Acute Pulmonary Embolism: From Morphology to Function

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Abstract

This article reviews the current diagnostic strategies for patients with suspected pulmonary embolism (PE) focusing on the current first choice imaging modality, computed tomographic pulmonary angiography (CTPA). Diagnostic strengths and weaknesses and associated cost-effectiveness of the diagnostic pathways will be discussed. The radiation dose risk of these pathways will be described and techniques to minimize dose will be reviewed. Finally the impact of new dual energy applications which have the potential to provide additional functional information will be briefly reviewed. Imaging plays a vital role in the diagnostic pathway for clinically suspected PE. CT has been established as the most robust morphologic imaging tool for the evaluation of patients with suspected PE. This conclusion is based on the high diagnostic utility of CT for the detection of PE and its unique capacity for accurate diagnosis of conditions that can mimic the clinical presentation of PE. Although current cost-effectiveness evaluations have established CT as integral in the PE diagnostic pathway, failure to acknowledge the impact of alternate diagnosis represents a current knowledge gap. The emerging dual energy capacity of current CT scanners offers the potential to evaluate both pulmonary vascular morphology and ventilation perfusion relationships within the lung parenchyma at high spatial resolution. This dual assessment of lung morphology and lung function at low (< 5 millisievert) radiation dose represents a substantial advance in PE imaging.

Keywords

► CTPA
► pulmonary embolism
► acute PE
► dual-energy CT
► thoracic CT

Pulmonary embolism (PE) occurs when clots in the systemic venous system break free and migrate to the pulmonary arteries, leading to either total or partial occluded pulmonary arterial blood flow to the lung parenchyma. Acute PE can be rapidly fatal and is considered the third most common acute cardiovascular disease after myocardial infarction and stroke.1 Untreated chronic PE can lead to pulmonary hypertension, a symptomatic life shortening disease. Anticoagulation is the primary treatment modality for PE. However, anticoagulation therapy needs to be used appropriately, since it is associated with significant morbidity and potential mortality.

PE typically presents with nonspecific chest pain and shortness of breath, symptoms that are common with other chest conditions. Clinical prediction tools have been developed to provide structured patient evaluation in an attempt to improve the clinical probability of PE.2–4 The most useful laboratory test is the D-dimer level. The specificity of the D-dimer test has been improved through the use of enzyme linked immunosorbent assay (ELISA) techniques. However, any thrombotic process within the body will elevate the D-dimer level; therefore the D-dimer test is not specific for venous thromboembolism or PE. Patients with high probability of clot (e.g., trauma, postoperative) or patients with
physiological elevations in D-dimer (e.g., later stages of pregnancy) are not appropriately screened for PE using D-dimer. Patients at high clinical risk of PE are also not appropriate for D-dimer screening. Excluding these situations, patients with a negative D-dimer can be managed as having PE excluded. Incorporating D-dimer test with diagnostic imaging has shown to increase the positive-PE diagnosis rate from 5 to approximately 15% in clinical trials.\(^2,4–6\) Imaging is most appropriately used in patients with medium to high clinical probability or a positive D-dimer test. At this time, imaging exams are the most accurate diagnostic tools for PE.\(^1,6,7\)

Identification and prompt treatment of PE improves patient prognosis and directs clinical management. A variety of articles and reviews have been published exploring the accuracy of different imaging examinations for suspected PE.\(^1,6,8–11\) Since the comprehensive review article in 2007,\(^12\) the most commonly used first choice imaging examination in patients with suspected PE is computed tomographic pulmonary angiography (CTPA).\(^7,13\) This recommendation is based on two strengths of current multidetector CT imaging in suspected PE. First, it has been shown that CTPA has greater than 85% sensitivity and greater than 95% specificity for the diagnosis of PE. Second, CTPA is unique in imaging studies for PE in its ability to detect other disease processes (lung infection, pneumothorax, cardiac failure, pleural disease, etc...) that can mimic the clinical presentation of PE.

