values, ranging from 10 to 70 mGy. The variation in values is related to CT parameter settings, differences in size and configuration of breast tissue, and methods to calculate or directly measure radiation dose. Clearly, all CT-associated breast radiation dose values reported are substantial when compared with the average glandular dose of 3 mGy for standard two-view screening mammography.

With appropriate clinical indications, the risk-benefit ratio of spiral CT for PE strongly favors this examination, owing to the high sensitivity and specificity of the test for PE and the strong alternative-diagnostic ability of the examination for conditions that may mimic PE. However, the substantial radiation exposure of the examination demands that appropriate triage occur to prevent unnecessary radiation exposure, especially in children and young adults. As with all CT examinations, the minimum radiation dose that provides diagnostic-quality studies is recommended. In this light, the use of all available equipment-specific dose reduction techniques is strongly endorsed.

Current Role of MR Imaging and Scintigraphy in the Diagnostic Work-up of PE

MR Imaging

Substantial technical developments in pulmonary MR angiography have been introduced in recent years. Continued improvements are ongoing and include

the use of parallel imaging, view sharing, and the time-resolved echo-shared angiography technique, or TREAT (84–86). These techniques have shortened the acquisition time of MR angiography, made it less susceptible to motion artifacts, and improved spatial resolution.

A meta-analysis of studies of gadolinium-enhanced MR for the depiction of acute PE published as of March 2003 in which conventional pulmonary angiography was used as the reference standard reported a broad range of sensitivities of 77%–100% and uniformly high specificities of 95%–98% (87). In the most recent of these studies, the sensitivity of MR was 100% for PE in the central and lobar arteries, 84% in the segmental arteries, but only 40% in the subsegmental branches (88).

With regard to suspected acute PE, the accuracy of MR with a state-of-the-art three-component protocol (true fast imaging with steady-state precession, perfusion MR imaging, and MR angiography with a parallel acquisition technique) has been reported recently (85). The per-patient sensitivity and specificity, respectively, were 85% and 98% for the true fast imaging sequence, 77% and 100% for MR angiography, and 100% and 91% for perfusion MR imaging. The combined protocol had a sensitivity of 100% and a specificity of 93%. The per-embolus sensitivities for segmental PE were 86% for the true fast imaging sequence, 83% for MR angiography, and 97% for perfusion MR.

The sensitivity of MR angiography for subsegmental clot in this study was only 55%, compared with 93% for perfusion MR imaging. Perfusion MR is sensitive but not specific, while true fast MR and MR angiography are specific but not as sensitive, particularly for subsegmental PE. Overall, the combined MR protocol was both reliable and sensitive, as compared with 16-section CT. The MR angiography voxel size ($0.7 \times 1.2 \times 1.5$ mm) was comparable to that of multidetector CT, and the average MR examination time was approximately 10 minutes (85).

The potential of MR to provide a "one-stop" procedure to evaluate for PE and DVT in a single examination was recognized early on, prior to that of CT. Many studies, even with early techniques, have shown MR venography to have high sensitivity and specificity (90%–100%), compared with conventional venography (89–94). Moreover, for iliocaval DVT, the accuracy of MR venography exceeds that of conventional venography and of color duplex US (92,94–96). More recent advances in MR venographic technique include the use of contrast enhancement, a stepping table, and a parallel acquisition technique (93,97–100). The latter enables the entire venous system, from the ankles to the inferior vena cava, to be imaged in less than 10 minutes, without any radiation exposure or nephrotoxicity (100).

Several recent studies have confirmed the clinical feasibility of a combined MR examination for both acute PE and DVT (97,101). Using the three-component chest protocol referred to above followed by stepping-table MR venography without additional contrast agent administration, Kluge et al (97) demonstrated that a complete MR VTE study can be completed in less than 20 minutes.

