**Imaging in Acute Pulmonary Embolism With Special Clinical Scenarios**

Andetta R. Hunsaker, MD; Michael T. Lu, MD; Samuel Z. Goldhaber, MD; Frank J. Rybicki, MD, PhD

Major advances in computed tomography (CT) technology, specifically multidetector CT (MDCT) with vastly improved spatial and temporal resolution, have led to a surge in the diagnosis of acute pulmonary embolism (PE) using computed tomography pulmonary angiography (CTPA). For persons between 35 and 74 years old, hospital diagnosis rates in 1981 for PE were 127.7 per 100,000 for blacks and 98.2 per 100,000 in whites. The reported incidence ranges from 43.7 to 145.0 per 100,000. These data are based on epidemiological studies based on physical examination and history, which underestimate the actual frequency of disease. However, data from autopsies confirm that only a small number of cases of PE are recognized clinically. If untreated, the hospital mortality rate for major PE is 30%, whereas the mortality drops markedly in anticoagulated patients, emphasizing the need for rapid, accurate imaging for diagnosis and prognosis.

Although CTPA has largely solved the diagnostic question, “Does the patient have PE?” new questions have arisen. These include: Do patients warrant concurrent CTPA plus imaging of the pelvis and lower extremities? What is the risk for subsequent PE after negative CTPA? Is there an ideal management algorithm in patients with isolated subsegmental PE? What is the optimal imaging tool for evaluation of women who are either pregnant or of child bearing age? How can the patient radiation doses be reduced without compromising diagnostic capabilities? This review is to address these questions and looks toward the future of PE imaging.

**Imaging Approaches in Patients With Suspected PE**

Before the mid 1990s, ventilation perfusion scanning (V/Q) was the imaging modality of choice for the evaluation of patients with clinically suspected acute PE. In 1979, V/Q lung scanning was used for 80% of patients. By 2001, CT use surpassed V/Q imaging. In a meta-analysis of 15 studies in which CTPA was used to exclude acute PE, the clinical validity of CTPA was found to be similar to conventional angiography (1.0% to 2.8% for CTPA and 1.1% to 2.9% for conventional angiography). Clinical validity is defined as the accuracy with which a test identifies or predicts a patient’s clinical status. For CTPA, this includes the ability of the technology to exclude clinically significant PE. This is consistent with the replacement of conventional invasive pulmonary angiography with MDCT. Ghaye et al reported that with a 4-detector MDCT scanner, the peripheral pulmonary arteries to the fifth order could be accurately analyzed using 1.25-mm-thick slices. Similar results have been shown by others. However, visualization does not directly imply accuracy; confirmation is challenging but required to fully evaluate advanced CT technology.

The prognostic significance and clinical importance of small filling defects remain subject to debate. Burge et al assessed the association between the increasing use of CT for suspected acute PE and the annual rates of PE diagnosis and mortality (Figure 1). Based on the New York State’s Planning and Research Cooperative System database for PE diagnosis and mortality between 1994 and 2004, the rate of PE diagnosis from better imaging did not have a corresponding decline in mortality.

The data from Burge et al emphasize that imaging should be supported with clinical risk stratifications. These systems include the Wells criteria, which use a 12.5-point scale (Table 1), Geneva Prognostic index which uses an 8-point scale, PE rule out criteria or the Pisa model. As demonstrated in the Christopher study (Figure 2) of 3306 patients, a D-dimer within normal limits eliminates the need for further imaging in patients with an unlikely clinical probability score, with a 3-month incidence of venous thromboembolic disease of 0.5%. These data were subsequently validated in a prospective study. In addition, cardiac biomarkers including troponin and natriuretic peptides are important to determine prognosis.