**CTPA for Suspected PE**

The development of CT in the 1970's and its evolution to the current multidetector row dual energy capable format has revolutionized the role of imaging in the diagnosis of PE. State of the art CT scanners are able to provide diagnostic whole body scans from head to toe in less than 5 seconds. These scans provide in vivo images that have similar information content to visual inspection at gross anatomic dissection. The scans can be obtained in essentially all body sizes and shapes with minimal limitations on the patient’s clinical condition and minor artifact arising from implanted medical devices or medical monitoring equipment. Finally, CT is well accepted by referring physicians and patients since examinations are generally highly accurate and can be performed with minimal discomfort.

Compared with the plain radiograph, which provides a projection of shadows caused by differences in X-ray attenuation within the patient, CT images are composed of cross sections composed of point attenuation values. The cross sectional viewing perspective eliminates the overlapping shadows seen in the chest on the plain chest radiograph, greatly increasing the detection of pulmonary emboli, and thus diagnostic accuracy of the image. CT can provide a cross sectional perspective because the acquisition process obtains 800 to 1400 plain radiographic views around the patient. Transverse cross sectional images can be computer manipulated into sagittal, coronal and oblique image planes to facilitate visualization of central, segmental and subsegmental pulmonary arteries. However, the hundreds of projections required by the CT reconstruction process are associated with substantially greater radiation dose (100–400 times) than the single view plain radiograph.

The tissue attenuation values of clot and flowing blood are very similar; therefore the attenuation value of flowing blood must be transiently elevated by the addition of iodine containing intravenous contrast media to detect pulmonary clot.\(^4–6\)

Fig. 1 (A–C) Three contiguous transverse CTPA sections showing a saddle pulmonary embolus (arrows) draped over the origin of the right and left pulmonary arteries. The low attenuation clot is surrounded by high attenuation contrast enhanced flowing blood. CTPA, computed tomographic pulmonary angiography.
emboli. In physiologically tolerated concentrations, iodine containing contrast media (atomic number 53) almost doubles the effective atomic number of blood ($Z_{\text{blood}}$ approximately 5.9–7.5, $Z_{\text{iodinated-blood}}$ approximately 11–12), increasing the X-ray absorption by a factor of 8. This causes flowing blood to appear white on CT images. Since intravenous contrast media does not penetrate into pulmonary emboli, the emboli remain at intermediate gray soft tissue attenuation ($Z_{\text{emboli}} \approx 7.5$) on CTPA image (Fig. 1). This difference in attenuation between emboli, flowing blood and surrounding air renders the emboli visible on the images. With good contrast enhancement (flowing blood > 200 Hounsfield unit [HU] in the main pulmonary artery), minimal motion artifact and the high spatial resolution of current multidetector scanners (1 × 1 × 1 mm) CTPA is sensitive and specific for the detection of emboli down to 2 to 3 mm diameter subsegmental pulmonary arteries (Fig. 2). Using the CT reconstruction process, it is possible to target the reconstruction to a smaller region of interest, improving spatial resolution and enhancing pulmonary artery visualization to the fifth and sixth generation. However, the clinical relevance of this capability is questionable and in our experience seldom used clinically.

Finally, in addition to accurately detecting PE to the level of the subsegmental pulmonary arteries, CTPA provides excellent detection of all other pathologies that cause gross anatomic changes in the chest. This capacity is unique in PE imaging modalities. Thus CTPA can accurately detect and diagnose a large number of other clinical conditions that may mimic the clinical presentation of acute PE including cardiac abnormalities (Fig. 3), pneumothorax, pneumonia, rib fractures, upper abdominal pathology, etc. In some cases PE may be only one of multiple abnormalities in the chest and CTPA may provide a “one stop shop” for multiple diagnoses (Fig. 4). In many cases the absence of PE or any other abnormality on CTPA provides referring clinicians with sufficient information to confidently discharge patients from the emergency room. This capacity for alternate diagnosis is a critical driver of the popularity of CTPA amongst referring clinicians.

