Scintigraphic Diagnosis of Acute Pulmonary Embolism: From Basics to Best Practices

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In this article the technique, interpretation, and diagnostic performance of scintigraphy for the diagnosis of acute pulmonary embolism (PE) are reviewed. Lung scintigraphy has stood the test of time as a reliable and validated examination for the determination of PE. Ventilation/perfusion (V/Q) lung scintigraphy assesses the functional consequences of the clot on its downstream vascular bed in conjunction with the underlying ventilatory status of the affected lung region, in contrast to CT pulmonary angiography (CTPA), which visualizes presence of the clot within affected vessels. Most-commonly used ventilation radiopharmaceuticals are Technetium-99m labeled aerosols (such as 99mTc-Technetium-DTPA), or ultrafine particle suspensions (99mTc-Technegas) which reach the distal lung in proportion to regional distribution of ventilation. Perfusion images are obtained after intravenous administration 99mTc-labeled macro-aggregated albumin particles which lodge in the distal pulmonary capillaries. Both planar and tomographic methods of imaging, each favored in different geographical regions, will be described. Guidelines for interpretation of scintigraphy have been issues by both the Society of Nuclear Medicine and Molecular Imaging, and by the European Association of Nuclear Medicine. Breast tissue is particularly radiosensitive during pregnancy due to its highly proliferative state and many guidelines recommend use of lung scintigraphy rather than CTPA in this population. Several maneuvers are available in order to further reduce radiation exposure including reducing radiopharmaceutical dosages or omitting ventilation altogether, functionally converting the study to a low-dose screening examination; if perfusion defects are present, further testing is necessary. Several groups have also performed perfusion-only studies during the COVID epidemic in order to reduce risk of respiratory contagion. In patients where perfusion defects are present, further testing is again necessary to avoid false-positive results. Improved availability of personal protective equipment, and reduced risk of serious infection, have rendered this maneuver moot in most practices. First introduced 60 years ago, subsequent advances in radiopharmaceutical development and imaging methods have positioned lung scintigraphy to continue to play an important clinical and research role in the diagnosis of acute PE.

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Pulmonary embolism (PE) remains a diagnostic challenge. Both missed and excess diagnoses have undesirable consequences. Undiagnosed PE can be fatal in up to 30% of patients,1 while overdiagnosis and unnecessary anticoagulant therapy carries risk of bleeding,2 exacerbated by the trend towards indefinite duration of anticoagulant therapy in many patients.3,4 Diagnostic management of patients with suspected acute PE is based not on a single and definitive test but on the application of an integrated diagnostic strategy, which begins with clinical probability assessment and D-dimer testing. In patients with a nonhigh or unlikely clinical probability but
positive D-dimer, and in patients with a high or likely clinical probability, lung imaging is required. CT pulmonary angiography (CTPA) and ventilation/perfusion V/Q lung scintigraphy represent two noninvasive imaging options which have been validated for the diagnosis of PE. These examinations leverage differing diagnostic approaches; CTPA visualizes the clot within the vessel, while ventilation/perfusion (V/Q) scintigraphy assesses the functional consequences of the clot on the distal arteriolar pulmonary blood flow, that is, the downstream vascular bed, in conjunction with evaluating the ventilatory status of the affected lung region.

CTPA is currently the most-commonly performed imaging test for PE. While well-validated, it is not without limitations, including administration of iodinated contrast, a rate of approximately 5% inconclusive examinations, relatively high radiation exposure to the breasts in comparison to many alternative tests, and growing concern regarding possible overdiagnosis and overtreatment of PE.

Lung scintigraphy, the subject of this article, has also been widely validated in diagnostic accuracy and management outcome studies. It has a critical clinical role to play in patients who cannot tolerate iodinated contrast material and has been promoted over CTPA in specifically vulnerable patient groups due to a more favorable radiation profile. Scintigraphic methods also have a unique quantitative and physiologic nature and continue to be used to advance our understanding of pathophysiology of thromboembolic disease and its resolution.