**Specific Imaging Considerations**

**CT Angiography Alone or With CT Venography**

Performing CTPA with CT venography of the pelvis and lower extremities to increase the diagnostic yield of CTPA...
has been a subject of debate. The 2006, PIOPED II publication\(^2\) concluded that in patients with suspected acute PE, CT angiography–CT venography of the thigh and pelvic veins has higher sensitivity (90%) than CTPA alone (83%). With the addition of CT venography, the gain in negative predictive value\(^2\) was 2%, from 95% to 97% (14 additional patients with PE among a total of 824 patients with a reference diagnosis). Hunsaker et al\(^28\) assessed the utility of routinely performing CT venography with CTPA in all patients and found that CT angiography–CT venography yielded an incremental value of 3.4% for the entire studied cohort of 824 patients. However, when patients were divided into high-risk and low-risk groups, the incremental value was only 0.72% for the low-risk group and 2.6% for the high-risk group, defined as patients with prior history of deep venous thrombosis or PE or with symptoms in the legs consistent with deep venous thrombosis. Similar results were reported by Kalva et al\(^39\); this group also reported an increase in radiation dose. Based on collective data, we do not recommend or routinely perform CT venography in patients scheduled for CTPA.

The Clinical Value of a High Image Quality Negative CTPA

A great value of MDCT is the ability to rapidly exclude PE in patients with challenging clinical presentations. Goodman et al\(^30\) found, using single detector CT, that the prevalence of clinically evident PE after negative CTPA using was 1.0%. Even the value of 1% (99% negative predictive value) may be conservative for a high image quality modern CTPA with MDCT. Goodman et al\(^30\) concluded that a negative CTPA was reliable enough to withhold anticoagulation therapy; this is standard practice. Donato et al\(^41\) found a rate of 1.7% embolic events in their cohort of 239 patients, concluding that a negative helical CT has an excellent prognosis for the absence of future venous thromboembolic disease. In the largest series, using helical CT, Swensen et al\(^42\) found a 0.8% incidence of venous thromboembolic disease among patients whose scans were interpreted as normal.

### Table 1. Wells Model for Determining the Clinical Probability of Pulmonary Embolism

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical signs and symptoms of DVT (objectively measured leg swelling and pain w/palpitation in the deep-vein system)</td>
<td>3.0</td>
</tr>
<tr>
<td>Heart rate &gt;100 beats/min</td>
<td>1.5</td>
</tr>
<tr>
<td>Immobilization for ≥3 consecutive days (bed rest except to go to bathroom) or surgery in previous 4 weeks</td>
<td>1.5</td>
</tr>
<tr>
<td>Previous objectively diagnosed pulmonary embolism or DVT</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>1.0</td>
</tr>
<tr>
<td>Cancer (with treatment within past 6 months or palliative treatment)</td>
<td>1.0</td>
</tr>
<tr>
<td>PE likely or more likely than alternative diagnoses (on the basis of history, physical exam, chest radiography, ECG, and blood tests)</td>
<td>3.0</td>
</tr>
</tbody>
</table>

The following criteria are used in scoring: ≤4, low probability, >4, high probability, <2, low probability, 2.0 to 6.0, moderate probability, and >6.0, high probability.\(^{16,21,24}\)

*Table from Stein et al.\(^2\) Reprinted with permission from the New England Journal of Medicine.

**MDCT Is the Imaging Test of Choice for Patients With Clinically Suspected PE**

CTPA with MDCT is the first-line imaging study (Figure 3 and Figure 4).\(^5\) Conventional pulmonary angiography, once considered the gold standard for the diagnosis of PE, is now performed only when noninvasive imaging modalities have been exhausted or when a catheter intervention is planned. We recommend CTPA even when intervention is planned because MDCT gives valuable information on clot burden for the entire pulmonary arterial tree (Figure 5 and Figure 6). A retrospective reexamination of PIOPED II cases in which there was discordance between the findings on CTPA and catheter angiography demonstrated that catheter angiography can miss PE detected with CTPA, particularly at the subsegmental level.\(^33\)

The absence of deep venous thrombosis does not exclude PE. Any patient with cardiorespiratory symptoms should undergo CTPA, with V/Q scintigraphy as a second option to be used primarily for patients with severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m\(^2\)) or for specific clinical scenarios (described below).

