

Imaging of Pulmonary Thromboembolism

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Pulmonary thromboembolism (PE) is the third most common cardiovascular disease after myocardial infarction and stroke [1]. It is also one of the most controversial disorders, with ongoing debate as to the best approach for diagnosis and the best means of treatment.

PE is not a single entity. Approximately 90% of all pulmonary thromboemboli originate from deep veins of lower extremities [2]. Together, deep venous thrombosis (DVT) and pulmonary embolism constitute venous thromboembolism. The older literature states that when untreated, PE is fatal in 30% of patients. With better imaging able to diagnose smaller pulmonary thromboemboli, it is likely that 10% is a more realistic rate [3].

Fatality rates fall to 2% to 10% with proper diagnosis and treatment with anticoagulants [4–7]. Nevertheless, anticoagulant therapy has serious risks, including hemorrhage. Therefore, false-positive diagnosis must be kept to a minimum. Because clinical symptoms and laboratory findings of PE are nonspecific and seldom provide definitive diagnosis, the diagnosis relies on imaging methods. Chest radiography, ventilation/perfusion (V/Q) scan, venous Doppler ultrasound of the lower extremities, and pulmonary angiography have been used frequently. Chest radiographic findings are nonspecific and V/Q scans are often not definitive. Pulmonary angiography, still considered the “gold standard,” is invasive, time consuming, and underutilized.

With the introduction of helical CT in the early 1990s, direct visualization of PE became possible. Advances in CT technology have made CT pulmonary angiography (CTA) the most frequently used

diagnostic method for PE in recent years [8]. MRI also provides direct imaging of PE; however, its value in large patient populations has not been tested and its use in critically ill patients is somewhat limited.

Chest radiography

Chest radiography is the first-line imaging method in the evaluation of PE. The most commonly seen findings of PE on chest radiographs are atelectasis, small pulmonary opacities, and pleural effusion [9,10]. Hampton’s hump is a peripheral wedge-shaped, pleural-based parenchymal density representing a pulmonary infarct. This pleural-based parenchymal density may also be seen in other diseases such as pneumonia and septic pulmonary emboli. Westermark’s sign refers to reduction in size of occluded pulmonary arteries. It is sometimes difficult to recognize this sign unless the patient has comparison films (Fig. 1A, B). This finding is also nonspecific and may be seen in emphysema or old infections. Another sign is the enlargement of a major arterial trunk at the hilum. None of these three signs is seen frequently.

The chest radiographic signs of PE are all nonspecific [11]. Patients who have PE often have normal chest radiographs. Further investigation with other imaging methods is mandatory. The role of the chest radiograph in evaluation of PE is to rule out other disease processes such as pneumothorax or pneumonia, which can mimic symptoms of PE, and to guide V/Q scanning.

Ventilation/perfusion scanning

PE is recognized as one or several perfusion defects on perfusion scans (Fig. 2). Because there

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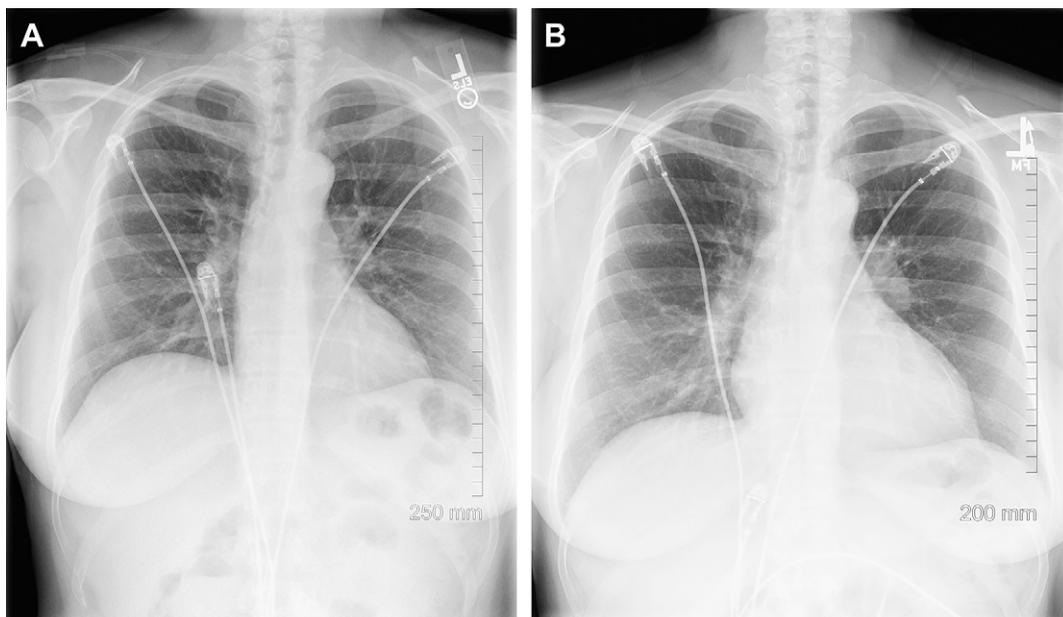


