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The Role of Multidetector Computed Tomography Angiography for the Diagnosis of Pulmonary Embolism

Paul Cronin, MD, MS,* John G. Weg, MD,† and Ella A. Kazerooni, MD, MS*

From a radiological point of view, computed tomography pulmonary angiography (CTPA) has effectively become the de-facto first-line imaging test for the evaluation of pulmonary embolism (PE), as patients with a high-quality negative CTPA do not require further examination or treatment for suspected PE. We are likely to see further technical developments in CT technology in the near future. These advances will most likely further improve image quality. Several questions or issues remain, including strategies for further imaging when CT is inconclusive or contraindicated, issues regarding radiation exposure, the prevalence of PE in specific populations, best tests and pathways in specific patient groups, including patients with specific comorbidities such as oncology patients or patients with chronic obstructive pulmonary disease. Also, the question whether all PE patients need anticoagulation, the clinical effect of follow-up imaging, and the accuracy of different clinical prediction rules, remains.
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As the third most-common cause of cardiovascular death after myocardial ischemia and stroke, pulmonary embolism (PE) is a common, potentially fatal condition associated with significant morbidity and mortality.[1] The nonspecific signs and symptoms of PE, such as chest pain or shortness of breath, and can be found in diseases of the lung, pleura, heart, and gastrointestinal tract, making the diagnosis challenging. Many more patients are evaluated for PE than are confirmed to have the diagnosis. For example, in the original Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study,[2] only one-third of the 755 patients who underwent pulmonary angiography had the diagnosis of PE confirmed. Similarly, in the PIOPED II study, only 192 of 824 subjects who underwent computed tomography pulmonary angiography (CTPA) had a PE.[3] In many patients, the first diagnosis of PE is made when there is acute cardiac decompensation or, worse yet, postmortem. In the early 1970s, the annual incidence of PE was estimated to be between 300,000 and 600,000 cases, with approximately 50,000 to 100,000 deaths in the United States annually. In the past few decades, the incidence of PE has decreased substantially by 45%, whereas that of deep-vein thrombosis (DVT) is unchanged.[4] This change is likely attributable to a combination of factors that includes a decreased incidence of PE, decreased case fatality rate, venous thromboembolism (VTE) prophylaxis, and also changes in diagnostic patterns.[5]

Prompt and accurate diagnosis of PE has been shown to greatly influence patient outcome.[1,6] One-third of untreated patients with PE will die, compared with less than 10% of treated patients. Therefore, it is important to quickly and accurately diagnosis PE. When evaluating a patient with suspected PE, it is important to remember that PE is only one part of venous thromboembolic disease, the other being the venous thrombus that forms, most commonly in a lower extremity vein, and subsequently migrates into the pulmonary arterial circulation.

Many tests and algorithms have been suggested for the evaluation of patients with suspected VTE, from the history and physical examination to the electrocardiogram, chest radiography, echocardiography, ventilation-perfusion scintigraphy, catheter pulmonary angiography, lower-extremity vein evaluation with venography, sonography, CT venography (CTV) and MR venography, CT and MR angiography. Although the diagnostic accuracy of laboratory tests such as D-dimer has increased, radiology plays an important role in

*Department of Radiology, Division of Cardiothoracic Radiology, University of Michigan Medical Center, Ann Arbor, MI.
†Department Internal Medicine, Division Pulmonary & Critical Care Medicine, University of Michigan Medical Center, Ann Arbor, MI.
Address reprint requests to Paul Cronin, MD, MS, Department of Radiology, Division of Cardiothoracic Radiology, University of Michigan Hospitals, B1 132G Taubman Center/0302, 1500 East Medical Center Drive, Ann Arbor, MI 48109-5030. E-mail: pcronin@med.umich.edu

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the diagnosis of PE, especially with the development of multidetector CT and increased use of CTPA. Currently, the PIOPED II investigators recommend stratification of all patients suspected of having PE according to an objective clinical probability assessment.[3] A negative D-dimer rapid ELISA result with a low or moderate probability clinical assessment can safely exclude PE.[3] If PE is not excluded, CTPA ± CTV is recommended.[3]

Imaging of PE

Ventilation-Perfusion (V/Q) Scintigraphy

V/Q scintigraphy was introduced in 1964 for the evaluation of pulmonary blood flow and has been used as the first-line examination for patients with suspected PE for several decades.[2,7-9] A high probability scan is sufficient diagnostic evidence of PE to begin anticoagulation therapy, and a normal V/Q scan is considered sufficient evidence to exclude PE. However, the frequency of low or intermediate probability scan results can be as high as 50% to 70%, carrying a 10% to 50% probability of PE, makes it difficult to decide whether or not to begin anticoagulation therapy based on the test result alone.[2,10] In the PIOPED study, only 40% of patients with PE had a high probability V/Q scan result, whereas another 40% of patients with PE had an indeterminate result and 14% had a low probability result.[2]

V/Q lung scintigraphy has the advantage of not requiring the iodinated contrast material used for CTPA, and decreased radiation. Therefore, if a patient with suspected PE has a history of an iodinated contrast reaction or renal impairment, V/Q lung scintigraphy is recommended as an alternate test to CT. V/Q lung scintigraphy is also recommended when obesity prevents a patient from either fitting into the CT gantry or is beyond the weight limit for the CT and/or angiography table.

Catheter Pulmonary Angiography

Since the late 1960s, pulmonary angiography has been considered the most accurate test for the evaluation of PE and the reference test to which new diagnostic techniques are compared.[11,12] However, catheter pulmonary angiography is invasive, with a 2% morbidity and small risk of mortality, which have contributed to under use.[13,14] Two studies conducted 12 years apart on a total of 1250 patients undergoing V/Q scans, demonstrated that only 12% to 14% of the 979 total combined patients with an inconclusive diagnosis of PE after the V/Q scan subsequently underwent pulmonary angiography.[15,16] In one of these studies, 16% of patients with a low-probability V/Q scan and 30% of patients with an intermediate-probability V/Q scan received anticoagulant therapy with no other documentation of emboli in the pulmonary arteries other than the V/Q scan result.[15]

Computed Tomography

In 1982, Sinner and coworkers reported the first series of consecutive patients with clinically suspected pulmonary thromboembolism, 21 patients total using nonhelical CT.[17]