The unique status of CTPA as an imaging modality for clinically suspected PE is recognized in the American College of Radiology (ACR) appropriateness criteria (Table 1). In acute chest pain, suspected PE, only the chest radiograph and CTPA reach the rank of 9 assigned in the ACR appropriateness criteria (Table 1). However, as noted in the table, the chest radiograph only has utility in detecting conditions “mimicking” PE and is unable to “directly” diagnose PE. Thus CT is the only examination capable of directly diagnosing PE that achieves a rank of 9. CT is highly sensitive and specific in this clinical setting and is currently the choice imaging examination for suspected acute PE.

Cost-effectiveness evaluations of diagnostic strategies incorporating CTPA in algorithms for the diagnosis of acute PE has recently been the focus of a systematic review (Diagnostic strategies incorporating CT angiography for PE). A systematic review of cost-effectiveness analyses. This review found evidence to support the use of clinical risk assessment to tailor the diagnostic algorithm for the investigation of PE. They reported that the usefulness of CTPA and D-dimer and the lack of need for more invasive test such as pulmonary angiography had been established. They noted a lack of published data on the diagnostic performance of CTPA in multidetector scanners with greater than four rows. In addition it was noted the capacity of alternate diagnosis in clinical PE was exclusive to CTPA but was not formally evaluated in any of the papers reviewed. Since alternate diagnosis is a major advantage in selecting CTPA as the diagnostic test for suspected PE, this contribution needs to be addressed in cost-effectiveness analysis.

ACR guidelines acknowledge the relatively high radiation dose of the CTPA examination. Increased awareness of the high level of medical radiation exposure has motivated researchers and equipment manufacturers to evaluate all aspects of the CTPA imaging chain searching for radiation Fig. 2 Transverse image from a low-dose Flash (pitch 3.2) CTPA (dose length product = 87 mGy.cm, 1.2 mSv) study reconstructed using weighted Filtered Back Projection (A) and Safire (Siemens Medical Solutions) IR (B) in a 47-year-old female patient. Both images show an intraluminal filling defect in a subsegmental pulmonary artery of the anterior basal segment of the right lower lobe (arrow) consistent with acute PE. Note the mildly reduced image noise and streak artifact across the ascending aorta on the IR image (B). CTPA, computed tomographic pulmonary angiography; IR, iterative reconstruction; PE, pulmonary embolism.

Table 1

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<tr>
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reduction strategies while retaining diagnostic accuracy.\textsuperscript{17–19} A brief review of radiation dose reduction measures is provided below along with suggested radiation dose efficient CTPA acquisition protocols.

**CTPA Image Acquisition Technique**

Accurate detection of clinically relevant pulmonary emboli in central, segmental and subsegmental pulmonary arteries requires a specific CTPA acquisition protocol. Intravenous contrast media must be employed to increase the density of flowing blood since the attenuation of pulmonary emboli nearly approximates that of flowing blood. CTPA examinations require visualization of all first to fifth generation pulmonary arteries during the first pass of 300 to 370 mg iodine/mL contrast media.\textsuperscript{20–22} In CTPA studies acquired with state of the art scanners, sixth generation pulmonary arteries may be detected, which is comparable to catheter pulmonary angiography studies.\textsuperscript{8} However, the clinical relevance of isolated subsegmental (fourth generation) or distal (fifth, sixth generation) vessel PE remains controversial and the focus of current investigations.\textsuperscript{8} Diagnostic CTPA exams have a contrast enhanced blood density of greater than 200 to 250 HU.\textsuperscript{23} With normal resting heart rates adequate contrast enhancement can be obtained with contrast injection rates of 3 to 4 mL/sec through arm veins. However, since the contrast media is diluted by the circulating blood pool, patients with elevated cardiac output require faster contrast media injection rates (4–5 mL/sec).\textsuperscript{22,23} Images should be obtained in either suspended or quiet breathing to minimize respiratory motion artifact. Newer high pitch acquisition protocols (pitch > 3) are less sensitive to respiratory and cardiac motion artifacts due to shorter data acquisition times (< 2 sec)\textsuperscript{24,25} and deliver lower radiation dose (\textsuperscript{Fig. 2}). Contiguous sections should be reconstructed using an intermediate spatial resolution algorithm at a thickness of 2 mm or less. Images should be viewed in cine mode on a workstation at window with of 450 to 600 HU and a level of 35 to 100 HU. Lung window images (width 1,200 to 1,500, level –600 to –750)