Fig. 1. Forty-five-year-old woman. Figs. 1–4 and 6 are from the same patient. (A) Initial chest radiograph from prior admission was normal. (B) Subsequent chest radiograph demonstrates reduced size of segmental and subsegmental pulmonary arteries in both upper lobes and the left lower lobe (Westermark's sign). The central pulmonary arteries are slightly increased in size.

are many causes of perfusion defects other than PE, such as obstructive airway disease, pneumonia, atelectasis, edema, and vasculitis, ventilation scans have been added to the perfusion scan to increase the specificity. Perfusion defects with normal ventilation strongly suggest PE.

V/Q scans are interpreted as negative, low, intermediate, and high probability. A normal V/Q scan essentially excludes the diagnosis of PE, and a high probability V/Q scan has a 96% positive predictive value in high-risk patients according to the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) data [12]. It is unfortunate that most of the V/Q scans (60%–70%) are interpreted as low or intermediate probability and are nondiagnostic [12–14]. When the chest radiograph is normal, however, as many as 80% to 90% of studies are definitive [15].

Pulmonary arteriography

On invasive pulmonary arteriography, emboli are seen as complete obstruction, intraluminal filling defects, or a decrease in flow rate [16]. For many years, pulmonary arteriography has been accepted as the gold standard and the most sensitive and specific method available for diagnosis of

PE. Pulmonary arteriography, however, is invasive, expensive, time-consuming, may not be readily available, and has complications. Accurate statistics for morbidity and mortality are difficult to obtain. In recent studies, the morbidity of pulmonary arteriography has been shown to be 1% and mortality was absent [17]. Many clinicians still have the exaggerated perception that pulmonary arteriography has moderate to high morbidity and mortality. There is no generally accepted indication for pulmonary arteriography, although it has been recommended as part of the workup for patients who have nondiagnostic scintigraphy. After the introduction of CTA, the role of conventional pulmonary arteriography has been questioned further. It is used significantly less frequently. Many investigators now question whether pulmonary arteriography should remain the gold standard [18,19].

Transesophageal echocardiography

Central pulmonary emboli are directly visualized with transesophageal echocardiography. Peripheral emboli are not imaged. Right ventricular overload can also be evaluated, which is important in assessment of the patient's