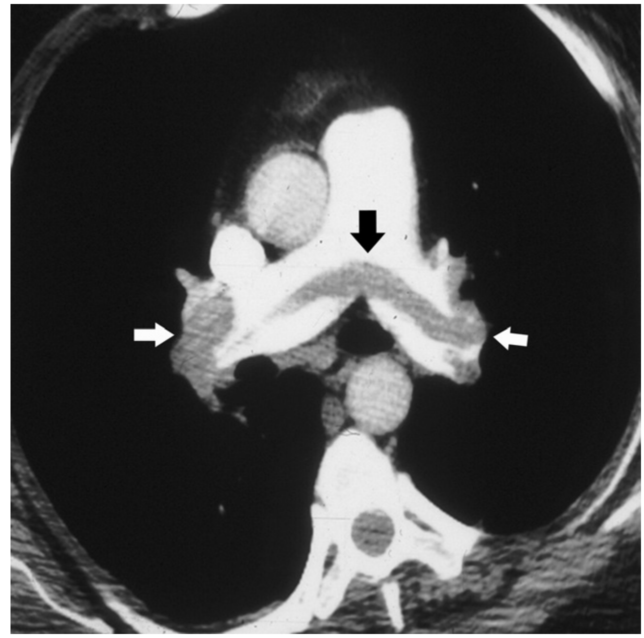

Figure 1 A 38-year-old man with acute pulmonary embolus (saddle embolus), main, left, and right pulmonary arteries (arrows).

They reported abnormalities within first (main) through third (lobar) order pulmonary arteries with central emboli. During the next decade, most reports on the use of CT for PE described the appearance of PE on nonhelical CT scans obtained for other reasons where PE was an incidental finding, or on the use of CT for massive or central PE.[18-23] In 1992 Remy-Jardin and coworkers first reported the use of helical CT for the evaluation of central PE in 42 patients, using selective pulmonary angiography as the reference test.[24] Helical CT quickly evolved from being performed on single-detector scanners using 5-mm collimation and 1-second gantry rotation times, on which most of the published data for CTPA versus catheter angiography is based, to the current techniques described in the next section (Figs. 1 and 2).

Multidetector CT (MDCT)

MDCT scanners with 4-, 8-, 16-, 32-, and 64-detector-rows are now several years old. The collimation or slice thickness used today is commonly at or near 1-mm, with subsecond gantry rotation speeds of 0.3 to 0.5 seconds resulting in improved spatial and temporal resolution, as discussed below in greater detail. The increased number of detectors means that a greater craniocaudal thickness of the thorax is included in each gantry rotation; hence, more detectors means faster scanning. Scan times range from 18 to 28 seconds on 4-MDCT, 8 to 13 seconds on 16-row MDCT, and 4 to 6 seconds on 64-MDCT. These scan times allow high-resolution imaging of small pulmonary arteries throughout the entire thorax in a single breath-hold even in dyspneic patients.[25] Soon scanners with an even greater number of detector row systems will become more widespread, and there is even the possibility of a volume CT scanner that would allow imaging of the entire thorax in a single gantry rotation (Figs. 3-5).

Figure 2 A 52-year-old man with acute lobar and segmental pulmonary embolus.

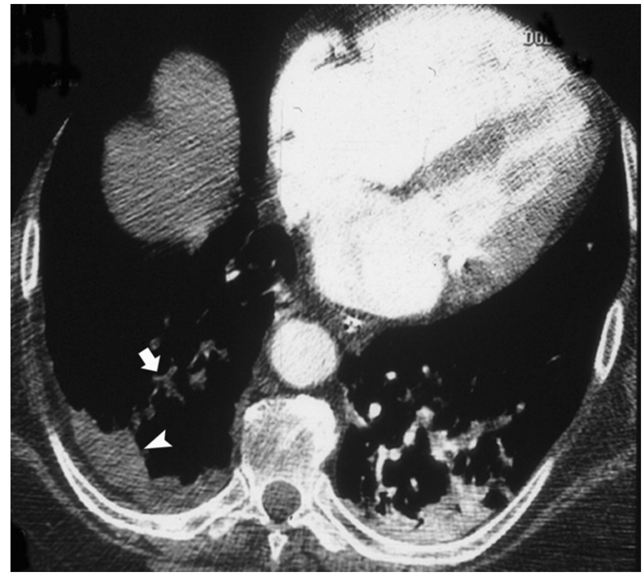

Figure 4 A 61-year-old woman with acute right pulmonary embolus (arrow) and left pulmonary arteries pulmonary infarcts (arrowhead).

CT has the ability to depict other conditions that clinically mimic PE, such as acute pneumonia, lung abscess, pneumothorax, pneumomediastinum, pleural or pericardial effusion, aortic dissection, cardiovascular disease, mediastinitis, mediastinal abscess, esophageal rupture, malignancy, and interstitial pulmonary fibrosis. In addition, 64-detector scanners have the additional ability to detect coronary artery disease during the same study, if the appropriate parameters are set. Other conditions have been reported to have been found in 11% to 70% of CT examinations performed for suspected acute PE.[26-32] CT is better able to depict other conditions than V/Q scintigraphy, pulmonary angiography, and MR angiography.

Accuracy of Imaging

Computed Tomography

The 1992 report by Remy-Jardin and coworkers was the first to compare helical CT for the evaluation of central PE to selective pulmonary angiography as the reference test, demonstrating 100% sensitivity and 96% specificity in 42 patients.[24] At that time, exams were interpreted hard copy, and image collimation was 5-mm on a single detector scanner. As with many first reports, the accuracy estimates may be high because of the selection of more ideal patients for study. Overall, sensitivities for detection of PE using CT range from 63-100% and specificities from 67-100%.[10,24,27,28,33-45] Sev-

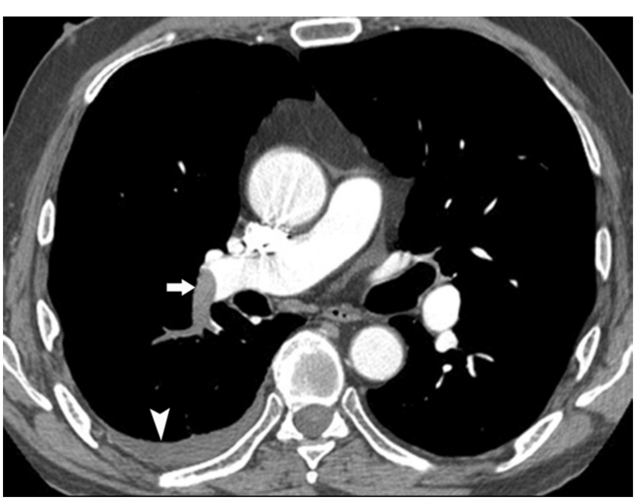

Figure 3 A 28-year-old woman with right interlobar artery pulmonary embolus (arrow) and small right pleural effusion (arrowhead).

