Key words: pulmonary embolism; lung scan; lung scintigraphy; SPECT; pneumology

Pulmonary embolism from a nuclear medicine perspective

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Dr. Patrick Reinartz is Assistant Medical Director of the Department of Nuclear Medicine at the University Hospital in Aachen. He started his training in 1997 and received board certification in 2002. He is currently involved in research on methodological optimization of ventilation/perfusion lung scintigraphy. His other research interests include osteology with a particular emphasis on SPECT imaging in bone metastases and positron emission tomography in patients with joint replacements, as well as molecular imaging of hypoxia in oncology.

Abstract

Lung scintigraphy is an indirect imaging method which non-invasively visualizes the perfusion defect caused by an embolus instead of the embolus itself. Since the perfusion defect is a great deal larger than the clot causing it, the procedure is highly sensitive and easily detects even small embolisms on a subsegmental level. To improve the specificity of the method, each perfusion scintigraphy should be coupled with a ventilation scan. For best results, single photon emission computed tomography (SPECT) should be used; this technique increases the diagnostic accuracy of the method to 0.94. In addition to SPECT imaging, the use of the new ultrafine aerosol Technegas as ventilation agent is highly recommended. In the field of image interpretation, the use of the complex PIOPED system and its unsatisfactory probability classes can no longer be advised. Instead, definitive diagnoses should be given by assessing all mismatch defects of at least half segment size as pulmonary embolisms. As far as the diagnostic efficiency of lung scintigraphy in clinical trials is concerned, there is a trend to compare advanced tomographic imaging modalities such as multislice or electron beam CT with planar scintigraphy acquired in a technique similar to that of the 20-year-old PIOPED study. For a balanced comparison, it is essential to use state-of-the-art techniques for all modalities.

Lung scintigraphy was introduced in 1964, making it one of the longest established non-invasive imaging modalities in the diagnosis of pulmonary embolism.[1] Unlike angiography, lung scintigraphy is an indirect imaging procedure which detects the perfusion defect caused by an embolus instead of the embolus itself. Such an indirect approach has advantages as well as disadvantages. On the one hand, the method is exceptionally sensitive because the perfusion defect is a great deal larger than the clot causing it. Therefore, even small embolisms at the sub-segmental level are easily detected by this method. In addition, only lung scintigraphy is able to exactly quantify the functional fraction of lung tissue that is unaffected by an embolism. On the other hand, specificity is a weak point of the procedure since pulmonary perfusion defects are not only caused by emboli but by a multitude of other diseases and pathological processes. To amend this deficit, the acquisition protocol of lung scintigraphy was complemented by the ventilation scan in 1968.[2] Today, the term 'lung scintigraphy' always implies both the perfusion and the ventilation scan.

The scintigraphic manifestation of pulmonary embolism is the 'mismatch defect' – this is defined as a pulmonary region with regular ventilation but severely reduced or no perfusion. Apart from embolism, mismatch defects are induced by only a few and, more importantly, rare non-embolic diseases. Accordingly, the specificity of lung scintigraphy is substantially improved by the ventilation scan.

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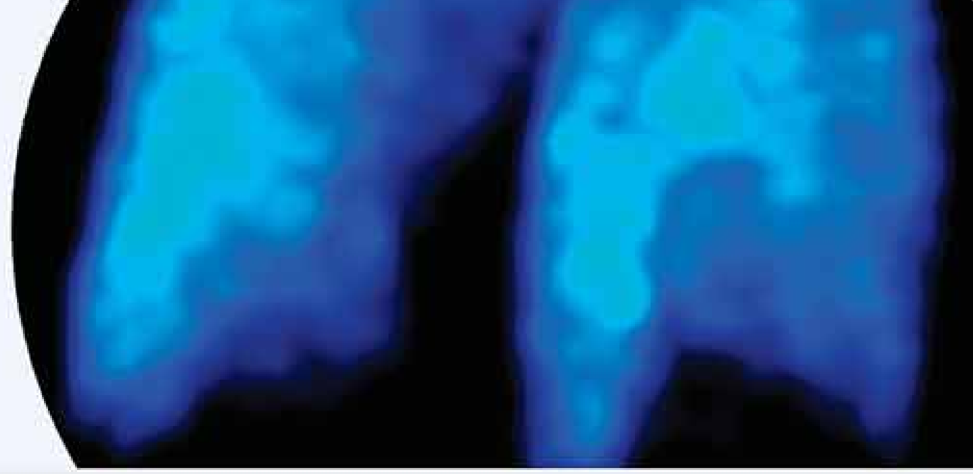

Figure 1 shows a typical mismatch defect caused by pulmonary embolism. In contrast, most of the non-embolic pulmonary diseases lead to *match defects* in the scintigraphy which are defined as regions affected by a severe reduction or complete loss of perfusion, while the ventilation in the same region is likewise distinctly reduced. Figure 2 shows such a match defect caused by a malignant tumour.