Therefore, MR angiography of the pulmonary arteries and MR venography for DVT performed with state-of-the-art techniques can potentially serve as a second-line examination in the evaluation of suspected acute PE in patients who are unable to receive iodinated contrast material for CT or for whom ionizing radiation is of concern. However, other initial advantages of MR over CT, including the "one-stop" combined imaging of PE together with MR venography, the evaluation of cardiac function, and pulmonary perfusion, all have diminished as a result of recent advances in multidetector CT. Furthermore, compared with CT, MR examinations are more complex and less robust, examination times are longer, and patient access to MR is more limited. Furthermore, the limited ability to detect pulmonary disorders other than PE is a serious disadvantage compared with CT. In addition, patients with a pacemaker or various implanted devices are largely excluded from MR.

Weighing these advantages and disadvantages, Medicare currently reimburses for MR angiography of the chest for the diagnosis of PE only when intravascular iodinated contrast material is contraindicated in the patient (102).

It should be noted that a caution has recently been raised regarding the use of gadolinium-based contrast agents for MR in patients with advanced renal failure. An association between gadolinium-based contrast agents and the development of nephrogenic systemic fibrosis (also called *nephrogenic fibrosing dermopathy*) has been suggested (103–105). The second U.S. Food and Drug Administration (FDA) public health advisory on this subject notes that as of December 21, 2006, the FDA had received reports of 90 patients with moderate (glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2) to end-stage (GFR < 15 mL/min/1.73 m^2) kidney disease who developed nephrogenic systemic fibrosis (106).

The accuracy and role of state-of-the-art combined gadolinium-enhanced pulmonary MR angiography and MR venography are currently being evaluated further in the PIOPED III trial, sponsored by the National Heart, Lung, and Blood Institute. In this prospective study, a total of 1000 subjects will be studied at eight clinical centers. The accuracy of MR will be assessed by using a composite reference standard that includes combined CT angiography and CT venography. The results of this trial are expected in the Spring of 2008.

Scintigraphy

The salient and documented facts about scintigraphy are as follows. A normal perfusion scan excludes PE with a negative predictive value close to 100% (107–109). A low-probability ventilation-perfusion scan combined with low-probability clinical assessment results showed PE in only 4% of patients (110). A high-probability ventilation-perfusion scan in a patient with high-probability clinical findings showed PE in 96% of patients (110). With other combinations, PE was present in 16%–88% of

patients, and further evaluation was needed. Furthermore, scintigraphy is safe, technically robust, and widely available. The problems are that most patients (about 75% in PIOPED) do not have a definitive result from scintigraphy, and scintigraphy provides limited alternative diagnostic information. Newer concepts in scintigraphy have focused on identifying patients in whom a definite diagnosis can be expected, improving interpretation methods, and reducing technical complexity and cost.

In PIOPED I, a ventilation-perfusion scan in patients with a normal chest radiograph was diagnostic (high probability or normal to nearly normal) in 52% of patients suspected of having PE (111). More recently, a ventilation-perfusion scan was shown to be diagnostic in 91% of patients suspected of having PE and whose chest radiograph was normal (112).

If scintigraphy is used, elimination of the ventilation scan can reduce cost and radiation. Although this is not common practice in most centers, there is evidence from two studies that the ventilation scan can be eliminated without compromising diagnostic accuracy. The PIOPED group retrospectively analyzed perfusion scans alone and found the results to be equivalent to results from the ventilation-perfusion technique (113). A different approach to analyzing the perfusion scan was used in the Prospective Investigative Study of Acute Pulmonary Embolism Diagnosis (PISA-PED) trial (114). In that study, the ventilation scan was omitted and the perfusion scans were classified according to the shape of the perfusion defects, irrespective of the chest radiographic findings. At variance with the PIOPED I (110,113) study in which the ventilation-perfusion scans were classified in graded probability, the interpretation of the abnormal perfusion scan in the PISA-PED study (114) was dichotomous (ie, either compatible or not compatible with PE). The sensitivity and specificity of the abnormal perfusion scan compatible with PE were 86 and 93%, respectively (114). In addition, better sensitivity was achieved when the scans of the PIOPED I (110) study were reread by a blinded observer using the perfusion images alone (114).

Accordingly, scintigraphy can be considered as a preferred alternative chest imaging technique for patients who cannot undergo CT angiography, with reduced cost and radiation dose.