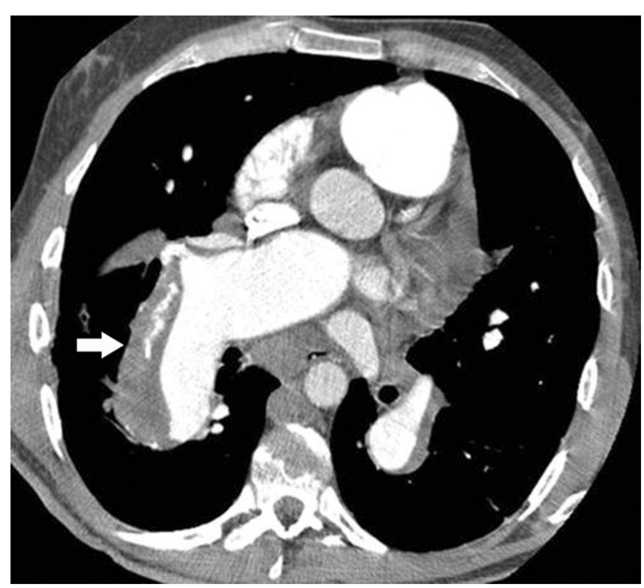

Figure 5 A 57-year-old man with chronic pulmonary embolus (arrow) and pulmonary hypertension.

eral groups followed with investigations of CTPA, using catheter pulmonary angiography as the reference tested; sensitivity ranged from 53% to 97% and specificity 78% to 97%.[10,34,37,38,40,46] Many of these studies suffer from selection bias, with accuracy estimates not reflective of a population of consecutive patients with suspected PE undergoing CT. For example, a small series of 20 patients by Goodman and coworkers reported sensitivity of 63%.[34] However, this study was not intended to be a consecutive group of all patients with suspected PE, but specifically evaluated patients with either an intermediate-probability V/Q scan or a mismatch between the V/Q scan result and the clinical suspicion of PE, making them a group of patients that were a diagnostic challenge, and lowering diagnostic accuracy estimates for CT. The title of that publication was appropriately "Detection of PE in patients with unresolved clinical and scintigraphic diagnosis: helical CT versus angiography," reflects the sampling bias, however, others have used this and other similar studies to suggest that the sensitivity of CT is poor. With any rapidly evolving technology it may be difficult to ever know what the true accuracy of the technique is.

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.[47] Eng and coworkers performed a systematic literature review of the accuracy of CT in the diagnosis of PE.[48] They selected 6 systematic reviews and 8 primary studies and found combined sensitivities of CT for detecting PE of 66% to 93% across the systematic reviews and combined specificities of 89% to 97%. Only one of the systematic reviews reported a combined sensitivity of greater than 90%. Among the 8 primary studies, sensitivities ranged from 45% to 100% and specificities from 78% to 100%. Only 3 of the 8 primary studies reported a sensitivity greater than 90%. However, none of the primary studies used scanners with 4 or more detectors.[48]

MDCT

With multidetector CT, the reported sensitivity and specificity range from 83% to 100% and 89% to 97%, respectively.[3,41,49] In 2 studies each of fewer than 100 patients sensitivities for the detection of PE with 4-slice CTPA have been reported to be 96% and 100%, with respective specificities of 98% and 89%.[43,49]

PIOPED II is the largest and most significant study assessing the use of MDCT in the diagnosis of PE. In PIOPED II, the sensitivity of CTPA for PE was 83% and specificity 96%. In subjects in which CTV also was performed, the combined sensitivity for PE and DVT was 90% and the specificity 95%.[3] Positive predictive values (PPV) were 96% (95% confidence interval [CI] 78-99%) with a concordantly high probability of VTE on clinical assessment 92% (95% CI 84-96%) with an intermediate probability on clinical assessment, and 58% (95% CI 40-73%) or nondiagnostic if clinical probability was discordant.[3] Negative predictive values (NPVs) were 96% (95% CI 92-94%) percent with a concordantly low probability of VTE on clinical assessment, 89% (95% CI 82-93%) with an intermediate probability on clinical assessment, and 60% (95% CI 32-83%) or nondiagnostic if clinical probability was discordant.[3]

CT Versus V/Q Scintigraphy

Anderson and coworkers compared CT and V/Q scintigraphy for the diagnosis of PE. They concluded that CTPA was not inferior to V/Q scanning.[50] Blachere and coworkers reported statistically significant greater accuracy for PE detection for CTPA (sensitivity = 94.1%, specificity = 93.6%, positive predictive value = 95.5%, negative predictive value = 96.2%) than for V/Q scans (sensitivity = 80.8%, specificity = 73.8%, PPV = 95.5%, NPV = 75.9%).[33] Grenier and coworkers reported similar results with sensitivities and specificities for helical CT of 87% and 95%, respectively, versus 65% and 94% for V/Q scintigraphy.[51] Many believe these results are sufficient justification for CTPA to replace V/Q scintigraphy in the diagnostic algorithm for suspected acute PE.[52]

In the PIOPED II study, the overall sensitivity, specificity and predictive values of CTPA for the diagnosis of PE are comparable with V/Q scintigraphy when there is a high probability scan result, the latter being associated with a greater than 85% likelihood of PE, and low probability results equate to a <20% likelihood of PE.[2] Furthermore, data from the PIOPED II study showed that with the exclusion of patients with intermediate or low probability, the sensitivity of a high probability (PE present) scan finding was 77.4% (95% CI 69.7-85.0%), whereas the specificity of very low probability or normal (PE absent) scan finding was 97.7% (95% CI 96.4-98.9%).[53] The percentage of patients with a PE present and PE absent scan finding was 73.5% (95% CI 70.7-76.4%).[53] Another study based on data from PIOPED II also showed that very low probability lung scans (defined as <10% PPV) in combination with low probability objective clinical assessment reliably excludes PE.[54]

In PIOPED II, the positive predictive value of a positive MDCT pulmonary angiogram was only 58% when clinical probability was low and the negative predictive value of a negative MDCT pulmonary angiogram was only 60% when clinical probability was high.[3] Very similar results were found in PIOPED I for the V/Q scan which showed a positive predictive value of 56% when such discordance was present.[2]