\textsuperscript{Fig. 3} (A) A transverse CTPA section at the level of the mid-left ventricle showing a focal region of diminished perfusion in the lateral free wall (arrows) of the heart. Review of the remaining images in this study showed no evidence of PE to the subsegmental level. This cardiac finding accounted for the patient’s clinical presentation of chest pain and shortness of breath. (B) Transverse CTPA section through the level of the mitral valve demonstrating acute prolapse of the posterior leaflet of the mitral valve (arrow) with associated bilateral pleural effusions and acute pulmonary edema within lung parenchyma of the right lower lobe. This finding accounted for the patient’s clinical presentation of chest pain and shortness of breath. Review of the remaining images in this study showed no evidence of PE to the subsegmental level. CTPA, computed tomographic pulmonary angiography; PE, pulmonary embolism.

\textsuperscript{Fig. 4} (A) PA chest radiograph showing a soft tissue mass overlying the aortic-pulmonary window region (arrow) in this pregnant female patient with acute shortness of breath and pleuritic chest pain. (B) Transverse CTPA image in the same patient at the level of the left pulmonary artery demonstrating a low density filling defect within the proximal left pulmonary artery consistent with an acute pulmonary embolus (curved arrow). A malignant thymoma is also seen in the anterior mediastinum (straight arrow). CTPA, computed tomographic pulmonary angiography; PA, pulmonary angiography.
must also be reviewed for alternate diagnosis information. High quality CTPA examinations should have a noise level of 22 HU or less in regions of uniform attenuation (e.g., measured at the descending thoracic aorta lumen).

**Radiation Risk of CTPA**
Current radiation risk models extrapolate risk from high dose exposures (> 200 mSv) to low dose values. The risk at radiation exposures that result in an effective dose < 200 mSv remains controversial. However, since radiation is described as weakly carcinogenic, the radiation safety community has established the ALARA principle, that is—As Low As Reasonably Achievable. Using the lowest radiation dose possible to achieve diagnostic quality images ensures we mitigate the unknown risk of radiation at low levels, while enabling clinicians to obtain diagnostic quality images. A simple ratio of benefit (PE mortality) to radiation induced cancer mortality risk has been shown by Woo et al to demonstrate that the benefit-risk ratio is strongly in favor of clinically indicated CTPA examinations for both men and women from ages 15 to greater than 80 years. However, dose reduction for all CT exams is an important venture, by reducing dose we mitigate future deleterious risk within our population.

**Radiation Sensitivity of Patients**
Current radiation risk models have identified age and gender of the patient at exposure as important influences of developing radiation related effects. Young patients are more susceptible to radiation-related effects, as are females compared with males (below the age of 60 years). Risk decreases with increasing age, being very low above the age of 80 years. Up to the age of 60 years, females are more sensitive to radiation than males of the same age. Although this effect is partially modulated by breast tissue in females up to the age of 50 years, above this age breast tissue is relatively radiation insensitive and the chest organs at most risk in both males and females are bone marrow and lung parenchyma. However, current models stipulate that the onset of radiation-induced effects may occur 10 to 15 years after exposure. For older patients, this does not necessarily mean lower risk, instead, that other competing disease processes acquired over their lifetime potentially have a greater effect on their mortality (i.e., smoking, diet, weight, diabetes, etc.).