Study Technique

The scintigraphic diagnosis of PE is made by comparing the distribution of ventilation (V) and perfusion (Q) within the lungs. Ventilation images are acquired after inhalation of radioactive inert gases (133Xenon), aerosols (such as 99mTc-Technetium-DTPA), or ultrafine particle suspensions (99mTc-Technegas) which reach the distal lung in proportion to regional distribution of ventilation. Xenon-based methods allow for a highly physiologic assessment of lung volumes and regional ventilation (Fig. 1) however their routine use is hampered by lack of availability. Furthermore, because Xenon images are acquired in a dynamic and not steady-state condition, they are typically only captured in one conjugate view (anterior and posterior projections) which may hamper visualization of defects, and limits comparison with findings from the perfusion study. Ventilation methods that employ 99mTc-labeled aerosols have become dominant in the United States, based on their availability, ease of use, and ability to be imaged in multiple projections. In countries where approved for use, 99mTc-Technegas, an ultrafine particle which exhibits near optimal distribution properties, has become the preferred radiopharmaceutical for ventilation imaging. Perfusion images are obtained after intravenous administration of several hundred thousand 99mTc-labeled macro-aggregated albumin (MAA) particles, which lodge in the lung capillary network according to regional blood flow.

Particle sizes range between 10 and 90 μm, avoiding particles larger than 150 μm, so that each particle occludes a single capillary and has a minimal effect on overall hemodynamics.

In standard lung scintigraphy, ventilation is performed first, followed by perfusion. While both phases of the examination typically utilize 99mTc-labeled compounds, it is possible to sequentially perform the second examination without interference from the first radiopharmaceutical because the amount of the second-administered radiopharmaceutical is 3 to 4-fold greater than the amount initially administered. In this manner, the activity remaining from the initial examination is rendered relatively insignificant compared to the second, larger dosage.

For many years, the standard method of scintigraphic lung imaging has been the planar technique, where a handful of 2-dimensional images are acquired about the chest. Six or eight views are typically obtained (anterior, posterior, right and left posterior oblique, right and left lateral, right and left anterior oblique); by imaging in various obliquities, defects can be seen to advantage, and location of abnormalities can be disambiguated according to their differing appearance on various projections (Fig. 2). At present, planar imaging remains the predominant method of imaging in the United States. While small defects may be missed due to an imperfect sensitivity, consensus is that larger defects of clinical significance are adequately visualized.

Pulmonary scintigraphy can also be performed using tomographic techniques, resulting in a 3-dimensional representation of pulmonary activity. In this method, the gamma-camera acquires as many as 120 low-count images while revolving around the patient. These data are then reconstructed to determine the underlying distribution of activity within the thorax, a method termed “single photon emission computed tomography” or “SPECT.” The advantage of SPECT imaging over conventional 2-dimensional imaging is the ability to minimize effect of overlapping structures, better visualize the medial-basal segment, and more precisely characterize the size, shape, and location of defects (Fig. 3). SPECT imaging also allows co-registration of the scintigraphic data with CT images, routinely available on current-generation SPECT-CT cameras; the latter can be also used to perform attenuation correction of the scintigraphic images. V/Q SPECT has been widely implemented in daily practice in Australia, Canada, and Europe.

Over the last decade, efforts have been made to translate success in lung SPECT imaging to positron-emission tomography (PET), relying on identical physiologic principles but leveraging the superior imaging characteristics of PET. In these instances, the 99mTc-radionuclide used to label both Technegas and MAA in SPECT imaging has been exchanged with 18F, a generator-based positron-emitting radionuclide with a 68 minute half-life. As of today, these efforts remain exploratory, at least in part due to the more restricted availability of PET cameras.

Hand-in-hand with developments in imaging technology have been innovations in the fields of image analysis, processing and artificial intelligence, techniques which have all
been applied to lung scintigraphy. These advanced methods include methods of shortening acquisition times and improving image reconstruction, automatic segmentation of lung, creation and display of parametric images which compare V and Q, and computer-aided detection and diagnosis of abnormalities. As in much of diagnostic imaging, further developments are being rapidly pursued in this domain. A systematic review of artificial intelligence in lung scintigraphy appears elsewhere in this Seminars issue.

**Image Interpretation and Diagnostic Performance**

**Physiologic Underpinnings**

Perfusion scintigraphy was initially introduced in 1964, based on the concept that a PE will occlude a segmental or subsegmental pulmonary arterial branch and prevent lodging of radiopharmaceutical in the downstream capillary bed. While sensitive to the detection of emboli, presence of perfusion defects was determined to lack specificity for PE. Areas of pulmonary hypoxia, as may be seen in pneumonia or bronchospasm, also lead to reflex vasoconstriction which mimics the appearance of embolic defects. To improve specificity, several groups therefore suggested contrasting perfusion images with those of ventilation in order to differentiate primary perfusion defects (caused by PE) from those that are secondary to regions of hypoventilated lung (which do not usually represent PE). While the hallmark of PE is therefore “mismatched” perfusion defects (normal ventilation and abnormal perfusion), a situation where PE may also present with regionally decreased ventilation is when embolism has proceeded to pulmonary infarction. In this circumstance, the matched ventilation-perfusion defect also corresponds to a radiographic density.
reflecting infarction and intrapulmonary hemorrhage. Correlation with chest radiograph helps exclude this possibility in the setting of a matched defect. Common pulmonary disorders and their manifestation on V/Q scintigraphy are described in Table 1.