CT Versus Pulmonary Angiography

Helical CT has also shown that catheter pulmonary angiography is not as accurate as once thought, is particularly poor for evaluation of the small pulmonary arteries, and is an imperfect gold standard or reference test. Baile and coworkers[55] compared CTPA with catheter pulmonary angiography for the detection of subsegmental-sized PE using postmortem methacrylate casts of the pulmonary arteries as the reference test in 16 pigs. Methacrylate beads measuring 3.8 and 4.2 mm inserted into the pulmonary arteries via the jugular vein were used to simulate emboli. Afterward, both CT and catheter pulmonary angiography were performed. The sensitivity for 3-mm collimation helical CT was 82% (95% CI 73-88%), 1-mm collimation helical CT 87% (95% CI 79-93%), and catheter angiography 87% (95% CI 79-93%) ($P = 0.42$).[55] Not only was there no difference between CT and catheter angiography, with the authors concluding that CTPA is comparable with angiography for detection of pulmonary emboli, but catheter angiography was only 87% sensitive (not 100%).[55] In studies that evaluate the accuracy of CTPA using catheter angiography as the reference test, this should be kept in mind. If the CT is positive and the catheter angiogram negative, which is correct? If the angiogram is presumed correct, then a false-positive result is assigned to the CT, when in fact in reality it may really be a false-negative catheter angiogram. When looking at the smaller pulmonary arteries, particularly the subsegmental vessels, there is considerable interobserver disagreement as to the presence or absence of an embolism at pulmonary angiography.[2]

More recently, a retrospective evaluation of the causes of discordant CTPA and conventional pulmonary angiographic readings from the PIOPED II study found that at angiography there was one false-positive examination and 13 false-negative examinations.[56] At CT, there were 2 were false-negative examinations. Four studies that were true-negative at CT became positive for thrombus by the time of angiography. This gave sensitivities for detection of PE of 87% for CT and 32% for angiography ($P = 0.007$).[56]

Interobserver Agreement

Computed Tomography

On a per-patient basis, CTPA interobserver agreement for the detection of acute PE is moderate to almost perfect, with kappa values ranging from 0.59 to 0.94.[29,33,35,38,39,41,51,57-62] Chartrand-Lefebvre and coworkers showed excellent overall interobserver agreement ($k = 0.85$) and intraobserver agreement ($k = 0.87$).[57] Interobserver agreement was also better in larger vessels, with interobserver agreement at the lobar level ($k = 0.70$) than at the segmental level ($k = 0.47$).

Ruiz and coworkers using single-detector CT with 3-mm collimation compared with catheter pulmonary angiography have shown that CTPA yielded kappa values for the main, lobar, segmental, and subsegmental pulmonary arteries of 0.91, 0.78, 0.56, and 0.21, respectively.[62] In a larger group of 299 patients, Perrier and coworkers using single-detector CT at 3-mm collimation, reported almost perfect interobserver agreement ($k = 0.82$-0.90).[35] Thinner collimation improves interobserver agreement, with a kappa value of 0.98 using 2-mm collimation versus 0.94 with 3-mm collimation ($P < 0.05$).[29]

MDCT

Patel and coworkers showed that MDCT with thin collimation (1.25-mm) significantly improved visualization of segmental and subsegmental arteries and improved interobserver agreement in detection of PE compared with single detector CT,[31] as did Raptopoulos and coworkers.[63] Schoepf and coworkers showed that, when using MDCT, interobserver agreement was substantially better with the use of thinner collimation (1-mm and 2-mm sections) than with the use of thicker (3-mm sections).[64]

CT Versus V/Q Scintigraphy

There is considerable inter- and intraobserver variability in the interpretation of V/Q scintigraphy for PE, with poor intraobserver and interobserver agreement ranging from $k = 0.22$ to 0.61.[33,39,43,51,65] Despite modifications of interpretation schemes, there has been no significant improvement in interobserver agreement.[66] Significantly better interobserver agreement ranging from $k = 0.72$ to 0.85 has been reported with CT.[33,39,43,51]

CT Versus Pulmonary Angiography

Pulmonary angiography is less accurate than previously thought, particularly at the subsegmental level.[55] Although interobserver agreement for the central arteries is 89%, it is only 13% to 66% for the subsegmental arteries.[67-69] Qanadli and coworkers found that interobserver agreement was slightly better for CT ($k = 0.78$-0.94) than selective pulmonary angiography ($k = 0.67$-0.89) in 158 patients.[41]

Indirect CTV

Imaging

In 90% of patients with PE the source of the emboli is the lower-extremity veins (ie, DVT). CTV can be combined with CTPA without requiring any additional intravenous contrast material. Performing CTPA combined with CTV was first described by Loud and coworkers in 1998.[70] The same authors subsequently assessed CTV in 71 patients, 19 of whom had DVT revealed on CTV.[71] Several studies in which single-detector and MDCT angiography were used have shown that the addition of CTV to the CTPA examination increases the percentage of patients requiring anticoagulation by 5-27%.[72-78] A further advantage of CTV is the ability to evaluate the pelvic and abdominal veins not always assessable to ultrasound, specifically the inferior vena cava and iliac veins. Indirect CT venography may be performed as contig-

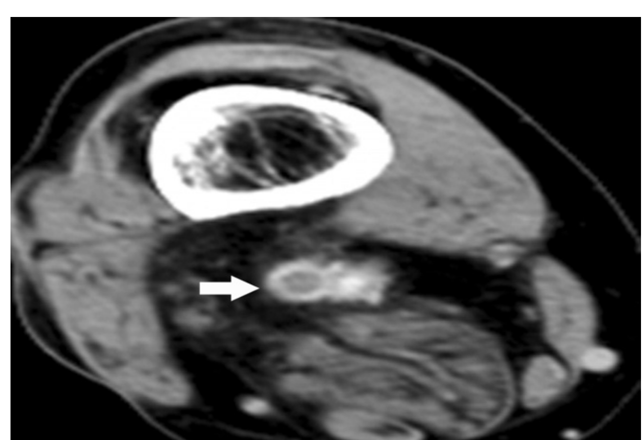

Figure 6 A 69-year-old woman with acute right deep venous thromboses.

uous helical imaging or discontinuous CT imaging of the lower extremities for the detection of DVT (Fig. 6).[79]

Accuracy

The sensitivity of CTV ranges from 71% to 100%, specificity 94% to 100%, PPV 67% to 100% and NPV 97% to 100%.[52,71,74,80-87] When CTV is compared with sonography or conventional venography, the weighted average sensitivity is 94.5% and specificity is 98.2%. In a large multicenter study using CTPA and CTV in 541 patients, DVT was present in 8% of patients. DVT was correctly identified on CTV but was missed on sonography in 4 patients; there were no false-negative CTVs.[81] The PIOPED II researchers concluded that, in patients with suspected PE, multidetector CTPA with CTV had a greater diagnostic sensitivity than CTPA alone, with similar specificity.[3]