**Radiation Dose Reduction Strategies**
Several radiation dose reduction strategies exist on modern CT scanners and should be used where appropriate. Since it is recognized patient radiation risk is influenced by age and gender, CTPA protocols should vary as noted below. Radiation dose reduction strategies include: tube current modulation, tube voltage modulation, scan length adjustment, collimator shutter action to avoid z-axis overscan and iterative reconstruction. Full discussion of these acquisition issues is beyond the scope of this paper. It is noted that routine use of bismuth shields is discouraged when tube current modulation and peripheral dose reduction techniques are available. The AAPM recommends that alternatives to bismuth shields be

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<th>Radiologic procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL</th>
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<tr>
<td>X-ray chest</td>
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<td>To exclude other causes of acute chest pain. Complementary to other examinations</td>
<td>1</td>
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<tr>
<td>CTA chest (noncoronary) with contrast</td>
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<td>Current standard of care for detection of PE</td>
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<td>Tc-99m V/Q scan lung</td>
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<td>–</td>
<td>3</td>
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<td>US lower extremity with Doppler</td>
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<td>If chest X-ray is negative and index of suspicion is high</td>
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<tr>
<td>CTA chest with contrast with CT venography</td>
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<td>–</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary angiography with right heart</td>
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<td>If suspicion is high and CTA is inconclusive, or if intervention is needed</td>
<td>4</td>
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<tr>
<td>MRA pulmonary arteries without and with contrast</td>
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<td>If patient is unable to receive iodinated contrast, may be alternative to V/Q scan. See statement regarding contrast in text under “Anticipated Exceptions”</td>
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<td>MRA pulmonary arteries without contrast</td>
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<td>Limited experience. Has been used for central pulmonary emboli</td>
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<td>US echocardiography transesophageal</td>
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<tr>
<td>US echocardiography transthoracic resting</td>
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<td>To assess for RV strain or failure in the presence of major pulmonary embolism</td>
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*Rating scale: 1, 2, 3 usually not appropriate; 4, 5, 6 may be appropriate; 7, 8, 9 usually appropriate.

Abbreviations: CT, computed tomography; MRA, magnetic resonance angiography; PE, pulmonary embolism; RRL, relative radiation level; US, ultrasound.

*Note: Separate criteria available for pregnant patient. [Reproduce with permission from American College of Radiology.]

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Table 1 ACR appropriateness criteria—adult with acute chest pain—suspected PE
considered, as in specific circumstances, these shields could increase radiation dose and may limit image quality.

**Suggested CTPA Protocols**

All patients should have validated clinical probability of PE calculated (Pulmonary Embolism Rule-Out criteria, Wells score, Geneva score), with D-dimer when indicated.

Patient requisition should be reviewed by radiologist prior to booking to determine appropriateness, patient age and gender, and determine the level of radiation dose reduction used:

1. Highest radiation dose reduction; < 30 years of age; 120–100–80 kVp depending on patients BMI or automatic tube voltage selection; 150 mA tube current with x, y, z tube current modulation; 2-mm section thickness, iterative reconstruction at minimum 40% or level 2 strength, using higher strength as clinical familiarity with iterative reconstruction improves.

2. Intermediate radiation dose reduction; 30 to 60 years of age; 120–100–80 kVp depending on patients BMI or automatic tube voltage selection; 200 mA tube current with x, y, z tube current modulation; 2 mm section thickness, iterative reconstruction at 40% or level 2 strength.

3. Lowest radiation reduction; > 60 years of age; 120 kVp; 200 mA tube current with x, y, z tube current modulation; 2 mm reconstruct section thickness, Filtered Back Projection or Iterative reconstruction as clinically desired.

