

Lung Ventilation/Perfusion SPECT: The Right Technique for Hard Times

One of the main problems encountered in the analysis of ventilation/perfusion (V/P) lung scans for the diagnosis of pulmonary embolism (PE) is difficulty in assessing the size of the perfusion defect, which then influences the probabilistic classification described in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study (1). In the original study, high probability was defined as 2 large mismatched defects (a defect being 75% of a segment), 1 large and 2 moderate mismatched defects (25%–75% of a segment), or 4 moderate mismatched defects (1). However, the task of distinguishing moderate (60%) from large (80%) defects was occasionally difficult.

A study conducted on healthy volunteers using $^{81\text{m}}\text{Kr}$ pointed out these difficulties, even for trained physicians (2,3). In this study, Morrell et al. (2,3) created segmental defects for the 18 segments of the lungs by placing an occluding balloon catheter in each of the segments during fiber-optic bronchoscopy and by delivering $^{81\text{m}}\text{Kr}$ into the nonoccluded lung. Planar scintigraphy was used to assess the detectability of these defects in anterior, posterior, lateral, and posterior oblique views and the agreement between experienced observers in the classification of these defects into small, moderate (subsegmental), and large (segmental) defects (2). Three important points were revealed: (a) defects involving the medial basal segment of

the right lower lobe were undetectable on any view; (b) lateral and posterior oblique views optimally visualized defects located anterior to the hilum and posterior to the hilum, respectively, whereas posterior and anterior views provided inadequate visualization of these defects; and (c) experienced observers tend to underestimate the size of segmental defects. Only 44% of these segmental defects were interpreted as being >75% of a segment. Seventeen percent were classified as small, and 40% were classified as moderate (subsegmental). The most underestimated defects involved the anterior and lateral basal segments of both lower lobes.

These results are explained by shine-through of overlying radioactivity from the contiguous segments; this impedes the visualization of defects in the same lung by the effect of radioactivity from the surrounding segments as it overlaps the edges of the defect, particularly in the lung bases where the segments are tightly packed. This is critical because it is the most commonly reported site of PE. From these results, it can be hypothesized and extrapolated that, if defects that are actually segmental are described erroneously as subsegmental or small in healthy subjects, the misinterpretation will be greater for patients. This will reduce the proportion of high-probability scans, increasing the proportion of intermediate scans.

For these reasons, the revised PIOPED criteria introduced the concept of segmental equivalents: Moderate perfusion defects can be added together to achieve the same level of significance as the equivalent number of large defects (4). Stein et al. (5) then proposed the use of the term “mismatched vascular defects” because

they had found, when reanalyzing PIOPED data, that the diagnostic value of mismatched moderate defects is the same as for mismatched large segmental defects. The total number of mismatched vascular defects, whatever their size (unless >25% of a segment), has the same diagnostic power as the number of mismatched segmental equivalents. Depending on the absence or presence of prior cardiopulmonary disease, the positive predictive value for PE is, respectively, 80% and 68% for 1 defect and 89% and 77% for 2 defects. Although the analysis of large and moderate defects has been improved, there is clearly a shift in focus, moving the problem toward small defects.

Among the criteria for very low probability of PE (<10%), there are also some categories for which accurate assessment of the size of the defect is needed (i.e., a perfusion defect smaller than a chest x-ray abnormality or 3 small defects) (6); otherwise, a patient with a low or intermediate probability of PE could be classified erroneously in the very-low-probability category. These successive modifications of lung scan criteria are sometimes difficult to understand by the referring physician, who generally looks at the lung scan in light of the original PIOPED conclusions (i.e., a high percentage of intermediate scans, a high percentage of PE [12%] in the low-probability category, and a minority of patients with PE having high-probability scans [41%]) (1). Moreover, the extreme refinement of the latest modified criteria and the use of ^{133}Xe in the PIOPED study make it difficult to apply these criteria to a routine nuclear medicine practice in which ventilation is generally performed with aerosol or $^{81\text{m}}\text{Kr}$.

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Currently, strategies proposed for the diagnosis of PE use a range of noninvasive techniques, such as measurement of plasma D-dimers or lower-limb compression sonography. These noninvasive techniques have meant increasing competition for V/P scintigraphy, particularly since the introduction in the late 1990s of a powerful imaging technique: helical CT. The first reports of this technique were enthusiastic, and before long it was suggested as a replacement for the V/P lung scan, with some authors claiming that it had not only higher specificity but also greater sensitivity (7).