CTV with CTPA compared with CTPA alone did not significantly increase the PPVs, 96% CTPA with CTV to 96% CTPA without CTV with a concordantly high probability on clinical assessment or NPVs, 96% CTPA with CTV to 97% CTPA without CTV with a concordantly low probability on clinical assessment.[3] The combination did increase NPVs slightly from 89% CTPA with CTV to 92% CTPA without CTV with an intermediate probability on clinical assessment, but increased NPVs significantly from 60% CTPA with CTV to 82% CTPA without CTV if there was a discordant high clinical probability.[3] However, the combination decreased PPVs values slightly from 92% CTPA with CTV to 90% CTPA without CTV with an intermediate probability on clinical assessment, and decreased slightly from 58% CTPA with CTV to 57% CTPA without CTV if there was a discordant low clinical probability.[3]

Interobserver Agreement

Over all, interobserver agreement for DVT on CT venography is moderate to almost perfect with kappa values of 0.56 to 0.88.[74,80,81] When the use of CTV is compared with sonography or conventional venography, there is moderately good to almost perfect interobserver agreement, with kappa values of 0.59 to 0.88 reported.[60,74,83]

Clinical Outcome After a Negative CTPA

When PE is diagnosed by CTPA, specificity is high. Therefore, a positive diagnosis of PE on CT is usually accepted. Several studies have reported that a negative CT pulmonary angiogram for PE is comparable to a negative catheter pulmonary angiogram in terms of patient outcome.[26,30,33,43,88-100] Thus, in most patients with suspected acute PE and no symptoms, anticoagulation therapy can be safely withheld after negative CTPA.

V/Q Scintigraphy

Recently, Gottschalk and coworkers[54] evaluated the positive predictive value of a very low probability interpretation of ventilation/perfusion lung scan using data from the PIOPED II study, finding an 8.2% PPV for very low probability V/Q scans. Furthermore, among patients with suspected PE and both a low clinical probability objective clinical assessment and a very low probability V/Q scan result, the PPV was 3.1% overall, and 2% for women 40 years of age and younger. The authors concluded that very low probability V/Q scan together with a low probability clinical assessment reliably excludes PE.

CT Versus Catheter Pulmonary Angiography

After a negative catheter angiogram, fewer than 2% of patients develop PE. Two published series of 380 and 167 patients after a negative catheter pulmonary angiogram reported a 1.6% and 1.7% incidence of PE over the next 6 to 12 months.[101,102] However, similar results have been reported after a negative CTPA, for a total of 4233 patients with a weighted average incidence of 1.3% for venous thrombotic disease and 0.4% for fatal PE.[26,30,33,43,71,74,80-100] In a recent meta-analysis of 15 studies that used contrast 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 and coworkers reported that the clinical validity of using a CT scan to rule out PE is similar to that reported for conventional pulmonary angiography.[103]

Radiation Exposure From CTPA

Computed Tomography

Using an anthropomorphic phantom, Resten and coworkers reported 6.4 ± 1.5 mSv as the mean dose for single-detector CTPA.[104] Rademaker and coworkers using a single-detector CT scanner calculated the radiation dose to be approximately 2.2 mSv for the chest.[105]

MDCT

In most protocols for helical 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.[106] In a study by Kuiper and coworkers, the average effective dose for 4-row multidetector CTPA was 4.2 mSv.[107] In PIOPED II, the radiation dose to the chest using 16 and 64 detector CT scanners was estimated to be 3.8 mSv. More recently, Hurwitz and coworkers[108] reported the radiation dose from a 64-detector CTPA protocol with an anthropomorphic female phantom to be 19.9 ± 1.38 mSv. They also estimated that the lifetime attributable risk (LAR) of lung cancer ranged from 38 excess cases per 100,000 in 55-year-old men or 51 excess cases per 100,000 in 25-year-old men to 86 excess cases per 100,000 in 55-year-old women or 118 excess cases per 100,000 in 25-year-old postpartum women. In addition, the LAR of breast cancer ranged from 20 excess cases per 100,000 in 55-year-old women or 503 excess cases per 100,000 in 25-year-old postpartum women.[108] Although radiation exposure is greater with the use of MDCT, the benefit of MDCT is improved visualization of the segmental and subsegmental pulmonary arteries and greater accuracy for PE diagnosis.[109]

Indirect CTV

CTV has the limitation of additional radiation dose, add Doppler ultrasound should be considered in younger patients. Estimates of pelvic radiation vary considerably according to the specific CTVprotocol used. In PIOPED II, subjects underwent continuous helical CT scanning from the iliac crest to the tibial plateau.[3] The calculated radiation doses to the pelvis, and thighs were 6.0, and 3.2 mSv, respectively.[110] Rademaker and coworkers using a single-detector CT scanner calculated the radiation dose to be approximately 2.5 mSv for the pelvis. Kalva and colleagues showed that the effective radiation dose for CTVwas 5.2 mSv ± 0.5 SD for the pelvis and 0.6 mSv ± 0.2 SD for the lower extremities, and suggested that CTV could be limited to the lower extremities to reduce overall radiation dose.[111]

Goodman and coworkers, using data from 150 PIOPED II subjects, compared whether discontinuous incremental CT of the lower extremities with skip areas between images is as accurate as contiguous helical scanning for the detection of DVT. They found that there was agreement for the presence of DVT in at least one leg (same leg) or for the absence of DVT in both legs in 133 of the 150 study patients (89%). The authors concluded that although there was good agreement between continuous helical and discontinuous axial imaging for the detection of DVT, given the interobserver and intraobserver variation, there appeared to be little difference between the 2 approaches, supporting the use of adopting discontinuous imaging as a dose-reduction strategy.

CT Versus V/Q Scintigraphy

Young women represent a large segment of the population undergoing CTPA for suspected PE, as pointed out in the recent American College of Radiology white paper on radiation dose.[112] Breast radiation estimates using 4-detector CT vary from 20 to 60 mSv[105,113,114] compared with approximately 0.28 to 0.9 mSv for V/Q scintigraphy.[115] Einstein and coworkers estimated that 64-detector thoracic CTA delivers a breast dose of 50 to 80 mSv.[116] The estimated radiation exposure from CTPA suggests a non-negligible increase in LAR of breast cancer, that is as high 1 in 143 for a 20-year-old woman and 1 in 284 for a 40-year-old woman.[116] The lifetime risk of breast carcinoma has been estimated to increase by 14% above the background rate after a single 10-mGy dose to the breast in a 35-year-old woman.[117] Hurwitz and coworkers estimated that, for a 64-detector CTPA protocol using an anthropomorphic female phantom for breast cancer, the LAR ranged from 20 excess cases per 100,000 in 55-year-old women to 133 excess cases per 100,000 in 25-year-old women postpartum.[107]