**Dual-Energy Computed Tomography Technology**

DECT acquisitions can be obtained by modification of either the CT X-ray tube or the CT detector array. In scanners using a single X-ray tube (General Electric 750HD, Milwaukee, WI), the tube voltage (kVp) can be rapidly switched between 80 and 140 kVp providing adjacent projections at two energy levels. Using a dual X-ray tube configuration (Definition Flash, Siemens Medical Solutions, Forchheim, Germany) one tube can be run continuously at 80 or 100 kVp while the other operates at 140 kVp. In the second generation configuration of the dual tube scanner additional X-ray filtration (tin filter) has been applied to the 140 kVp X-ray tube, improving DE separation. In clinical studies, this improved contrast separation between iodine and calcium by up to 290%, decreased the noise in virtual contrast images and provided radiation doses lower than tradition single energy CTPA. Dual-energy CT (DECT) can also be implemented through modifications of the detector array in a single X-ray source dual-detector DECT (SSDD-DECT) scanner. In this DECT implementation, the detector array is composed of two layers, one targeting lower energy photons and the other higher energy photons. A prototype using this technology has been developed by Philips HealthCare and addresses
temporal and spatial limitations of existing single and dual-source single detector scanners. Potential advantages and disadvantages of the various implementations of DE technology are listed in Table 2.

**DECT Applications to Pulmonary Embolism**

Applications of DECT technology to clinically suspected PE has grown rapidly over the past 4 years as technology has advanced. An excellent review of the current state of DECT in the lung is provided by Lu et al. This paper has extensive discussion of DECT’s potential role in clinically suspected PE and suggested scanning protocols. A demonstration study of the clinical utility of combined xenon enhanced ventilation and iodine enhanced perfusion DECT has been performed by Zhang et al. This paper shows that using their acquisition protocol, DECT can provide morphologic evaluation of the pulmonary arteries to the subsegmental level with excellent image quality, evaluate ventilation perfusion relationships of the lung parenchyma at millimeter spatial resolution and perform both with an average radiation dose of 4.8 ± 1.4 mSv (range, 2.7–7.5 mSv). In the 28 patients studied, they found ventilation perfusion mismatch in 17 lobes of 8 of 10 patients with clinically proven PE. They conclude that DECT lung ventilation perfusion can be added to morphologic evaluation of the pulmonary arteries within an acceptable radiation dose envelope. Further evaluation of the clinical impact of this technology will be necessary within larger clinical trials. DECT also offers the potential to reduce iodinated contrast load in patients with impaired renal function compared with single energy CT. It is likely that future technical advancements in scanner design, X-ray detection (i.e., photon counting) and image processing will enable sub-mSv DECT for investigation of PE. These advances will further minimize radiation dose concerns regarding CTPA studies in young patients. A current limitation of DECT is restricted clinical availability which should be addressed with ongoing equipment renewal over the next 5 years.

**Summary**

Based only on morphologic imaging, CTPA has been recognized as the first choice examination for suspected PE. This reflects the excellent sensitivity and specificity for the diagnosis of PE and its unique ability to diagnose significant chest pathology that clinically mimics PE. Education of referring
clinchans on the utility of clinical prediction tools and D-dimer laboratory testing improves the appropriateness and diagnostic yield of CTPA exams. Given the large population imaged for query PE, radiation dose reduction techniques are important and should be utilized. Radiation dose reduction is most important in young patients due to their increased radiation susceptibility. Reliable contrast media injection protocols need to be used to ensure that diagnostic levels of contrast enhancement are achieved in the pulmonary arteries. DECT is emerging as a new CT technology that offers the potential to reduce radiation dose, reduce contrast media volume, improve diagnostic accuracy and provide function information on ventilation perfusion relationships. Further research is required for CT to realize its full potential as both a morphologic and a functional imaging modality for PE.

References
33 AAPM Position Statement on the Use of Bismuth Shielding for the Purpose of Dose Reduction in CT Scanning. Policy no. PP-26-A; 2012