However, recent studies have shown that, like V/P lung scanning, helical CT has difficulty in coping with abnormalities of subsegmental and segmental arteries. Perrier et al. (8) conducted a well-designed study of 299 patients with clinically suspected PE and a plasma dimer level of $>500 \mu\text{g/L}$. The diagnosis of PE was established using a validated algorithm including clinical assessment, lower-limb compression sonography, lung scanning, and pulmonary angiography. The sensitivity of helical CT was 70%, and the specificity was 91%. The likelihood ratio was 8.0 for positive results and 0.3 for negative results (similar to the value recorded for low-probability scans). CT did not show any isolated subsegmental emboli, and the likelihood of false-positive results increased according to the anatomic level studied (main pulmonary artery, 0%; lobar pulmonary artery, 15%; and segmental pulmonary artery, 38%). The sensitivity is too low for these CT scans to be used to rule out PE, and the specificity declines for segmental and subsegmental arteries. The results of the study, designed for outpatients, may not apply to hospitalized patients, where comorbidity would further decrease the specificity of CT. A high rate of false-positive results with helical CT scans was also observed for 4-mm vessels in an experimental pig model of PE (9). In spite of these findings, because helical CT is useful for directly highlighting pulmonary vessels, it continues to be of prime importance, either as a

complement or as a competitor to scintigraphy. Therefore, any technique that can improve the performance levels of V/P scans would obviously be very welcome.

It has been suggested that the limitations of V/P scans may be solved by SPECT. As early as 20 y ago, Osborne et al. (10) showed the higher sensitivity of lung perfusion SPECT over planar scintigraphy by studying dogs and detecting PE induced at the segmental and subsegmental levels. Lower-lobe focal segmental experimental emboli, confirmed by angiography, were induced, and their evolution was monitored over an 8-wk period by serial perfusion lung scans. Although selective segmental angiography was the most sensitive method, SPECT appeared to be much more sensitive than planar scintigraphy in detecting emboli at the segmental and subsegmental levels. Premortem angiography identified 5 subsegmental emboli, whereas SPECT identified 4 and planar scintigraphy identified 1 (10).

At the time, the use of lung SPECT in clinical practice was restricted by the slow data acquisition time, but its advantages were noted (11). More recently, Corbus et al. (12) suggested in a retrospective study that lung SPECT provided higher specificity than planar V/P in PE. Magnussen et al. (13) used a computerized model of PE to highlight the superiority of SPECT over planar scintigraphy in the accurate assessment of the size of the defect. However, up to now, V/P SPECT had no independent gold standard reference, which raised questions as to its actual sensitivity and specificity in PE.

In this issue of *The Journal of Nuclear Medicine*, Bajc et al. (14) provide some important answers, paving the way for much needed clinical evaluations. The authors compared V/P SPECT using $^{99\text{m}}\text{Tc}$ -diethylenetriaminepentaacetic acid (DTPA) aerosol and $^{99\text{m}}\text{Tc}$ -labeled macroaggregated albumin with planar lung scintigraphy for detection of small PE of porcine pulmonary vessels. They used 2 groups of pigs and produced 2 types of experimental emboli calibrated to the size of

comparable vessels in human subsegmental arteries: cylindrical emboli made of latex balloons and 3-tailed latex flat emboli, which better mimic natural emboli. The innovative idea introduced in this work was the labeling of the emboli with ^{201}Tl . This constitutes an independent gold standard for accurate localization of emboli, which means a proper assessment can be made of the perfusion defects observed on planar and SPECT images. Three independent observers interpreted the V/P scans randomly, whereas another observer identified the location of the emboli in the ^{201}Tl window. A true-positive finding was thus defined as a perfusion defect peripheral to the position of an embolus.

Bajc et al. (14) showed that the sensitivity and specificity were always higher for SPECT than for planar images, reaching 100% for cylindrical emboli. For the 3-tailed emboli, the sensitivity and specificity were 64% and 79%, respectively, for the planar scintigraphy, whereas SPECT yielded 91% and 87%, respectively. These results, obtained with a gold standard delineation of small perfusion defects, are of paramount importance. They constitute the first convincing evidence of the superiority of V/P SPECT over planar scintigraphy in the assessment of PE, showing it at the subsegmental level. More efficient cameras, the use of multiple-head detectors, and iterative reconstruction all increase SPECT quality and decrease interobserver variation, which means the study can be conducted with a very short acquisition time.

The differences in SPECT performance observed in this study, comparing the 2 types of experimental clots, show that great care must be taken when one draws clinical conclusions regarding the value of an imaging technique on the basis of the results obtained using an experimental model. Furthermore, the size and branching pattern of the pulmonary vasculature of the pig are substantially different than the human equivalent. Bearing these limits in mind, even when using smaller-diameter emboli (2.2–2.5 mm

vs. 3.8–4.2 mm), higher values were found for the sensitivity and specificity for the SPECT study than those in the report of Baile et al. (9) on helical CT in a pig model. Bajc et al. (14) sensibly suggested that the potential improvement in clinical diagnosis offered by SPECT might be studied further.

Another important point raised by the study (14) is the use of a computed normalized V/P image. Although the impact of the computation was not quantified, as was the case in a previous study from the same group on humans (15), the inclusion of V/P images was considered to be a way of facilitating the interpretation. It should be noted that the PIOPED criteria were determined mainly by morphologic thinking and did not take advantage of all information available from nuclear medicine examinations and made no attempt at any quantification.