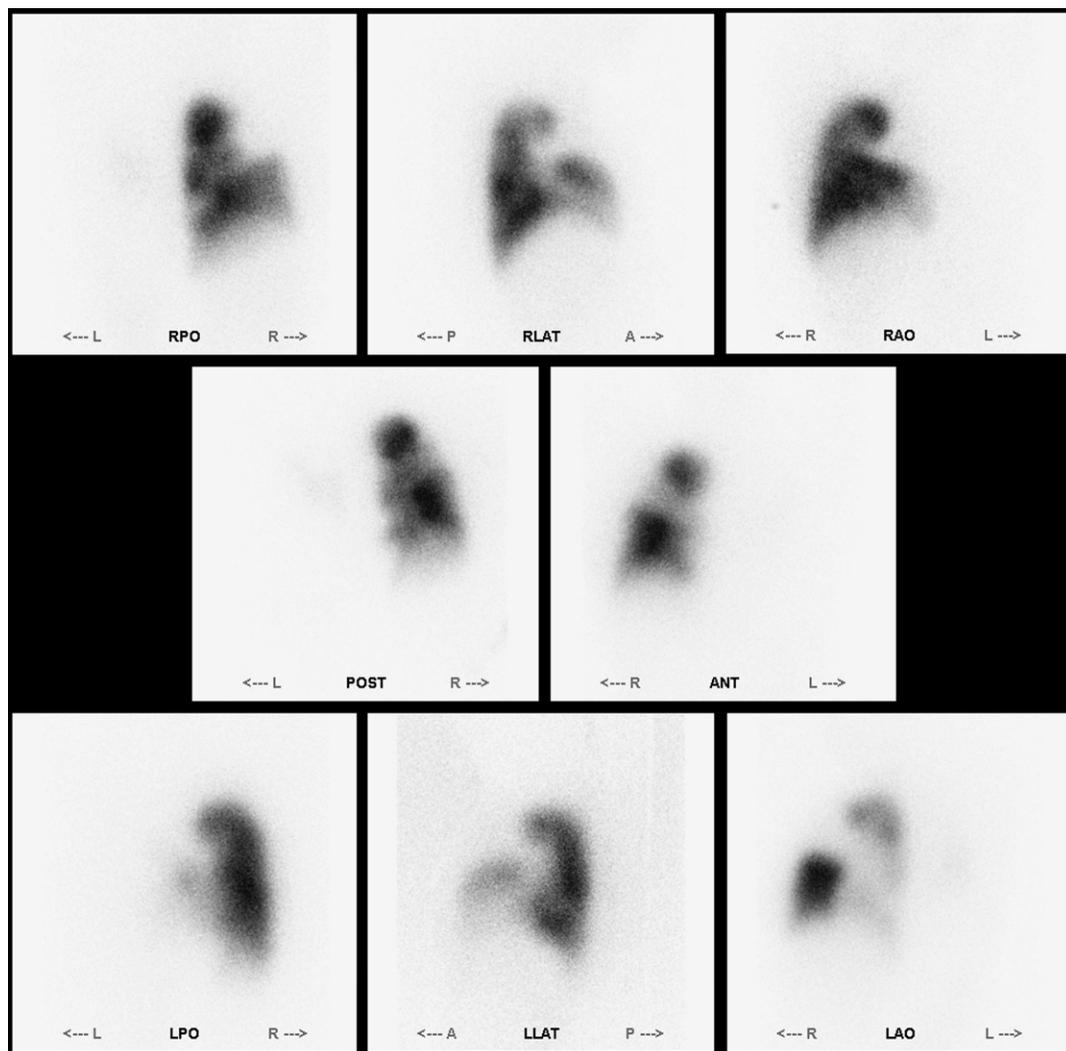


Fig. 2. V/Q scan demonstrates no perfusion of the entire left lung and multiple segmental perfusion defects predominantly in the upper lobe of the right lung.

cardiopulmonary status and prognosis. Transesophageal echocardiography may not be available at all centers. Its primary role is in patients who have suspected massive emboli and are too unstable to move elsewhere for imaging.

Doppler ultrasonography

Lower-extremity venous Doppler ultrasonography is widely available and easily obtained for patients who have symptoms of DVT. It is non-invasive and inexpensive. DVT is seen as partial or complete filling defects in the veins, with lack of compressibility of the vessel (Fig. 3). Doppler

ultrasonography has high sensitivity and specificity (95% and 96%, respectively) [20]; however, this is true only for the popliteal, femoral, and saphenous veins. Its sensitivity is much lower for calf vein, and evaluation of the inferior vena cava and iliac veins is often not possible with ultrasound, depending on patient factors [21]. Another drawback of Doppler ultrasound is its insensitivity in the detection of nonocclusive thrombi [22–24].