In pregnant women with suspected PE, a high percentage of studies are negative. For example in a prospective study of 120 pregnant women undergoing V/Q scintigraphy with suspected PE, 74% were normal, 24% were low/intermediate probability results, and only 2% were high-probability scans.[118] CTPA imparts a substantially greater maternal radiation exposure than scintigraphy,[113,114,117] and the latent carcinogenic effects of irradiating radiosensitive, proliferating maternal breast tissue could place patients at increased risk. In pregnancy, concern over fetal radiation exposure is paramount, and it is common practice to perform half-dose perfusion scintigraphy, without a ventilation study.[119] This imparts a lower fetal dose than standard lung scintigraphy. However, in pregnant patients, the mean fetal dose with single-detector CT has been reported as less than that for V/Q scanning at varying gestational ages: 100 to 370 mGy for V/Q scanning versus 3.3 to 20.2 mGy (first trimester), 7.9 to 76.7 mGy (second trimester), and 51.3 to 130.8 mGy (third trimester) for CT, doses well below that considered safe for fetal exposure.[120]

CT Versus Pulmonary Angiography

Resten and coworkers also reported that average radiation dose for single-detector CTPA of 6.4 ± 1.5 mSv is 5times smaller than the 28 ± 7.6 mSv for catheter digital subtraction pulmonary angiography.[104] For 4-detector CTPA Kuiper and coworkers reported the average effective dose was 4.2 mSv for CT compared with 7.1 mSv for digital subtraction angiography.[106]

Preference

In a recent survey of imaging practices for diagnosing acute PE among physicians practicing in the United States that explored factors associated with practice decisions Weiss and coworkers surveyed 855 physicians selected at random from membership lists of 3 professional organizations (general internists, pulmonologists, and emergency medicine specialists) by mail.[121] Completed questionnaires were received from 29.8% participants practicing in 44 states. The authors found that 86.7% of respondents believed that CTPA was the most useful imaging procedure for patients with acute PE compared with 8.3% for V/Q lung scintigraphy and 2.5% for conventional pulmonary angiography.[121] After chest radiography, CTPA was the first imaging test requested 71.4% of the time compared with 19.7% for V/Q scintigraphy and 5.8% for lower-limb venous ultrasound. Participants reported that they received indeterminate or inconclusive results 46.4% of the time for V/Q scintigraphy, 10.6% of the time for CTPA, and 2.2% of the time for conventional pulmonary angiography.[121] With respect to availability, 88.3% of participants reported that CTPA was available around the clock versus 53.8% for V/Q scintigraphy and 42.5% for conventional pulmonary angiography. 68.6% of respondents reported that they received CTPA results in 2 hours or less versus 37.5% for V/Q scintigraphy and 22.9% for conventional pulmonary angiography.[121] CTPA was also reported to provide an alternate diagnosis to PE or showed other significant abnormalities 28.5% of the time, and these findings frequently altered management. The authors of this study concluded that US clinicians unequivocally prefer CTPA in patients with suspected acute PE. Reasons for this preference

Figure 7 A 28-year-old man with isolated right lower lobe posterior basal segmental pulmonary embolus (arrow).

included availability and timely reporting, a lower rate of inconclusive results, and the additional diagnostic capabilities that CTPA can provide.[121]

Isolated Subsegmental PE

Although subsegmental PE in the absence of segmental or larger PE may indicate the harbinger of DVT that has not yet embolized, there is uncertainty as to whether treatment of these small emboli results in any improvement in clinical outcome, particularly if lower extremity ultrasound is negative. Anticoagulation is not without complications, including a 5% incidence of major bleeding that is even higher in postoperative and elderly patients (Fig. 7).[122]

With the advent of MDCT, small peripheral PE that may have previously gone undetected may now have become apparent. With the advent of 64-detector CT systems, detection will likely improve further. The prevalence of PE involving only the subsegmental pulmonary arteries was 6% at catheter angiography in PIOPED I[123]; other reports vary from 10% to 36%.[34,68] Coche and coworkers[43] in a prospective study of outpatients examined with 4-detector MDCT found isolated subsegmental PE in 4.2% of patients. In a recent retrospective review of the radiology reports on 1435 consecutive patients who were examined with 8- and 16-detector MDCT scanners, 5.4% of patients had isolated subsegmental PE without DVT.[124] Because the deep veins of the pelvis and lower extremities are the most frequent source of PE, many CTPA examinations include indirect CTV for the detection of DVT.[70] A CT that is negative for DVT makes it less likely that a small PE has been overlooked on CTPA, while a positive CT for DVT indicates that anticoagulation is indicated, whether or not PE is present or absent.

Since anticoagulation was rapidly accepted into clinical practice, at a time when diagnoses were crude and isolated small PE were rarely diagnosed, a true understanding of the consequences of small PE is difficult. There has been only one randomized control trial of anticoagulation in the modern diagnostic era, in which the recurrence and mortality rates among patients with proven VTE treated and not treated with anticoagulation therapy were compared. Nielsen and coworkers showed that at 3 months after diagnosis, 44% of patients in each group developed progressive VTE, either DVT or PE.[125] This would suggest that anticoagulation did not alter the course of VTE. There were no deaths among the 43 nonanticoagulated patients, despite progressive VTE in 19 of them. One patient undergoing anticoagulation therapy died.[125] General autopsy studies have shown evidence of PE in 51-90% of patients when there is careful examination of the pulmonary arteries suggesting that many patients with small PE are not suspected clinically premortem.[125-127]

Swensen and coworkers[128] have studied the outcome of patients with suspected acute PE in whom CT findings were negative for PE who did not receive anticoagulation, finding that the incidence of DVT, PE, and fatal PE is low. In a meta-analysis of 23 studies reported on 4657 patients with a negative CTPA who did not receive anticoagulation, the 3-month rate of subsequent venous thromboembolic events was 1.4%, and fatal PE was 0.51%.[129] These studies suggest that withholding anticoagulation in these patients is safe.