Current scintigraphy research is focused on validating the use of dichotomous criteria to yield a PE present, PE absent, or PE uncertain result. This may be particularly important for reproductive-age female patients whose chest radiograph is likely to be normal and for whom the breast irradiation dose from CT angiography can be minimized by using a perfusion scan as the first imaging test (79,110). Another application of perfusion scintigraphy could be in the follow-up of patients with proved PE who are undergoing anticoagulation. A recent study has shown that patients with persistent perfusion abnormalities are at risk of chronic thromboembolic pulmonary hypertension (115). For most patients, the ventilation-perfusion scan remains the standard scintigraphic study in most, but not all, centers.

Diagnostic Strategies in Acute VTE

The proliferation of diagnostic strategies for suspected acute VTE testifies to the complex variations in clinical situations and the limited scope of high-quality data. The goal is to have diagnostic pathways for common clinical situations that are based on high-quality clinical trials and that provide quantitative assessment of diagnostic certainty. The choice of diagnostic imaging tests depends on the pretest clinical probability of PE, the condition of the patient, the availability of the test, the risks of testing, the risk of an inaccurate positive or negative diagnosis, and the cost. Recommendations for the "usual" patient can now be formulated on the basis of the results of PIOPED II (4) and other studies (17,18,116) but with continued reliance on clinical judgment. However, in many clinical subgroups, definitive data are not available and expert opinion is still the primary guide.

Clinical Assessment and D-Dimer Measurement: Basis for Diagnostic Strategies

As has been described above, thorough clinical evaluation is the first step in raising the suspicion of PE, assessing prior probability, and selecting appropriate diagnostic strategies. Accordingly, recent guidelines (19,117) recommend that the clinical probability of the disease be assessed in each patient suspected of having PE before any laboratory testing or imaging is performed. The use of clinical prediction rules is strongly recommended (110,118–122). However, there is still a need for further research. The performance of different clinical models in different patient populations and clinical settings may vary (123), and it will be important to develop either generally robust prediction rules or a basis for selecting the correct prediction rule for a particular setting.

The measurement of plasma degradation products of cross-linked fibrin (D-dimer) has an important role in excluding PE (117,124–127). Plasma D-dimer concentrations above a given threshold (usually 0.5 $mg \cdot L^{-1}$) have a high sensitivity (95%) but a low specificity (55%) for VTE (126,128–130). Rapid enzyme-linked immunosorbent assays are recommended (126,127,130,131). The reliability of low clinical probability combined with negative D-dimer test results in safely excluding PE has been confirmed (132, 133). However, excessive prescription of D-dimer testing and poor adherence to published guidelines reduce cost-effectiveness (134). A negative D-dimer test is reliable in both inpatients and outpatients (135). The use of a D-dimer assay in inpatients may lead to numerous unjustified diagnostic evaluations for thromboembolism because of the excessively high false-positive rates (136). Accordingly, D-dimer testing normally should be limited to the well-validated role of excluding VTE in combination with low clinical probability of the disease, primarily in outpatients.

Evidence-based decision rules that combine clinical assessment and D-dimer testing are as follows:

1. If clinical probability is high, D-

dimer should not be measured and imaging should be performed. Measurement of D-dimer in this setting is not useful, because a negative D-dimer test does not exclude PE in more than 15% of patients with high-probability clinical assessment results (137,138).

2. If clinical probability is moderate or low, D-dimer should be measured by using a rapid enzyme-linked immunosorbent assay. If D-dimer levels are below the threshold value for presence of thrombosis, further evaluation with imaging is unnecessary since the posttest probability of PE is 5% or lower (137,138).

3. However, if D-dimer levels are not normal, imaging should be performed in patients with a low or moderate clinical probability. A positive rapid enzyme-linked immunosorbent assay result for D-dimer (likelihood ratio of 1.56 for PE and 1.7 for DVT [137]) results in an indeterminate posttest probability in patients with low or moderate clinical prior probability.

The Usual Imaging Strategy: Which Tests?