Contrast venography

Contrast venography is still considered the most reliable test and gold standard in diagnosis



Fig. 3. Doppler ultrasonography shows DVT in the left popliteal vein as an incomplete filling defect (*arrow*).

of DVT [25]. Contrast venography has the ability to completely image the pelvic, thigh, and calf veins; however, it is invasive, operator dependent, uses radiation, and requires the administration of iodinated contrast material. In addition, phlebitis is an infrequent complication. Since the introduction of Doppler ultrasound and CT venography, contrast venography has been used less frequently.

CT in acute pulmonary thromboembolism

With the introduction of helical CT in the early 1990s, acquisition of a volume data set in a single breath hold (18–30 seconds) at optimal contrast enhancement became possible. The first study comparing CTA with pulmonary arteriography was published in 1992 and reported 100% sensitivity and 96% specificity for the diagnosis of PE [26]. In a subsequent study using electron-beam CT, Teigen and colleagues [27] reported similar results of high sensitivity (95%) and specificity (80%) for spiral CT. These results, however, were for central pulmonary emboli only. Later studies evaluating central and subsegmental arteries demonstrated lower sensitivity and specificity [28].

Advances in CT technology, with the introduction of faster scanners and multidetector row CT, enabled acquisition of thinner slices in a shorter time period, decreasing respiratory-

motion artifacts. Higher-quality thinner images provided improved spatial resolution for the evaluation of the subsegmental arteries [29–33]. With multidetector CT scanning, the entire chest can be scanned in 4 to 8 seconds, depending on technical parameters and the CT technology used. This technology enabled routine visualization of subsegmental arteries on a good-quality CT angiogram without respiratory motion or increased image noise. Although investigators are questioning whether pulmonary angiography should still be considered the gold standard, most studies are still comparing CTA results with a pulmonary arteriography gold standard. By using thrombi casts in a pig model as a gold standard, Baile and colleagues [18] compared 1-mm-thin CTA slices to pulmonary angiography. They found similar sensitivities for detecting subsegmental PE. A recent PIOPED II analysis showed that in the 20 cases in which CTA and pulmonary angiography disagreed, an expert panel thought that the CTA diagnosis was right in 14 cases. They thought that the pulmonary angiographic diagnosis was right in two cases. In the four remaining cases, the panel felt that the CT was true negative initially, but that emboli were subsequently present when pulmonary angiography was done [19].

Interobserver variability of CTA is significantly dependent on the technical quality of the examination [34]. With the use of thinner slices and increased speed provided by multidetector row CTs, interobserver agreement has also improved [31,35,36]. PIOPED II found a kappa statistic for CT of 0.73 (95% confidence interval [CI]: 0.68%–78%) compared with a kappa statistic for angiography of 0.66 (95% CI: 0.48%–59%).

CTA enables direct visualization of PE. Acute PE can be seen as a complete, a central partial, or an eccentric partial filling defect (Fig. 4A, B). A central partial filling defect presents as “polo mint sign” or “railway track sign” when perpendicular or parallel to the long axis of the vessel, respectively. With complete filling defects, vessels may be enlarged compared with those of the same generation. Indirect signs of acute PE include wedge-shaped peripheral opacities, representing pulmonary infarcts. Atelectasis and pleural effusion are nonspecific findings of acute PE.