However, functional imaging of V/P ratios does provide invaluable information on blood gas exchange. By computing the actual regional V/P ratio, alveolar V/P unevenness throughout the lungs can be assessed. Although the analysis of the V/P units is limited to a large number of alveolar units because of camera resolution, it has been found that abnormal V/P ratios computed by scintigraphy correlate well with abnormalities in alveolar–arterial oxygen pressure difference (16) and match the results obtained by the multiple inert-gas elimination technique (17). PE is characterized by high V/P ratios caused by preferential reduction of perfusion. Therefore, the measurement of V/P ratios may be a different attempt to assess the V/P mismatch presenting a high V/P ratio in PE.

Using $^{81\text{m}}\text{Kr}$ for ventilation and perfusion, it has been possible to compute a regional V/P ratio with planar scintigraphy (18). Both images were normalized so that the global V/P is 1 (18). In each pixel of the lung area, the V/P was computed by dividing the normalized $^{81\text{m}}\text{Kr}$ ventilation image by the normalized $^{81\text{m}}\text{Kr}$ perfusion image. The computation of regional V/P for each perfusion defect using this technique

produced a high V/P ratio (mean, 1.96) in patients with mismatched defects and PE, even when the defects were small. A threshold of 1.25 improved the number of patients classified correctly as having PE compared with qualitative analysis (18). Sando et al. (16) adapted the methodology to SPECT in an attempt to improve the level of analysis and, in a small series of patients, described the results obtained using SPECT data acquired simultaneously with $^{81\text{m}}\text{Kr}$ and $^{99\text{m}}\text{Tc}$ -labeled macroaggregated albumin. However, the diagnostic value of this technique has not been assessed yet in a large group of patients.

Bajc et al. (14) used $^{99\text{m}}\text{Tc}$ -DTPA for ventilation. Hot spots caused by aerosol impactions as well as DTPA clearance required correction procedures. The relation between aerosol deposition and ventilation is weak. This explains why they could not compute the real V/P ratio. Instead, Bajc et al. computed a normalized V/P quotient described earlier by their group (15). A value of 1 is set to the pixels of 1 lung subvolume, where any point has a perfusion of >50% of the maximum and a ventilation of >50% of the maximum. A value of >1 is defined as a mismatch. This analysis disregards the overperfused regions of the lungs with a low V/P, which have some pathophysiologic implications (19), but the computation of the V/P image in SPECT appears to be a valid approach for quantifying the V/P scan and optimizing the visualization of the mismatched regions (15).

Bajc et al. (14) clearly show the advantages of the SPECT lung scan. Used in clinical routine, SPECT could decrease the number of intermediate-probability scans as moderate defects are larger, thus increasing the percentage of patients classified correctly as having PE. Abnormalities of an invisible segment such as the medial basal segment of the right lower lobe are detectable. Moreover, SPECT may be useful (a) in the follow-up of patients with acute PE, because 66% of them present with residual defects after 3 mo of treatment (20); and (b) in evaluating

the pulmonary vascular bed in patients with deep venous thrombosis (baseline lung scan). High-probability scans are observed in a large number of these patients, and a precise evaluation of the mismatches leading to risk stratification and better follow-up under treatment may be needed (21,22).

However, V/P SPECT and its quantitative analysis have not been evaluated yet in clinical practice, and the diagnostic value of V/P SPECT for the diagnosis of PE remains unknown. No consensus has been reached on which aerosol is better, and $^{81\text{m}}\text{Kr}$ is no longer available in the United States, which is a source of disappointment (23). However, a PIOPED-like study for lung SPECT assessment would be difficult to imagine and quite illusory. In fact, even if initial reports were unduly optimistic (7), helical CT remains an examination that is widely available, is able to visualize pulmonary vessels noninvasively, and is, therefore, very attractive. Many diagnostic strategies have been proposed for suspected PE, and 1 noninvasive strategy combines helical CT, V/P lung scanning, and D-dimer measurement (24). In other strategies, CT may replace angiography in patients with normal results on sonography and nondiagnostic results on lung scanning. This means that the SPECT lung scan may be assessed in the future only as part of these types of protocols and in parallel use with CT.

To the credit of Bajc et al. (14), they urge the performance of lung SPECT with quantitative analysis instead of planar scintigraphy in a way that allows comparison with helical CT using an up-to-date version of V/P scintigraphy for competitive performance. If we want nuclear medicine to stay in the flow chart of PE, we must continue to show that the lung scan can provide data that are impossible to attain using other techniques. We have the right technology, but times are hard. The article by Bajc et al. examined the diagnosis of PE; therefore, that has been the focus of my comments. However, we must keep in mind that quantified V/P SPECT may be a powerful tool in other fields of lung pathology (25,26)

and should be recommended for broader use. One promising application may be 3-dimensional V/P ratios measured in relation to the anatomy of lung segments.

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