Lower extremity US.—If the clinical and/or D-dimer evaluation indicates the need for imaging, the first consideration is whether to perform lower extremity US, which demonstrates DVT in 13%–15% of patients suspected of having PE (139,140) and in up to 40% proved to have PE (69), thereby allowing treatment with no further testing. In general, the use of US should only be considered if the patient has clinically localizing findings of extremity DVT only; patients who present with thoracic or systemic signs and symptoms should undergo chest imaging as the primary modality.

If US is negative, PE is not excluded (118,141–145) and CT angiography or scintigraphy (if the chest radiograph is normal) provides satisfactory evaluation for PE. MR also provides radiation-free evaluation for VTE, but its sensitivity and specificity and general applicability are still to be determined.

In patients whose initial imaging results are indeterminate, who have a low pretest probability, and who have reasonable cardiopulmonary reserve, Hull et al (146) and Perrier et al (147) have proved that serial negative US scans over the next 10 days provide additional assurance that anticoagulation is not required.

Multidetector chest CT and CT venography.—If multidetector CT angiography is not contraindicated, then it should be the first chest imaging test performed for suspected PE. Adding indirect CT venography to the examination is theoretically appealing, and retrospective studies have shown substantial increases in diagnostic yield from CT venography (148). In PIOPED II the increase in sensitivity from adding CT venography was 8% but was not statistically significant (4); nevertheless, a majority of the PIOPED investigators recommended the use of CT venography in the usual diagnostic evaluation (19). We interpret the data to show that the added yield is marginal if a proper clinical assessment has been performed, and we conclude that CT venography should be used selectively on the basis of risk-benefit considerations (eg, avoided in most female patients of reproductive age, and with examination technique tailored to minimizing radiation dose).

Evidence-based decision rules for the use of CT angiography and combined CT angiography with CT venography, when clinical assessment and D-dimer testing did not suffice to exclude PE, are as follows:

1. The diagnostic evaluation can safely end with a low-probability clinical assessment result and a negative CT angiogram or combined CT angiogram and CT venogram. In PIOPED II, among patients with a low-probability clinical assessment result, if the CT angiogram was negative then PE was present in 4%, while if combined CT angiography CT venography results were negative then PE was present in 3% (4). However, when the CT angiogram is positive in a patient with a low-probability clinical assessment result, reassessment of the patient is indicated. In PIOPED II, the reference diagnosis was positive for PE in only 58% of patients when the CT angiogram was positive (4).

2. With a moderate-probability clinical assessment result, most would recommend stopping the work-up if results from combined CT angiography and CT venography, or even from CT angiography alone, are negative. In PIOPED II patients with moderate clinical probability, the reference diagnosis was "PE present" in 11% if CT angiography findings were negative and 8% if the combined CT angiography and CT venography results were negative (4). Outcome studies in comparable patient groups have shown PE after 3 months in 1.0%-1.5% of patients (4,17,18,64,149). Conversely, in patients with moderate clinical probability, PE was present in 92% whose CT angiographic results were positive and in 90% whose combined CT angiographic and CT venographic results were positive (4). Treatment can be administered without further diagnostic studies.

3. With a high-probability clinical assessment result, if findings from either CT angiography or combined CT angiography and CT venography were positive, PE was present in 96% in PIOPED II (4). Treatment can be administered without further diagnostic studies. However, if the CT angiogram is negative in patients with a high clinical probability, reassessment of the patient is indicated. In PIOPED II, the reference diagnosis was "PE present" in 40% of patients; if findings from combined CT angiography and CT venography were negative, the diagnosis was "PE present" in 18% (4).

Important factors in the evaluation of discordant clinical and CT results include the size of the pulmonary embolus shown on and the quality of CT images. When an embolus was seen in a main or lobar pulmonary artery, PE was present in 97% of patients (4). If the largest vessel showing an embolus was segmental, PE was present in 68%; if the embolus was seen in a subsegmental branch, PE was present in 25% of patients (data were sparse in the subsegmental group) (4). Interestingly, although subsegmental PE was rare in patients with a high Wells score, patients with a low Wells score commonly had main or lobar emboli (H.D.S. and P. D. Stein, unpublished data, 2005). In addition, the interaction of embolus size and image quality should be considered important. A

solitary small embolus on a scan of poor technical quality may have different management implications than the same finding on a high-quality scan. The decision for further evaluation of discordant clinical probability and CT angiographic diagnosis requires exercise of informed clinical judgment in the context of the individual patient's complete clinical status, but this decision usually involves further imaging.