How sensitive and specific is CTA? How reliable is CT in excluding important pulmonary emboli? If CT is negative, how often do patients return with embolic problems in the next few months if they are untreated? There is a range of

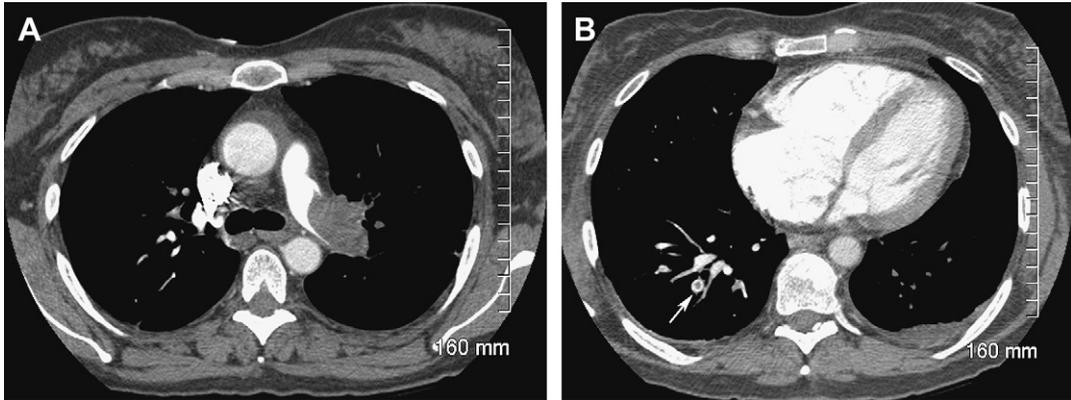


Fig. 4. (A) CTA demonstrates acute PE in the left main pulmonary artery as a complete filling defect; the vessel is enlarged. (B) At the level of ventricles, a central partial filling defect of the acute PE (arrow) is seen in the right lower lobe posterobasal segmental artery (Polo mint sign). Right ventricle and right atrium are moderately dilated, suggesting right heart strain.

sensitivities and specificities reported in the literature. Recently, PIOPED II reported a sensitivity and a specificity of 83% and 96%, respectively, whereas others have reported sensitivities of 90% or greater [35,37,38]. With current-generation scanners, the latter is probably a better estimate.

Numerous studies have been performed over the last 10 years that have followed-up CT patients who did not have evidence of PE and were not treated for pulmonary embolus. Quiroz and colleagues [39] reviewed 15 studies that had at least a 3-month follow-up. A total of 3500 patients were evaluated. The negative predictive value for CT was 99.1% (95% CI: 98.7%–99.5%). The negative likelihood ratio was 0.07 (95% CI: 0.05%–0.11%). There did not appear to be a significant difference in risk of subsequent PE using a single-slice versus a multislice detector. These studies support the view that a good-quality CT angiogram without pulmonary emboli justifies withholding treatment without further imaging. PIOPED II cautioned, however, that if the preclinical probability (Wells score) was high, then a negative CT angiogram may not always be reliable. Unless the CT is absolutely pristine and normal, additional imaging of the legs or lungs is warranted. Likewise, a positive CT and low clinical evaluation may require further evaluation when PEs are confined to small vessels.

Stein [3] tried to reconcile the discrepancy between the relatively high number of undetected pulmonary emboli (false negatives) in the PIOPED II study with the very low number of

subsequent pulmonary emboli found on 3-month follow-up. His statistical argument was based on PIOPED data. The authors included data from other studies and broadened the argument:

1. Assume 10% to 17% of PE are missed (CT false negative).
2. Assume 5% to 10% of patients who have small PE (presumably the ones missed on CT) have subsequent PE if untreated. (These estimates are based on PE recurrence in patients who were not anticoagulated after a low-probability V/Q scan).
3. Five percent to 10% of 10% to 17% equals 0.5% to 1.7%, which is approximately the 99.1% sensitivity calculated by Quiroz and colleagues [39].

The strongest argument against treating every small embolus comes indirectly from the outcome studies. If CTA is approximately 90% sensitive, and 10% of patients who have emboli—presumably small emboli—go undetected and untreated, then mortality and morbidity from pulmonary emboli in the next few months should be high. Quiroz and colleagues [39] showed that this mortality and morbidity is approximately 1%, which suggests that most difficult-to-diagnose (presumably small) emboli do not lead to unfavorable clinical outcomes.

Still to be determined is whether every patient who has a small pulmonary embolus needs treatment. There is a growing body of literature that suggests that patients who have small emboli,

no evidence of DVT, and good cardiopulmonary reserve may do better without anticoagulation than with anticoagulation [40–42].