The PIOPED study\(^3\) concluded that a high probability V/Q scan usually indicated PE, whereas a near normal/near scan indicated that PE was unlikely. V/Q scanning was unhelpful for diagnosis in patients whose scans were interpreted as indeterminate (73%, 676 of the 931 patients).\(^3\) Retrospective analysis of PIOPED II data\(^34\) excluded those patients with intermediate or low probability V/Q scans and analyzed only scans which were high probability, very low probability, or normal. This resulted in sensitivity and specificity values of 77.4% and 97.7%, respectively.\(^34\) Several studies (Table 2) have compared the sensitivity and specificity of CTPA versus V/Q imaging.\(^2,15,30,34–38\)

Magnetic resonance pulmonary angiography is the most recent modality that will be clinically used in a complementary role with MDCT (Figure 7); current literature includes small trials.\(^39–43\) Magnetic resonance pulmonary angiography
protocols are more time-consuming and complex than CTPA; details are described in a recent review. Briefly, static imaging typically uses 3-D fast spoiled gradient echo sequences before and after contrast using very short repetition time (≤5 ms) and echo time (≤2 ms) to acquire the full imaging data within a single 15 to 30 second breath-hold. State-of-the-art gradient systems are required to achieve short repetition and echo times; this probably is a reason for less widespread use of magnetic resonance pulmonary angiography. Dynamic imaging uses a modified time-resolved 3-D gradient-echo sequence with short spacing between frames to acquire at least 1 volume with arterial-only enhancement.40

Figure 2. Diagnostic algorithm for evaluation of patients with suspected PE. Adapted from the Writing Group for the Christopher Study Investigators. Reprinted with permission from the Journal of the American Medical Association.

Figure 3. Suggested imaging algorithms for suspected PE in selected clinical scenarios in patients with high clinical probability.
Early magnetic resonance pulmonary angiography studies report sensitivities and specificities ranging from 77% to 100% and 95% to 98%, respectively. A 2006 study from Kluge et al studied 62 patients, showing excellent results for the combination of balanced steady-state free precession (non-contrast imaging) plus 2 contrast-enhanced sequences: time-resolved imaging and gradient echo imaging with an acceleration of 2. Although it would be difficult to implement all sequences into a practical clinical protocol, magnetic resonance pulmonary angiography will be studied in PIOPED III.

Imaging Considerations in Specific Patient Groups

Patients With Isolated Subsegmental PE

High spatial resolution MDCT enables visualization of isolated subsegmental PE (Figure 5), but as noted above, the clinical significance of small emboli remains uncertain. The reported rate of these small clots ranges from 1.0% to 5.4%. Eyer et al studied the referring clinicians’ responses to results of CTPA in 207 patients; 77 with isolated subsegmental PE plus 130 patients with inconclusive findings. Most isolated subsegmental PE patients were treated. However, among the 32 patients who were not treated, no patient had recurrent PE after 3 months. It is also possible that the diagnosis was not correct, based on the poor positive predictive value of apparent subsegmental PE in PIOPED II. These observations raise the possibility that small PE are relatively common and healthy lungs act as a filter, protecting the pulmonary circulation.

Radiation Dose and Methods of Dose Reduction

It is important to consider patient radiation doses and weigh risk versus benefits of imaging. This is challenging in patients with clinically suspected PE because diagnosis heavily depends on imaging, particularly CTPA, and the risk from a radiation-induced cancer is impossible to assess with accuracy. Imaging should follow the ALARA (As Low as Reasonably Achievable) principle, noting that the shortest latent period (blood-borne malignancies) is roughly a decade and solid tumors is probably 20 years. Thus, for those patients with a life expectancy less than 10 years, high quality imaging should be performed without equivocation for radiation concerns. For imaging younger patients with a longer life expectancy, the radiation exposure, in particular limiting the use of serial imaging, must be an active part in diagnosis and management.