Specific Strategies for Special Situations

The above recommendations are evidence based and are grounded in data from several large well-designed clinical trials. However, they do not provide specific guidance for a number of common clinical situations, which include the following: *(a)* patients with allergy to iodinated contrast material, *(b)* patients with impaired renal function, *(c)* female patients of reproductive age, *(d)* pregnant patients, and *(e)* critically ill patients. We will briefly discuss these patients, grouping them according to shared clinical issues.

Allergy to iodinated contrast material or impaired renal function.—If clinical assessment and D-dimer assay fail to exclude PE, a venous US scan may be positive and guide therapy. If US fails to demonstrate treatable disease, patients with a mild to moderate iodine allergy or mild impairment of renal function may be treated with appropriate prophylaxis (19,150) and then undergo CT. However, with moderate or severe iodine allergy or renal impairment, pulmonary scintigraphy is a useful alternative. In many patients, as discussed above, perfusion scintigraphy alone will suffice, saving cost and radiation exposure (112–114). Accordingly, scintigraphy can be considered as the chest imaging technique of choice for patients with a negative or nondiagnostic US scan who cannot undergo CT angiography.

Other options for imaging evaluation when severe iodine allergy exists may include serial venous US (118,151), gadolinium-enhanced CT angiography, (152), and gadolinium-enhanced MR imaging (87,88,153,154) (this modality is currently undergoing a large-scale clinical trial in PIOPED III). For patients with severe renal impairment, we recommend US or scintigraphy as options. High-dose gadolinium agents are contraindicated in patients with renal failure (155,156).

Reproductive age.—Breast radiation exposure is a concern in all female patients, but the risk of death from undiagnosed PE far exceeds the risk of radiation-induced malignancy. The average absorbed dose to the breast from CT angiography has been calculated as 10–70 mGy (79–83). The absorbed dose to the breast with a perfusion lung scan has been estimated to be 0.28 mGy (80).

In women of reproductive age, if the D-dimer assay result is positive, venous US and perfusion scintigraphy are appropriate considerations as the next imaging test. If the clinical situation indicates it, CT angiography with venous US is an acceptable alternative; CT venography is not recommended. However, if CT venography is deemed necessary, it is advisable to eliminate pelvic vein imaging to reduce gonadal irradiation and to use techniques that minimize radiation dose in general.

Pregnancy.—In pregnant patients, D-dimer testing may be useful, although it may yield a positive result due to the pregnancy (157). Venous US should be the first imaging test used in most patients, because if the US scan is positive the need for radiographic imaging is eliminated. If imaging with ionizing radiation is necessary, some investigators (158,159) have recommended CT angiography rather than ventilation-perfusion lung scanning. Irradiation of the fetus is a primary concern, and published data are confusing. Some authors (160) indicate that the radiation dose to the fetus from 16-section CT angiography (0.24–0.47 mGy at 0 months and 0.61–0.66 mGy at 3 months) is of the same magnitude as a that from ventilation-perfusion scanning (0.25–0.36 mGy at 0 months and 0.31–0.32 mGy at 3 months) or perfusion scanning alone (0.21 mGy at 0 months and 0.30 mGy at 3 months). Others (80) indicate that the absorbed dose to the fetus is less with CT angiography than with perfusion scanning (0.01 mGy vs 0.12 mGy). CT venography is contraindicated.

The use of iodinated contrast medium is a second cause of concerns in pregnant patients because of the reluctance to expose a fetus to any drugs. An extensive literature search was carried out by the members of the Contrast Media Safety Committee of the European Society of Urogenital Radiology (161). As reported by this committee, mutagenic and teratogenic effects have not been described after administration of iodinated contrast media. Free iodine in radiographic contrast medium given to the mother has the potential to depress fetal and neonatal thyroid function. Consequently, if iodinated contrast medium is administered during pregnancy, neonatal thyroid function should be checked during the 1st week after delivery. However, the avoidance of iodinated contrast media and the reduction in absorbed dose achievable by using perfusion scanning without ventilation makes diagnostic strategies based on this technique worthy of particular consideration in the setting of clinical suspicion of PE during pregnancy.