Although prospective studies withholding anticoagulation from patients with isolated subsegmental PE in the absence of DVT have not been performed, there is some evidence that withholding anticoagulation therapy in patients with isolated subsegmental PE in the absence of DVT may not be harmful. In PIOPED I, 20 patients who had negative catheter pulmonary angiography results at their local hospital and therefore did not receive anticoagulation therapy were subsequently found to have PE by expert panel review of the pulmonary angiograms.[2] For these patients, the PE fatality rate was 2.5% and recurrence rate 3.5%, comparable with patients in PIOPED I who received anticoagulation therapy.[2,125] These 20 nontreated patients had a limited clot burden, with PE in only the segmental or subsegmental arteries in 84%. Eyer and coworkers reported that 37% of patients with isolated subsegmental PE and 85% of patients with inconclusive MDCT results did not receive anticoagulation, with primary care physicians choosing in 32% the patients to treat with anticoagulation. Two patients in each subgroup returned with signs and/or symptoms of PE, but all of the patients had negative repeat imaging results.[124]

In 1994, Hull and coworkers proposed that anticoagulation was not required in patients with adequate cardiopulmonary reserve and nondiagnostic V/Q scans, if serial studies of the lower extremities were normal.[130] Wells and coworkers proposed a similar strategy.[131] There appear to be subsets of patients with small or questionable PE in whom the risks associated with anticoagulation may outweigh the benefits, including (1) symptomatic patients who have PE limited to the subsegmental vessels, no DVT, and adequate cardiopulmonary reserve; (2) patients with indeterminate MDCT or V/Q scanning results, no DVT, and adequate cardiopulmonary reserve[124,130,131]; (3) asymptomatic patients with incidentally discovered small PE, no DVT, and adequate cardiopulmonary reserve; and (4) patients with contraindications to anticoagulation, isolated subsegmental PE or indeterminate MDCT results, and no DVT.[125,132,133] All of these scenarios have central to them isolated subsegmental PE or indeterminate MDCT results, and no DVT plus other features.

Assuming that 5% of the 657,000 patients in the United States tested for suspected PE[2] have isolated subsegmental PE without DVT yields 32,850 patients. If we assume a 3% rate of major bleeding (ie, cerebrovascular accident, retroperitoneal hematoma, etc.) secondary to warfarin therapy with a mortality rate of 0.5% at 3 months for patients with a well controlled INR,[134] and a 1-year mortality rate of 1% and morbidity rate of 7% in less well controlled patients,[135] and that all patients received anticoagulation, there would be 165 to 330 deaths and 986 to 2300 major bleeding complications from treating patients with isolated subsegmental PE and no DVT.

There is no clear consensus as to whether patients with isolated subsegmental PE without DVT should be treated with anticoagulation, with the decision to treat based on physician preference, clinical suspicion and other test results. Therefore, it is extremely important to know if the risk of developing a life-threatening PE in a patient with isolated subsegmental PE without DVT is greater than the risk of major complication from treating with anti coagulation.

CT Evaluation of Right Ventricular (RV) Dysfunction

The prognosis and optimal therapy in patients with PE are strongly influenced by the presence or absence of hemodynamic compromise. The main cause of death within 30 days from acute PE is RV failure (Fig. 8). Recent evidence indicates that the presence of RV dysfunction identifies a subgroup of normotensive patients with a much more guarded prognosis than patients without RV impairment. Rapid risk stratification is paramount for identifying high-risk patients and helps select the appropriate management strategy. Patient may benefit from intensive therapy with thrombolytic agents or surgery (embolectomy).[136,137] Thrombolysis, catheter intervention, or surgical embolectomy as adjuncts to anticoagulation may rapidly reverse RV failure and reduce the risk of recurrence and death. Reperfusion therapy is indicated in patients with cardiogenic shock and may be considered in selected patients with preserved systemic pressure and RV dysfunction.[138]

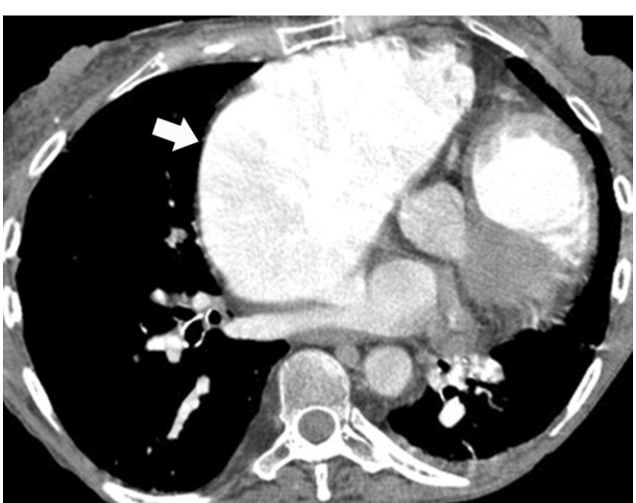

Figure 8 A 72-year-old woman with pulmonary embolism, marked right heart enlargement due to right heart strain (arrow).

ECG-Gated CTA of the Chest

There are a few of reasons that using ECG-gating during CTPA may be useful. An objective assessment of RV function could help stratify patients with RV dysfunction and guide certain therapeutic decisions. Also, 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.[109,138] In general, the use of ECG-gating adds additional radiation exposure.

PIOPED II

The results of the multicenter PIOPED II study, funded by the National Heart, Lung and Blood Institute, were published in June 2006.[3] PIOPED II was designed to evaluate the accuracy of MDCT for PE. Patient recruitment began September 2001, with a goal of recruiting 1068 patients. All centers used as a minimum level of technology 4-detector MDCT scanners, and as they acquired scanners with more detector-rows, used those scanners so that the trial results incorporated the best available CT technology and not technology that was many years old when published.

Excluding inconclusive studies, the sensitivity of CTPA was 83% and specificity 96%.[3] Positive predictive values were 96% with a concordantly high or low probability clinical assessment, 92% with an intermediate probability clinical assessment, and nondiagnostic if the clinical probability was discordant.[3] The sensitivity of CTPA in combination with CTV was 90%, and specificity 95%.[3] CTPA in combination with CTV was also nondiagnostic with a discordant clinical probability.[3] The authors concluded that, in patients with suspected PE, MDCTPA in combination with CTV has a greater diagnostic sensitivity than CTPA alone, with similar specificity. The predictive value of either CTPA or CTPA in combination with CTV is high with a concordant clinical assessment, but additional testing is necessary when the clinical probability is inconsistent with the imaging results.[3]

On the basis of data from the PIOPED II trial, the authors developed recommendations for the diagnostic pathways in acute PE.[139,140] The choice of diagnostic tests depends on the clinical probability of PE, condition of the patient, availability of diagnostic tests, risks of iodinated contrast material, radiation exposure and cost. The recommendations are based on probability of PE (low, intermediate, or high) on clinical assessment.[139,140]

Recommendations for Patients With Low-Probability Clinical Assessment

In patients with a low-probability clinical assessment (based on the empirical method, Wells model [extended or simplified], or Geneva score [revised]), a D-dimer rapid enzyme-linked immunoassay (ELISA) is recommended. No further testing is required if D-dimer is normal.[139,140] If the D-dimer result is positive, CTPA with CTV is recommended. CTV of only the femoral and popliteal veins is recommended to reduce radiation exposure. If CTPA or CTPA with CTV results are negative, treatment is not necessary.[139,140] With main or lobar pulmonary emboli at CTA, treatment is indicated. With segmental or subsegmental pulmonary emboli, the certainty of the CT diagnosis should be evaluated. CTPA or CTPA with CTV should be repeated if image quality is poor. In patients with segmental or subsegmental pulmonary emboli, either pulmonary scintigraphy, a single or serial venous ultrasound examination if only CTPA was performed and pulmonary digital subtraction angiography are optional.[139,140]