Another cause of ambiguity is when a patient in whom episodes of PE have been diagnosed in the past presents anew with acute symptomatology. If no intervening studies have been performed to document resolution of prior defects, presence of mismatched V/Q defects in the same distribution as those seen during the prior episode of embolism is ambiguous for recurrent PE as it is possible that the currently visualized defects remain from the prior episode and do not represent a new finding. For this reason, many authors have suggested that there is clinical utility in performing a follow-up V/Q scan after 3-6 months of anticoagulant therapy which then serves as a new baseline in cases of subsequent suspicion of PE (Fig. 2).

Criteria of Interpretation—Planar Scintigraphy

Much has been written on criteria of lung scan interpretation over the decades since it was introduced, we will focus on guidelines and best practices that reflect the current consensus views. Guidelines for interpretation of V/Q planar images have been elaborated by the Society of Nuclear Medicine and are largely modeled upon the revised PIOPED criteria (Table 2). Diagnostic strategies based on planar V/Q scintigraphy have been validated in large management outcome studies indicating that a normal perfusion study safely excludes the diagnosis of PE while a high probability V/Q scan (≥2 segmental mismatched Q defects) is considered diagnostic for PE in patients with appropriate pretest probabilities of disease. Between these two categories, low and intermediate probability V/Q scans are usually classified as “non-diagnostic” as further diagnostic testing (typically a
lower limb compression ultrasonography) is required to confirm or exclude the diagnosis. A number of ancillary lung scan findings have been described that are not included in published algorithms, which may provide a further degree of diagnostic refinement. A high rate of nondiagnostic results remains the most serious drawback of planar V/Q scintigraphy.

Criteria of Interpretation—Tomography
Tomographic (SPECT) imaging has been applied to lung scintigraphy in an effort to improve diagnostic performance. A binary reporting approach (“PE” or “no PE”) using a diagnostic cut-off of 1 segmental or 2 subsegmental mismatched perfusion defects has been proposed and is widely accepted within the nuclear medicine community, especially outside of the United States (table 3). In a recent systematic review of SPECT imaging, 13 diagnostic accuracy studies were identified. Sensitivity ranged from 83% (95% confidence interval [CI], 61-95) to 100% (95% CI, 77-100), and specificity from 87% (95% CI, 78-87) to 100% (95% CI, 93-100). Furthermore, SPECT imaging dramatically decreased the proportion of nondiagnostic scans (<5%). The European Association of Nuclear Medicine guidelines for lung scintigraphy strongly recommend SPECT imaging for PE diagnosis. Large management outcome studies assessing diagnostic strategies based on the V/Q SPECT are still lacking.

Table 1 Clinical Entities, Imaging Findings, Pathophysiologic Mechanisms, and Resultant Imaging “Pattern”

<table>
<thead>
<tr>
<th>Clinical Entity</th>
<th>Radiographic Findings</th>
<th>V Findings</th>
<th>V Mechanism</th>
<th>Q Findings</th>
<th>Q Mechanism</th>
<th>Pattern Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal lung</td>
<td>Clear</td>
<td>No defects</td>
<td>Patent airways</td>
<td>No defects</td>
<td>Patent PA flow</td>
<td>V/Q normal</td>
</tr>
<tr>
<td>Acute PE</td>
<td>Clear</td>
<td>No defects</td>
<td>Patent airways</td>
<td>Regional defects</td>
<td>Acute PA occlusion</td>
<td>V/Q mismatch*</td>
</tr>
<tr>
<td>COPD/Asthma</td>
<td>Clear</td>
<td>Regional defects</td>
<td>Decreased air flow</td>
<td>Regional defects</td>
<td>Reflex vaso-occlusion</td>
<td>V/Q match</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Parenchymal opacity</td>
<td>Regional defects</td>
<td>Debris in alveoli</td>
<td>Regional defects</td>
<td>Reflex vaso-occlusion</td>
<td>Triple match**</td>
</tr>
<tr>
<td>Pulmonary infarction</td>
<td>Parenchymal opacity</td>
<td>Regional defects</td>
<td>Debris in alveoli</td>
<td>Regional defects</td>
<td>Acute PA occlusion</td>
<td>Triple match**</td>
</tr>
<tr>
<td>Chronic PE</td>
<td>Clear</td>
<td>No defects</td>
<td>Patent airways</td>
<td>Regional defects</td>
<td>Chronic PA occlusion</td>
<td>V/Q mismatch*</td>
</tr>
</tbody>
</table>

COPD, chronic obstructive pulmonary disease; PA, pulmonary artery; PE, pulmonary embolism; Q, perfusion; V, ventilation.