MR imaging has also been suggested but requires further validation (87). Furthermore, adequate studies of gadopentetate dimeglumine have not been conducted in pregnant women and it is not known to what extent it is excreted in human milk (Magnevist [package insert]. Wayne, NJ: Berlex Laboratories, May 2000).

Critical illness.—It is unsafe or unfeasible to transport many critically ill patients, and the usual imaging approaches may have a high rate of technically inadequate results in such patients. Accordingly, real-time bedside imaging is preferable for patient care. However, techniques and results of such approaches are inconclusive to date.

Transthoracic or transesophageal echocardiography have been used primarily for the diagnosis of hemodynamically significant PE and to exclude other cardiovascular conditions that may clinically mimic PE (162). Few studies have prospectively addressed the diagnostic accuracy of echocardiography in patients suspected of hav-

ing PE (163–165). These studies have yielded conflicting results with broad values of sensitivity (51%–93%) and specificity (82%–94%). This may result from differences in clinical >setting, patient selection, severity of PE, and echocardiographic criteria adopted for confirming the disease. The sensitivity of transthoracic echocardiography for right ventricular enlargement or dysfunction in patients with massive PE or in unstable patients (combined data from three case series [166–168]) was 33 (100%) of 33. In the presence of any two of three indicators—high clinical probability, positive echocardiogram, positive US scan of the leg—the sensitivity for massive PE was 33 (97%) of 34, while the corresponding negative predictive value was 98% (165). Recently, Miniati et al (169) found that in unselected consecutive patients suspected of having PE, echocardiographic findings of right ventricular dysfunction had a positive predictive value of 98% for PE when associated with high pretest clinical probability and of 85% when associated with intermediate pretest clinical probability; conversely, a negative echocardiogram paired with low clinical pretest probability yielded a negative predictive value of 95%. When echocardiographic results and clinical probability were discordant, the posttest probability of PE was neither sufficiently high nor sufficiently low to confirm or exclude the disease (169).

However, for patients who are critically ill or *in extremis,* clinical options are limited. Accordingly, bedside echocardiography in combination with bedside leg US are recommended as rapidly obtainable tests that will not further destabilize the patient. Right ventricular enlargement or poor right ventricular function, in a proper clinical setting, can be interpreted as resulting from PE. A positive venous US scan in the appropriate clinical setting also indicates PE. A portable perfusion scan is a potential option, if available.

When the patient is stabilized and can be moved safely, further imaging studies appropriate to the clinical situation should be performed.

Unanswered Questions and Research Issues in Diagnostic Strategy

Further evaluation of proposed clinical pathways (19) by using decision analyses, evidence-based criteria, and cost-effectiveness assessment is needed. This would help to focus further clinical research, in particular regarding strategies for further imaging when CT is inconclusive or contraindicated. In addition, tests and pathways in specific patient groups have not been evaluated in detail. For example, there are many data on the use of D-dimer testing in emergency department patients but little on its use in inpatients or intensive care unit patients. Patients with specific comorbidities have not been studied extensively, and preliminary data suggest specific characteristics in oncology patients (170), patients with chronic obstructive pulmonary disease (15), and so forth. It will be of particular importance to resolve disparate assertions regarding radiation exposure from different imaging techniques.

An entirely different universe of issues has been opened up by the high accuracy and minimal invasiveness of CT. It may be that CT angiography can serve as a new in vivo reference standard for the diagnosis of PE and thus enable the use of imaging to study the pathophysiology of VTE in patient subgroups. A few of the previously inaccessible issues that can now be addressed include effects of clot load in patients with differing comorbidities, the question of whether all PE patients need anticoagulants, the prevalence of PE in specific populations, the clinical effect of follow-up imaging, the accuracy of different clinical prediction rules, and so forth.

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