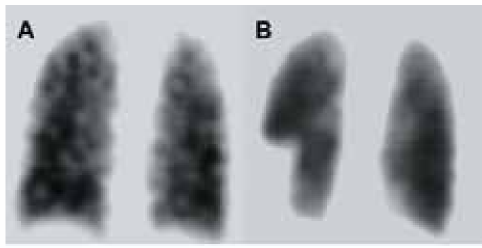

Figure 1. Coronal slices of a ventilation/perfusion lung scan (SPECT): while the ventilation (A) shows no substantial pathological changes, a large perfusion defect can be found in the lower lobe of the right lung (B). Diagnosis: mismatch defect caused by pulmonary embolism. R = right; L = left.

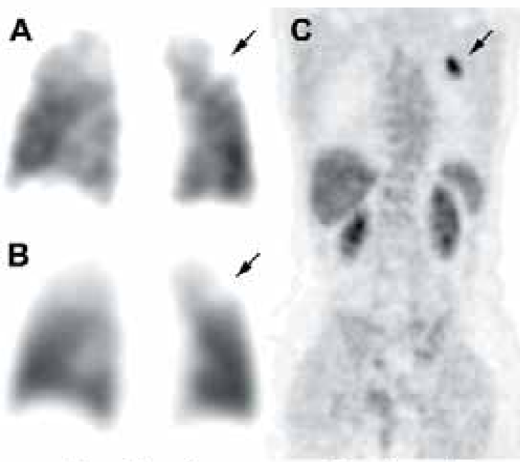

Figure 2. Coronal slices of a ventilation/perfusion lung scan (SPECT): both ventilation (A) and perfusion (B) show a subsegmental defect in the upper lobe of the left lung (arrows). Diagnosis: match defect, no embolism. The match defect is caused by a malignant tumour, as shown in the positron emission tomography with ^{18}F-labelled glucose (C, arrow). R = right; A = anterior; L = left.

The efficiency of lung scintigraphy has been substantially improved by recent technical developments. When considering the radiopharmaceuticals used for lung scanning, the ultrafine aerosol Technegas is definitely one of the most important innovations of the past decade. Technegas is a carbon-based ventilation agent whose pulmonary deposition rate reaches values of up to 20%, making it about 10 times more efficient than conventional aerosols.[3-5] This high degree of efficiency is achieved by the low aerodynamic diameter of the carbon particles which ranges between 30 and 90 nm. Since Technegas is ^{99m}Tc-labelled, it is easy to handle, cost-effective, and readily available. In comparison to aerosols, either conventional or ultrafine, radioactive inert gases are currently of only limited clinical relevance for lung scintigraphy.

Other new developments in the field of radiopharmacy aim to establish an alternative to conventional lung scintigraphy. Labelled antibodies, antibody fragments, or specific peptides have been designed for the direct detection of thrombotic clots. Target structures of these substances are either parts of the fibrin polymer or fragments of platelets.[6-8] However, at present, none of these radiopharmaceutical compounds is ready for market launch.

The introduction of Technegas in lung scintigraphy not only improved the ventilation scan but also facilitated another development which is now regarded as the single most important technique: Single Photon Emission Computed Tomography (SPECT). In the course of a SPECT scan, a three-dimensional image is obtained by rotating the detectors of the gamma camera around the patient. For evaluation, slices in any orientation can be reconstructed from the original three-dimensional scan. SPECT is a well-established imaging method that is widely used in modern nuclear medicine diagnostics. In particular, tomographic scans have almost completely replaced planar acquisitions in the fields of cardiology and neurology. Therefore, it is remarkable that this technique took such a long time before it finally became used in lung scintigraphy, and even more remarkably, it still is not widespread. This might be due to the relatively small number of patients requiring a lung scan, making the effort of changing the procedure economically unattractive. The effect of SPECT imaging on the diagnostic efficiency of the method is striking: while planar lung scans yield a sensitivity between 0.76 and 0.81,[9-11] in SPECT imaging, a substantial improvement up to 1.0 was found.[11-14] The same is true for the specificity which is reported to reach values of between 0.91 and 0.96 when using SPECT[9,11-13] (compared to values between 0.74 and 0.85 achieved by planar scintigraphy[9-11]). Diagnostic accuracy is affected accordingly: the advantages of the tomographic acquisition technique are illustrated in Figure 3 in which the segmental defect is detected by both the planar scintigraphy and the SPECT scan, while the defects on the subsegmental level can only be diagnosed by the SPECT scan.