*,**doppelgangers.
SPECT can be combined with low-dose CT images to portray nonthromboembolic findings such as thickened fissures, emphysema or pneumonia which may explain perfusion defects. V/Q SPECT-CT has similar sensitivity as V/Q SPECT but higher specificity for PE.33 It should be noted that the use of a low-dose CT instead of ventilation imaging results in a high rate of false positive results.43-45

Special Circumstances

Pregnancy

PE is a major complication of pregnancy and remains a leading cause of maternal mortality in the developed world.46

| Table 2 Criteria of Lung Scan Interpretation According to SNMMI/Modified PIOPED II Criteria |
|---------------------------------------------|-----------------------------------------------|
| High likelihood ratio                      | ≥2 large mismatched (V/Q) segmental defects   |
| Normal                                      | No perfusion defects                          |
| Very low likelihood ratio                   | Nonsegmental Q defect < CXR lesion           |
|                                            | 1-3 small segmental defects                   |
|                                            | Solitary matched defect in mid or upper lung |
|                                            | Solitary large pleural effusion              |
|                                            | ≥2 matched V/Q defects with regionally normal |
|                                            | CXR                                           |

Nondiagnostic (intermediate)

CXR, chest radiograph; Q, perfusion; V, ventilation.

*“Very low likelihood ratio” is folded into “Normal” in some implementations.

Nonetheless, because of the overlap of signs and symptoms between physiologic changes of pregnancy and venous thromboembolism, the prevalence of PE among pregnant women tested for suspected acute PE is low, less than 10%.47

Both CTPA and lung scintigraphy seem equally valid to rule out PE in pregnancy. In a recent systematic review and meta-analysis of CTPA and V/Q scanning performed in pregnant patients with suspected PE, the pooled rate of false negative test results was 0% for both imaging strategies.48

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<table>
<thead>
<tr>
<th>Table 3 Criteria of Lung Scan Interpretation Modified From EANM†</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
</tr>
<tr>
<td>No PE</td>
</tr>
<tr>
<td>Matched or reversed-mismatched V/Q defects of any size, shape or number in the absence of mismatch.</td>
</tr>
<tr>
<td>Mismatch that does not have a lobar, segmental or subsegmental pattern</td>
</tr>
</tbody>
</table>

Nondiagnostic for PE*

Multiple V/Q abnormalities not typical of specific diseases.

PE, pulmonary embolism; Q, perfusion; V, ventilation.

*“Nondiagnostic for PE” category is infrequently encountered and has been considered “No PE” in some implementations.

†SPECT imaging preferred to planar scintigraphy. “Tomographic imaging has higher sensitivity and specificity for PE compared with planar imaging.”

| Figure 4 Pregnancy. Twenty-six-year-old pregnant female with shortness of breath and tachycardia, referred for evaluation of pulmonary embolism. Planar perfusion-only study was performed with an imaging time of 3 minutes per frame following injection of 37 MBq of 99mTc-MAA. Perfusion is normal and no further imaging is necessary to exclude the diagnosis of pulmonary embolism. Total count of the anterior 3-minute image was 253 k-counts. Ant, anterior; L Lat, left lateral; LAO, left anterior oblique; LPO, left posterior oblique; Post, posterior; R Lat, right lateral; RAO, right anterior oblique; RPO, right posterior oblique. |
Furthermore, the pooled risks of a nondiagnostic test for CTPA and V/Q planar scintigraphy were comparable, 12% (95% CI: 8-17) and 14% (95% CI: 10-18), respectively. Indeed, the risk of a nondiagnostic CTPA is relatively high in pregnant women, in part because of hemodilution, and due to elevation of the diaphragm which accentuates the interruption of contrast by nonopacified blood from the inferior vena cava thereby leading to decreased contrast attenuation in branches of the pulmonary arteries. Conversely, compared to the general population, the risk of a nondiagnostic scintigraphic lung perfusion study is reduced in young women because they are less likely to have underlying parenchymal lung disease.