CT in chronic pulmonary thromboembolism

Chronic PE is seen on CT as an eccentric filling defect contiguous with the vessel wall, reduced diameter of pulmonary arteries, vascular bands, and webs (Fig. 5). Calcification within the clot is the most specific finding of chronic PE. Indirect findings include enlarged main pulmonary arteries secondary to pulmonary arterial hypertension, prominent collateral bronchial arteries, and mosaic perfusion of the lung. Small subpleural scars are nonspecific but commonly seen findings of chronic PE on CT [43]. Perfusion scanning often shows multiple perfusion defects.

It is important to consider the diagnosis of chronic thromboembolic disease in all patients presenting with unexplained pulmonary hypertension. In young patients who have suspected primary pulmonary hypertension, V/Q scanning is often an appropriate test to exclude thromboembolic pulmonary hypertension. In older individuals or those who have underlying lung disease, however, CTA is probably more specific because of the high frequency of indeterminate perfusion defects in this population. Although a proportion of cases of chronic thromboembolism may be missed on CTA [44,45], the presence of central thrombus on CTA is a useful predictor of the likelihood of improvement following thromboendarterectomy [46,47].



Fig. 5. Chronic PE in the right upper lobe pulmonary artery (*arrow*) is seen as an eccentric filling defect. Main pulmonary artery is moderately dilated.

CT venography

In 1998, Loud and colleagues [48] described the use of combined CTA and indirect CT venography of the lower extremities. Indirect CT venography was obtained without additional contrast administration. Three minutes after administration of intravenous contrast material for CTA, contiguous or sequential images were obtained through the pelvis and lower extremities. Acute DVT was visualized directly as a complete or partial filling defect within the vessel (Fig. 6). Acute thrombi may completely obstruct vessel lumen, and the veins are enlarged. There is also perivenous stranding and mural enhancement. In chronic DVT, veins are smaller compared with the accompanying arteries, and the most specific finding is calcification of the vein.

CT venography is routinely used after CTA in some institutions; however, there is considerable radiation to the pelvis, which is important, especially in young patients. At the authors' institution, patients younger than 40 years who do not have symptoms of DVT do not undergo CT venography. Pelvic radiation can be reduced further by using one 5-mm image every 2 cm rather than performing continuous imaging, and by scanning from the acetabulum rather than from the iliac crest because DVT isolated to the iliac veins is very rare [49].

Radiation exposure from CTA is lower than from pulmonary angiography, but CTA is associated with a higher radiation burden than V/Q scanning. Reducing the dose by using appropriate technical parameters and dose modulation

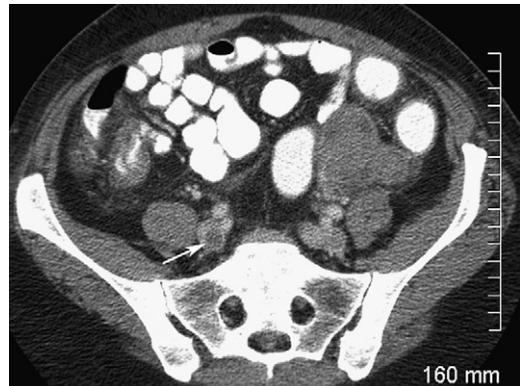


Fig. 6. Acute DVT in right common iliac vein is visualized as a near-complete filling defect (*arrow*). There is also a filling defect in left common iliac vein.

programs becomes especially important in patients followed-up with repeat CT angiograms.

Allergic reactions to iodinated contrast material, renal failure, and severe heart failure are contraindications to CTA. The use of gadolinium chelates instead of iodinated contrast medium in CTA has been reported and is promising for those who have allergic reactions to CT contrast media. The use of gadolinium in renal failure patients is debatable because of its potential to induce nephrogenic systemic fibrosis [50].