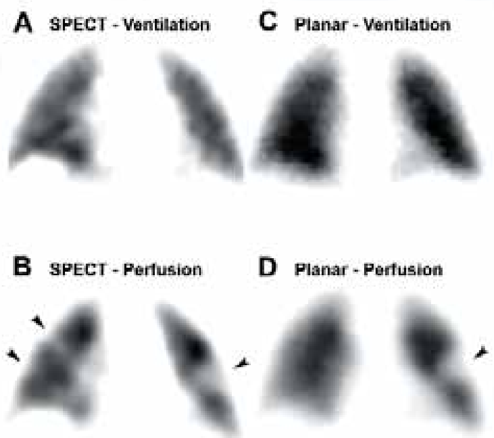

Figure 3. Patient with multiple embolisms in both lungs. The segmental mismatch defect in the left lung was detected by both SPECT (A, B) and planar scintigraphy (C, D). However, the subsegmental defects in the right lung (B, arrows) could only be diagnosed by SPECT.

In addition to SPECT imaging and ultrafine aerosols, several other techniques could significantly refine lung scintigraphy. Iterative image reconstruction algorithms,[13] respiratory-gated acquisitions,[15] the use of artificial neural networks for image interpretation,[16] and three-dimensional surface-shaded image processing[17] are only some of the techniques that show considerable potential. With regard to image interpretation, the use of the PIOPED criteria can no longer be recommended as the method of choice. The results of the PIOPED system are not a definitive statement on whether or not pulmonary embolism is present in a patient but merely a probability range. The criteria on which the system is based were developed in the course of a multicentre trial that was designed in 1983.[18] Since then, the data from the PIOPED study have lost some of their scientific value as they rely on imaging techniques that are largely outdated or even obsolete. It seems surprising that the opportunity was missed to integrate any of the above-mentioned modern imaging techniques into the study design of the PIOPED II trial that was planned in 2000.[19] Consequently, the results of that study will not be able to reflect the actual *status quo*. Instead of using the complex PIOPED system and its unsatisfactory probability classes, an alternative diagnostic approach is recommended which will give definitive and clear-cut diagnoses by assessing all mismatch defects of at least half segment size as pulmonary embolisms. By doing so, the diagnostic accuracy of the method is increased to 0.94.[11,20]

In summary, it can be seen that lung scintigraphy is a highly effective, non-invasive imaging procedure for the diagnosis of pulmonary embolism. Best results can be achieved by integrating modern techniques like SPECT imaging and ultrafine aerosols into the acquisition protocol. In this context, a worrying development can be observed in current study designs. Increasingly, articles are being published where an advanced tomographic imaging modality such as multislice or electron beam CT is compared with planar lung scintigraphy, acquired in a technique similar to that of the 20-year-old PIOPED trial – a study design that cannot give impartial results.[21,22] For a balanced comparison, we strongly recommend the use of state-of-the-art techniques for both modalities.[23]

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Key Learning

- Lung scintigraphy is exceptionally sensitive because it visualizes the relatively large perfusion defect caused by an embolus instead of the comparatively small embolus itself
- To increase specificity, lung scintigraphy should always comprise both a perfusion **and** a ventilation scan
- If technically possible, SPECT imaging should be used for the acquisition of all ventilation and perfusion scans. Planar scintigraphy can no longer be considered state-of-the-art
- Conventional and ultrafine aerosols have replaced radioactive inert gases as the ventilation agent of choice
- All mismatch defects of at least half segment size should be assessed as pulmonary embolism. The use of the PIOPED criteria for image interpretation can no longer be recommended
- All examinations should lead to a definitive and clear-cut diagnosis (embolism confirmed or disproved). Probability classes ought to be abandoned
- To realize a balanced and impartial study design for comparative trials, it is essential that lung scintigraphy is done using a state-of-the-art technique

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