A heightened consideration in the pregnant patient is radiation exposure to the mother and fetus. While the exact radiation dose is difficult to pinpoint due to differing technique and lack of high-quality data, it is generally agreed that radiation dose to the breast is significantly higher with CTPA than with lung scintigraphy. Breast tissue is particularly radiosensitive during pregnancy due to its highly proliferative state\(^4^9\) and the risk of radiation-induced breast cancer is therefore of particular concern in pregnant women with suspected PE. For this reason, a majority of guidelines recommend use of lung scintigraphy rather than CTPA in this population.\(^5^0\) With either CTPA or lung scintigraphy, radiation to the fetus remains well below accepted safety limits.

Several maneuvers are available in order to further reduce radiation exposure to the pregnant patient and fetus during lung scintigraphy. In a cooperative patient without underlying lung disease, V/Q studies can be performed with a 50% reduction in radiopharmaceutical dosages, resulting in diagnostic ventilation and perfusion images and achieving a concomitant 50% reduction in exposure. A more efficacious method which has achieved widespread adoption is performing perfusion imaging without ventilation scintigraphy; ventilation is only performed when perfusion is abnormal (Fig. 4). Because there is no need to overcome activity remaining in the lung from the prior ventilation study, the amount of activity needed for perfusion is typically reduced several-fold to 37 MBq or less. A large majority (80%-90%) of pregnant women with suspected PE have normal perfusion studies, which conclusively rules out PE without need.

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**Figure 5** Radiograph and planar perfusion images in 4 representative patients studied under a perfusion-only COVID-19 protocol. All chest radiographs demonstrate absence of significant opacities. A. 44-year-old woman, COV+ by PCR. No defects were noted on perfusion scintigraphy. The patient was not anticoagulated and was discharged without complication. B. 35-year-old woman, COV− by PCR. Well-defined segmental perfusion defect in the superior lingula, indeterminate for PE. CTPA demonstrated normal pulmonary arterial perfusion; patient was discharged home without anticoagulation treatment. C. 43-year-old man, COV+ by PCR, with elevated D-dimer (19.7 μg/mL). Multiple bilateral segmental defects, especially involving the right lung, indeterminate for PE. Patient subsequently was discharged on anticoagulation treatment. D. 59-year-old woman, COV− by PCR. There is global decrease in perfusion of the right lung, indeterminate for PE. CTPA demonstrated normal pulmonary arterial perfusion; patient was discharged home without anticoagulation treatment. Reprinted from Kumar A, Moadel RM, Haramati LB, Ye K, Freeman LM, Zuckier LS. Experience with a perfusion-only screening protocol for evaluation of pulmonary embolism during the COVID-19 pandemic surge. J Nucl Med 63:598-601, 2022.
for ventilation or other imaging tests. A secondary advantage to deferring ventilation until after perfusion in the minority of cases where it is actually needed is that duration of lung scintigraphy would be markedly shortened, and cost of the examination would be decreased. However, in patients where perfusion defects are noted, ventilation imaging is required given the risk of false positive results and the constraints and potential consequences of unduly treating a pregnant patient with anticoagulant therapy. Clinical and practical considerations are therefore paramount in determining which approach would be optimal in any given pregnant woman presenting with symptoms which may represent PE; performing a first line complete V/Q scan may be favored in given circumstances.

Respiratory Isolation (as in COVID-19)

The COVID-19 pandemic upended many previously settled areas of medicine, including the dogma of performing both ventilation and perfusion imaging for the scintigraphic diagnosis of PE. Because of concern regarding aerosolization of patient secretions, many investigators were loath to perform ventilation studies on patients suspected of COVID-19 infection. One of the options, implemented in various ways by disparate groups, was to perform the perfusion study first, as an initial screening test, in essence following the model used in pregnancy (Fig. 5). In contrast to pregnancy, where the objective is to decrease the patient exposure, in cases of respiratory isolation a full dose of 99mTc-MAA is typically used, designed to increase count rate and decrease the time of imaging. Only if defects are noted on the perfusion study is further investigation needed, whether ventilation study, CTPA, or correlation with pretest probability and/or noncontrast CT scan of the chest. In between 60 and 80% of patients studied in this manner, PE could be excluded without need for ventilation imaging. When defects are encountered but ventilation scintigraphy is not performed, clinicians should be cognizant of an increased risk of false positive results and further imaging is often indicated. These approaches should be periodically reviewed and revised based on changes in situational factors. As the pandemic recedes, and there is adequate availability of appropriate personal protective equipment which effectively limits the risk of viral contamination, it has become efficacious to maintain routine performance of ventilation imaging.

Conclusion

Pulmonary scintigraphy, typically entailing both ventilation and perfusion imaging, remains a robust modality for detection of PE. Advances in radiopharmaceutical development and imaging methods have positioned this modality to continue to play an important clinical and research role in the diagnosis of acute PE.

References