The effective radiation dose for CTPA protocols is generally between 2.2 and 7 mSv. Assuming a background dose of 2.5 mSv per year, the risk from CTPA is roughly 1 to 2.5 times that from background radiation exposure. The imaging field of view includes the lungs and breasts; dose can be reduced by shielding, lowering the peak kilovoltage or lowering the tube current. For CTPA, the most commonly applied techniques are lowering the peak kilovoltage...
can in some cases supplant imaging in the 120 to 140 range. Hurwitz et al\textsuperscript{47} found that a reduction from 140 to 120 peak kilovoltage reduced the average breast dose by 28%. When breast shielding was added, the dose reduction was 55%. The average reduction in lung dose was 47%. Additional studies\textsuperscript{54,55} demonstrate dose reductions of approximately 40% to 60% when the peak kilovoltage is lowered from 120 to 80. In general, lower dose protocols result in images with greater noise and thus reductions must consider image quality and diagnostic confidence\textsuperscript{56}.

Evaluation for PE in Pregnancy and in the Reproductive Period
The pregnant patient presents unique challenges. The D-dimer may be elevated because of pregnancy\textsuperscript{57–59} and is

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Figure 5. A, Axial image in mediastinal windows; and B, maximum intensity projection images in mediastinal windows are taken from a CTPA performed for suspected acute PE shows heavy clot burden bilaterally in the central, lobar, and segmental levels. Note how well clot burden is seen on the coronal maximum intensity projection image.

Figure 6. A, Axial image in lung windows; B, axial image in mediastinal windows; and C, maximum intensity projection image in mediastinal windows from CTPA study performed to assess for PE shows left-sided PE centrally extending into the lobar and segmental arteries to the left lower lobe. Note the small left-sided effusion and the consolidation in the left lung caused by pulmonary infarction.
therefore unreliable as a screening test. Regarding radiation, imaging must consider both the mother and the fetus. A 2006 United Kingdom survey study by Groves et al.\textsuperscript{60} assessed the radiation knowledge for CTPA and V/Q imaging among 161 health care providers. For the mother, the CTPA dose (2.2 to 6.0 mSv) was higher than V/Q (1.4 mSv); for the fetus, scintigraphy was much higher (640 to 800 Gy) when compared with CTPA (3 to 131 Gy). As the pregnancy approached term, the fetal radiation dose for both CTPA and V/Q increased, and the differences between modalities become less.

Scarsbrook et al.\textsuperscript{61} studied 105 pregnant patients with symptoms suggestive of acute PE who were primarily studied with nuclear perfusion lung scans using half the normal radioisotope to decrease radiation. Among the 105 patients, 94 had perfusion scans without ventilation, 9 had CTPA, and 2 had both. Fetal radiation dose was 0.01 to 0.06 mGy for CTPA and 0.11 to 0.22 mGy for perfusion scintigraphy.

Although compression sonography has been suggested as an initial imaging study,\textsuperscript{5} we recommend and promptly perform CTPA for patients with high clinical suspicion of PE, particularly where a delay in diagnosis can prove life-threatening. Regarding intravenous iodinated contrast media, there are no known mutagenic or teratogenic effects. However, suppression of neonatal thyroid function can occur. Although it is not our standard practice, the combination of compression ultrasound and V/Q is reasonable in pregnancy. If CTPA is performed, decreasing radiation exposure should be strongly considered, for example internal shielding with enteric barium sulfate\textsuperscript{63} or external shielding with bismuth shields.\textsuperscript{48} From a population radiation perspective, these dose reduction methods are even more important for imaging nongravid women of reproductive age. Using data from the Rochester Epidemiology Project,\textsuperscript{64} the reported incidence of venous thromboembolic disease is higher in the postpartum period than during pregnancy (511.2 versus 95.8 per 100,000), and the incidence of PE is 15 times higher in the first 3 postpartum months when compared with that during pregnancy (159.7 versus 10.6 per 100,000).\textsuperscript{65}