Recommendations for Patients With Moderate-Probability Clinical Assessment

In patients with an intermediate probability clinical assessment, the PIOPED II investigators recommend a D-dimer rapid ELISA. If the D-dimer rapid ELISA result is negative, no further testing is necessary, and either venous ultrasound or MRV are considered optional.[139,140] If the D-dimer result is positive, CTPA with CTV is recommended.[139,140] Treatment with anticoagulants while awaiting the outcome of diagnostic tests may be appropriate, particularly if the tests cannot be performed immediately. If either CTPA or CTPA with CTV results are negative, no treatment is necessary; venous ultrasound is recommended if only the CTPA was performed. If either CTPA or CTPA with CTV results are positive, treatment is recommended. With segmental or subsegmental pulmonary emboli, the certainty of the CT diagnosis should be re-evaluated, and options should be followed according to recommendations for patients with a low probability clinical assessment.[139,140]

Recommendations for Patients With High-Probability Clinical Assessment

In patients with a high-probability clinical assessment, D-dimer testing need not be performed because a negative D-dimer result in a patient with a high probability clinical assessment may not exclude PE. The patient should be treated with anticoagulants while they await the outcome if diagnostic tests. The PIOPED II investigators recommend the use of CTPA with CTV. If CTPA results are negative and CTV was not performed or was technically inadequate, venous ultrasound or MR venography examination is recommended. If either CTPA or CTPA with CTV results are negative, other options include serial venous ultrasound examinations, pulmonary digital subtraction angiography, and pulmonary scintigraphy. If either CTPA or CTPA with CTV results are positive, treatment is recommended.[139,140]

CTV

The PIOPED II study also evaluated the clinical value of CTV after multidetector CTPA with venous compression sonography for the diagnosis of VTE. The PIOPED II investigators found 95.5% concordance between CTV and sonography for the diagnosis or exclusion of DVT, with high interobserver agreement (kappa = 0.81).[141] The sensitivity and specificity of combined CTPA and CTV were equivalent to those of combined CTPA and sonography. Diagnostic results in subgroups, including patients with signs or symptoms of DVT, asymptomatic patients, and patients with a history of DVT, were similar whether CTV or sonography was used.[141] Patients with signs or symptoms of DVT were eight times more likely to have DVT, and patients with a history of DVT were twice as likely to have DVT. The PIOPED II investigators concluded that CTV and sonography showed similar results in diagnosing or excluding DVT. The incidence of positive studies in patients without signs, symptoms or history of DVT is low.[141] In terms of clinical significance, CTV and lower extremity sonography yield equivalent diagnostic results; the incidence of positive studies in patients without signs, symptoms, or history of DVT is low; thus the choice of imaging technique can be made on the basis of safety, expense, and time constraints.[141]

V/Q Lung Scintigraphy

The PIOPED II investigators evaluated the sensitivity and specificity of V/Q scintigraphic studies categorized as PE present or absent.[53] When excluding patients with intermediate- or low-probability results, the sensitivity of a high probability (PE present) scan finding was 77.4% (95% CI 69.7-85.0%). The specificity of very low probability or normal (PE absent) scan finding was 97.7% (95% CI 96.4-98.9%).[53] The percentage of patients with a PE present or PE absent scan finding was 73.5% (95% CI 70.7-76.4%). The PIOPED II investigators concluded that in a population similar to that in PIOPED II, results of V/Q scintigraphy can be diagnostically definitive in a majority of patients; thus, it can be considered an appropriate pulmonary imaging procedure in patients for whom CTPA may be disadvantageous.[53] Further research has also shown that among patients with suspected PE who had a low clinical probability objective clinical assessment and a very low probability V/Q scan ($<10\%$ probability of PE), the positive predictive value was 3.1%, and concluded that the very low probability V/Q scan together with a low probability clinical assessment reliably excludes PE.[54]

CTPA and Catheter Angiography

A study using PIOPED II data reviewed the all 20 discordant CTPA and catheter angiographic readings.[56] They determined that there was 1 false-positive and 13 false-negative catheter angiograms and 2 false-negative CTPA examinations.[56] There were 4 patients with true-negative CTPA exams but positive catheter angiograms. The largest missed thrombus at angiography was subsegmental in 8 patients, segmental in 2 patients, and lobar in 3 patients; at CT, it was subsegmental in 2 patients. The sensitivity for the detection of PE was 87% for CT and 32% for angiography (P = 0.007).[56] The mean time between CTPA and catheter angiography was 40 hours ± 21.[56] Although, there were no specific recommendations the authors concluded that in the interval between CT and catheter angiography, thrombi can remain the same, resolve, develop, or result from angiography.[56]

Clinical and Patient Characteristics

Clinical and patient characteristics of patients with acute PE enrolled in PIOPED II were evaluated.[142,143] Patients may present with dyspnea on exertion only. The onset of dyspnea is usually, but not always, rapid. Orthopnea may occur.[142] In patients with PE in the main or lobar pulmonary arteries, dyspnea or tachypnea occurred in 92%, with the largest PE was in the segmental pulmonary arteries in only 65%.[142] In general, signs and symptoms were similar in elderly and younger patients, but dyspnea or tachypnea was less frequent in elderly patients with no previous cardiopulmonary disease. Dyspnea may be absent even in patients with circulatory collapse.[142] Patients with a low-probability objective clinical assessment sometimes had PE, even in proximal vessels. Overall, the PIOPED II investigators concluded that symptoms may be mild, and generally recognized symptoms may be absent, particularly in patients with PE only in the segmental pulmonary branches, but they may be absent even with severe PE.[142] A high or intermediate-probability objective clinical assessment suggests the need for diagnostic studies, but a low-probability objective clinical assessment does not exclude the diagnosis, and maintenance of a high level of suspicion is critical.[142] The PIOPED II investigators also found that the sensitivity and specificity for PE for groups of patients aged 18 to 59, 60 to 79, and 80 to 99 years were not statistically significantly different, and nor were there statistically significant differences according to gender.[143] The specificity of CTPA was somewhat greater in women, but was ≥93% in both men and women. They concluded that the results indicate that multidetector CTPA and CTPA with CTV may be used with various diagnostic strategies in adults of all ages and both sexes.[143]

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