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Full Length Article

# New developments and future challenges of nuclear medicine and molecular imaging for pulmonary embolism☆

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ABSTRACT

Although widely validated, current tests for pulmonary embolism (PE) diagnosis, i.e. computed tomography pulmonary angiography (CTPA) and V/Q planar scintigraphy, have some limitations. Drawbacks of CTPA include the radiation dose, some contra indications and a rising concern about a possible overdiagnosis/overtreatment of PE. On the other hand, V/Q planar scintigraphy has a high rate of non-diagnostic tests responsible for complex diagnostic algorithms.

Since the PIOPED study, imaging equipment and radiopharmaceuticals have greatly evolved allowing the introduction of techniques that improve imaging of lung ventilation and perfusion. Single photon emission computed tomography (SPECT) and SPECT/CT techniques are already largely used in daily practice and have been described to have greater diagnostic performance and much fewer non-diagnostic tests as compared with planar scintigraphy. However, they have not yet been firmly validated in large scale prospective outcome studies. More recently, it has also been proposed to image pulmonary perfusion and ventilation using positron emission tomography (PET), which has an inherent technical superiority as compared to conventional scintigraphy and may provide new insight for pulmonary embolism. Regardless of modality, these new thoracic imaging modalities have to be integrated into diagnostic strategies.

The other major challenge for venous thromboembolism diagnosis may be the potential additional value of molecular imaging allowing specific targeting of thrombi in order, for example, to differentiate venous thromboembolism from tumor or septic thrombus, or acute from residual disease.

In this article, the new imaging procedures of lung ventilation perfusion imaging with SPECT, SPECT/CT and PET/CT are discussed. We also review the current status and future challenge of molecular imaging for the in vivo characterization of venous thromboembolism.



## 1. Introduction

Pulmonary embolism (PE) remains a diagnostic challenge in daily practice. Both missed diagnosis and excess diagnosis have undesirable consequences. Untreated PE is reported to have a mortality rate of up to 30% [1] while anticoagulant therapy exposes patients to a significant risk of bleeding [2]. Ventilation/perfusion (V/Q) scintigraphy has been the first non-invasive procedure validated for PE diagnosis [3–5]. The most important limitation of V/Q planar imaging is the high proportion of non-diagnostic scans, resulting in complex diagnostic algorithms. This was responsible for the decreasing popularity of V/Q scintigraphy as compared with computed tomography pulmonary angiography (CTPA). CTPA is currently the first-line imaging modality in most institutions for PE diagnosis. Some might argue that there is no point in developing new imaging procedures since CTPA solved the challenge of PE diagnosis. However, CTPA has several drawbacks, including higher radiation dose, especially to the breast, contraindications such as allergy to iodine contrast media or renal impairment, or non-diagnostic results because of technical failure. Most importantly, there is increasing concern about the risk of overdiagnosing and overtreating non-clinically relevant PE when using CTPA [6,7].

Furthermore, other aspects of PE diagnosis remain a challenge in daily practice and may benefit from advances in imaging. Providing an objective and rapid quantification of the extent of vascular obstruction whose relationship with PE recurrence risk is debated, might be of value. The clinical relevance of sub segmental PE is still another matter of debate. Above all, a major challenge in the field of venous thromboembolism (VTE) diagnosis is the in vivo characterization of the clot, for example for the differentiation between a thrombus and a tumoral clot, or between an acute or a residual thrombus.

We will discuss in this article, the new imaging procedures of lung V/Q studies with single photon emission computed tomography (SPECT), SPECT combined with computed tomography (CT) and positron

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emission tomography (PET). We will also review the current status and future challenge of molecular imaging for the in vivo characterization of the clot.