### Table 2. Comparison of Modalities in Evaluation of Acute PE: CT Versus V/Q or Conventional Angiography

<table>
<thead>
<tr>
<th>Study</th>
<th>All levels of acute PE</th>
<th>PE Present</th>
<th>PE Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author (ref)</td>
<td>CT Detector</td>
<td>Sensitivity</td>
<td>Specificity</td>
</tr>
<tr>
<td>Drucker\textsuperscript{37}</td>
<td>1</td>
<td>53%, 60%/...</td>
<td>81%, 97%/...</td>
</tr>
<tr>
<td>Remy-Jardin\textsuperscript{34}</td>
<td>1</td>
<td>91%/...</td>
<td>78%/...</td>
</tr>
<tr>
<td>Goodman\textsuperscript{28}</td>
<td>1</td>
<td>97%/90%</td>
<td>98%/94%</td>
</tr>
<tr>
<td>Qanadli\textsuperscript{35}</td>
<td>2</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Coche\textsuperscript{36}</td>
<td>4</td>
<td>96%/86%</td>
<td>98%/88%</td>
</tr>
<tr>
<td>Winer-Muram\textsuperscript{13}</td>
<td>4</td>
<td>100%/86%</td>
<td>89%/100%</td>
</tr>
<tr>
<td>Sostman\textsuperscript{33}</td>
<td>...</td>
<td>.../77.4%</td>
<td>.../97.7%</td>
</tr>
<tr>
<td>Stein\textsuperscript{24}</td>
<td>4</td>
<td>83%/...</td>
<td>96%/...</td>
</tr>
</tbody>
</table>

PE indicates pulmonary embolism; V/Q, ventilation/perfusion scan; CT, computed tomography; Angio, conventional angiography; PPV, positive predictive value; and NPV, negative predictive value.

### Right Ventricular Structure and Function

Risk stratification based on echocardiography assessment of right ventricular (RV) size and function is the best validated approach to prognostication in patients with acute PE.\textsuperscript{66} Moderate or severe RV hypokinesis, persistent pulmonary hypertension, a patent foramen ovale, and free-floating thrombus in the right atrium or RV help identify patients at high risk of death or recurrent thromboembolism.\textsuperscript{67–70} Echocardiography is often useful to assess for an alternative cause of shock such as pericardial tamponade, ventricular rupture, aortic dissection, or myocardial infarction. Patients without signs of RV dysfunction are unlikely to have a hemodynamically

![Figure 7. A, Coronal contrast-enhanced CT; and B, Gadolinium-enhanced coronal MRI images from pulmonary studies performed for suspected PE in the same patient shows filling defect in the left lower lobe lobar artery consistent with acute PE.](http://circimaging.ahajournals.org/.../7.png)
significant PE. For those patients in whom transthoracic imaging is unsatisfactory, transesophageal echocardiography can be performed.

**Cardiac Biomarkers**

Cardiac biomarkers include cardiac troponin and natriuretic peptides, and when elevated portend an ominous prognosis. Elevated cardiac troponin levels in acute PE are only briefly and mildly elevated but appear to correlate with the extent of RV dysfunction. The pathophysiology is postulated to be an abrupt increase in RV wall tension with compression of the right coronary artery and myocardial microinjury. Elevated levels of brain natriuretic peptides are related to ventricular myocyte stretch and indicate RV dysfunction. The combination of RV hypokinesis demonstrated by echocardiography plus elevated cardiac biomarkers identifies the highest-risk patients.

**CTPA Evaluation of the RV**

Several CTPA signs of RV dysfunction have been described. Because the CTPA craniocaudal field of view includes the heart, evaluation of the RV extends the role of CT to include prognosis. RV enlargement portends a complicated hospital course. The best studied parameter to evaluate RV enlargement is the RV/left ventricular (LV) diameter ratio, as first suggested by Reid and Murchison. This ratio can be measured on either a 4-chamber reformatted view or from the standard axial CTPA images. There is increasing evidence, including evaluation of more than 600 patients using 30-day mortality as an end point, that RV/LV diameter ratios measured from the standard axial CTPA images are equivalent to those obtained from reformatted views and thus the time needed for 4-chamber reformations and the dependence on advanced postprocessing tools are probably unnecessary.

When a prior negative CTPA is available for comparison, it should be used to distinguish acute RV dilatation from PE as opposed to baseline enlargement of the RV that can occur due to underlying conditions such as chronic lung disease. An interval increase in the RV/LV diameter ratio is significantly more accurate for predicting mortality after acute PE when compared to measurements made from one isolated chest CT scan.