Indeterminate CT angiograms usually result from respiratory artifacts or inadequate opacification of pulmonary arteries and from increased image noise in obese patients. The prevalence of indeterminate CTA examinations has been reported to be 2% to 13% [35,36,42]. This prevalence is much less than that of V/Q scanning and is similar to that of pulmonary angiography.

Because CTA is widely available and readily accessible, it is considered the first-line modality in evaluation of PE in most institutions, rather than V/Q scanning. CTA is a rapid procedure. It provides alternative diagnoses responsible for symptoms of the patients, which cannot be determined by other diagnostic tests for PE. It is also cost-effective in the diagnostic workup of PE, although its cost varies among countries and even institutions. The severity of the pulmonary embolism can also be assessed with CTA by the evaluation of right ventricle dilatation, suggesting right ventricular failure [51].

Magnetic resonance angiography

Lack of radiation and iodinated contrast material administration are major advantages of MRI over CT. Currently, high-resolution magnetic resonance angiography (MRA) images can be obtained with gradient echo techniques during a single breath hold and using intravenous gadolinium by performing dynamic imaging. Like CT, deep veins of the pelvis and lower extremities can be evaluated with magnetic resonance venography (MRV) as a combined approach with MRA. MRV has very high sensitivity and specificity for pelvic venous imaging and DVT [52–54]. Emboli are directly visualized as filling defects in MRA and MRV, as in CT and pulmonary arteriography. Although MRI is noninvasive, the length of examinations and limited patient access to critically ill, dyspneic, and monitored patients are disadvantages. It is also expensive and operator and reader dependent.

Several investigators compared MRA with pulmonary arteriography [55–57]. Sensitivities of MRA ranged between 48% and 100%. Following intravenous administration of gadolinium and using very short echo times, pulmonary perfusion can also be visualized. Kluge and colleagues [58] evaluated the diagnostic accuracy of three MRI techniques (real-time MRI, MRA, and MR perfusion imaging) and compared them with 16-multi-detector row CT to assess acute PE to the subsegmental level. They found the combined MR protocol to be reliable and sensitive compared with 16-multidetector row CT in the diagnosis of PE. MR perfusion imaging was sensitive for the detection of PE, whereas real-time MRI and MRA were specific.

Recently, the use of gadolinium in renal failure patients has been shown to cause nephrogenic systemic fibrosis, suggesting that allergy to iodinated contrast is the only current indication for MRI [50].

Diagnostic algorithm

PIOPED II has recently emphasized the value of objective pretest probability scoring (eg, Wells score) and the use of D-dimer in eliminating the need for imaging in a significant number of outpatients [59]. This step should be the first in patient triage, before imaging is considered.

Imaging of PE begins with the chest radiograph. It is helpful to rule out other disease processes that can mimic symptoms of PE. When the chest radiograph is normal, patients are usually evaluated with V/Q scan to take advantage of its low radiation and high negative predictive value. When the chest radiograph is not normal or the V/Q scan is inconclusive, the patient undergoes CTA.

Patients who have symptoms of DVT alone undergo Doppler venous ultrasonography of lower extremities. At the authors' institution, CT venography is routinely obtained after CTA in patients older than 40 years. Pulmonary arteriography is reserved for patients who have inconclusive CTA. Patients who have iodine allergy or are pregnant may be referred to MRI.

The optimal imaging evaluation of pregnant patients for PE is controversial. Although V/Q scan has a lower effective dose of radiation to the mother compared with CTA, the reverse is true for the fetus. Normally, a V/Q scan is preferred as first-line imaging after a normal chest radiograph to rule out PE, especially in young patients, but in

pregnant patients, CTA is preferred to V/Q scan because it gives less radiation to the fetus. Imaging starts with lower-extremity ultrasound. When DVT is detected, the lungs are not imaged.

Summary

Introduction of helical and multidetector row CT technology has changed the algorithm of PE imaging. With multidetector row CTs, thinner images can be obtained in a shorter time, greatly increasing the diagnostic yield. CT can also provide alternative diagnoses that cannot be made by other methods, and CT venography can provide evaluation for DVT as part of the same examination.

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