When compared with echocardiography, the advantage of CTPA assessment of the RV is the simplicity in determining the RV/LV diameter ratio from the same images used to diagnose PE. Echocardiography is an additional cost and requires an appropriate acoustic window and technical expertise; this study is often not immediately available in the evenings and/or weekends. The principal advantage of echocardiography is the assessment of cardiac motion and function. As noted below, this can be evaluated with ECG-gated CTPA, but ECG gating is not routine in CTPA, primarily because it delivers more radiation. To our knowledge, there has been no direct comparison between CTPA and echocardiography markers of RV dysfunction.

Other CTPA prognostic markers such as pulmonary arterial obstruction index, bowing of the interventricular septum, and reflux of contrast into the inferior vena cava or hepatic veins have been used with varying degrees of success. However, the RV/LV diameter ratio should be reported on all studies; we have maintained this practice for the last several years.

**Future Directions**

**ECG-Gated CTPA**

CTPA with ECG gating does not improve pulmonary artery visualization when compared with a routine acquisition. Longer scan times may exacerbate artifacts from respiratory movement and bolus timing. Prospective gating generally decreases the radiation burden in comparison to retrospective gating. However, even with optimized protocols and wide area detectors, scan times and radiation levels exceed those with optimized nongated protocols.

Although ECG-gated CTPA may not improve diagnostic accuracy for the diagnosis of PE, it may help evaluate prognosis. Imaging of both systole and diastole enables computation of RV and LV ejection fraction. However, even with the fastest technology, the temporal resolution of CT remains inferior to echocardiography. Nevertheless, small ECG-gated CT studies have demonstrated feasibility. The first study (29 patients with PE and 37 patients without PE) found that RV ejection fraction, RV/LV diameter ratio, and RV end-systolic volumes were significantly different between those patients with and without PE. The second study of 30 patients with PE found that ECG-gated end-diastolic RV/LV diameter ratios do not differ significantly from non gated RV/LV ratios and suggested that retrospective ECG gating with modest temporal resolution is unlikely to improve prediction of mortality after PE.

**CT Perfusion**

Although not used clinically at present, recent work in 117 patients with suspected PE demonstrated that a dual-energy protocol has the potential to assess the pulmonary arteries plus perfusion in a single scan. The reported radiation doses were comparable to standard CTPA. Wide-area detector CT has up to 16 cm craniocaudal coverage per axial acquisition and has been used anecdotally for pulmonary perfusion. One possible application is patients with isolated subsegmental PE; specifically, conservative management without anticoagulation could be supported with normal or near-normal perfusion in the associated region. Perfusion imaging may also be helpful to differentiate between pulmonary hypertension from chronic thromboembolic disease versus nonembolic causes.

**V/Q Single-Photon Emission CT**

Newer technetium-based ventilatory agents, although not yet routinely available in the United States, have a smaller particle size with respect to Xe-133 and thus greater lung distribution. Single-center reports suggest that single-photon emission CT scintigraphy is more accurate and has a lower indeterminate rate than planar scintigraphy. Just as there is a need to evaluate the latest CT technology for PE, so is there a need to evaluate single-photon emission CT so that nuclear imaging test characteristics can be optimized for clinical algorithms.
Molecular Imaging
A fibrin-targeted, gadolinium-based MR contrast agent has been used in porcine models to visualize PE. A phase II trial (11 humans, known arterial thrombus) did not include PE patients but was promising for thrombus visualization. The reported optimal temporal imaging window is at least 2 hours after injection; this would limit clinical utility for emergent imaging.

Summary
An imaging strategy consisting of clinical pretest probability, the D-dimer, and CTPA should be the mainstay of diagnosis in patients with suspected PE. Alternative imaging strategies may be tailored to specific clinical situations. New diagnostic modalities and refinement of currently available techniques ensure that the imaging of PE will continue to evolve.

Disclosures
Dr Rybicki received research grants (significant) from Toshiba Medical Systems Corporation, Bracco Diagnostics, and Vital Images.

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Circ Cardiovasc Imaging. 2010;3:491-500
doi: 10.1161/CIRCIMAGING.109.855981
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-9651. Online ISSN: 1942-0080

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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