## 2. Advances in ventilation/perfusion imaging

### 2.1. V/Q SPECT

The diagnosis of PE with V/Q scintigraphy is made by comparing pulmonary ventilation and perfusion after administration of radiotracers. Ventilation is acquired after inhalation of inert gases such as $^{81m}$Krypton or $^{99m}$Technetium ($^{99m}$Tc)-labeled aerosols that reach terminal bronchioles in proportion to regional distribution of ventilation. Perfusion is imaged after intravenous administration of $^{99m}$Tc-labeled macroaggregated albumin (MAA) particles, which are trapped in the lung capillaries so that local activity is related to the regional blood flow. The hallmark of acute PE with V/Q scintigraphy is the mismatched perfusion defect, i.e. areas with absent perfusion but preserved ventilation. V/Q images were traditionally acquired in a planar mode, which has the inherent drawback to be limited by the small number of 2-dimensional views [6 to 8], each representing a summation of data that includes overlapping activity. Planar V/Q scintigraphy was used in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study which is the landmark accuracy study with V/Q scan versus pulmonary angiography [3]. In that study performed more than 25 years ago with equipment and ventilation radiotracers that would currently be considered obsolete in most departments, the performance of planar V/Q scan was insufficient to allow a binary reporting approach (PE or no PE). Probabilistic reporting criteria were therefore proposed, resulting in a high rate of non-diagnostic scans, which remains the most important limitation of V/Q scan.

Since that time, imaging equipment and radiopharmaceuticals have greatly evolved, allowing the introduction of SPECT. SPECT is a method of scintigraphic image acquisition that offers the advantage of tomographic sections (see Fig. 1). Of note is that the only difference between planar and SPECT V/Q is the acquisition mode of scintigraphic data. Similar gamma cameras and radiotracers (and accordingly the radiation dose, the contra indications, etc.) are used. The same physiological processes are therefore imaged, and, similar to planar V/Q scan, the principle of interpretation also relies on the identification of mismatched defects. However, by using 3-dimensional imaging, V/Q SPECT has an inherent technical advantage over conventional 2-dimensional planar imaging through its ability to eliminate overlap of activities; its visualization of the medial-basal segment; and its ability to better characterize the size, shape, and location of defects [8]. Simplistic comparison could be done between planar and SPECT images for V/Q scintigraphy, versus chest radiography and CT scan of the lungs in radiology. Of note is that most of nuclear medicine scans (bone, heart, brain) are now performed using SPECT image acquisition. Accordingly, in the eyes of most of nuclear medicine physicians, it does not make sense to perform planar V/Q scintigraphy nowadays or to discuss the superiority of SPECT over planar imaging. The nuclear medicine community mostly encourages its use for diagnosing PE. For example, the European Association of Nuclear Medicine guidelines for V/Q scintigraphy, strongly recommend the use of SPECT for PE diagnosis [9]. However, according to the lack of numerous and large validation outcome studies, these recommendations remain an expert opinion. In fact, a recent survey of practices regarding V/Q scintigraphy in Australia, Canada and France showed that more than 2/3 of nuclear medicine departments performed SPECT rather than planar images for PE diagnosis [10].

Nevertheless, SPECT is still described by the nonnuclear medicine communities as a future potential test rather than an imaging modality currently used routinely [11,12]. The relatively low acceptance of SPECT by clinicians may be explained by the fact that, although the literature consistently reported the superiority of SPECT over planar, the technique has not yet achieved the same standard of validation than the other tools for PE diagnosis, including CTPA [13,14], V/Q planar [3–5], or D-dimer testing [15,16]. Indeed, many accuracy studies have been performed. They consistently reported superior reproducibility and diagnostic performances of V/Q SPECT as compared with planar imaging [17–19]. In particular, V/Q SPECT has been reported to dramatically reduce the proportion of non-diagnostic tests, typically less than 5% [20,21]. A binary reporting approach has been used in almost all studies, with promising perspectives to simplify the diagnostic algorithms based on V/Q scintigraphy [22]. However, the exact accuracy of V/Q SPECT for PE diagnosis is still unknown because of methodological issues [23]. Indeed, in many studies, there is an incorporation bias with the V/Q SPECT result participating in the final diagnostic conclusion used as the reference standard to determine accuracy. In addition, the ventilation agents and interpretation criteria varied widely across studies, so that firm conclusions cannot be drawn. Similarly, outcome studies have reported the safety of excluding PE on the basis of a negative V/Q SPECT [24,25], but there was no standardized a priori defined diagnostic algorithm and management. To date, no formal management

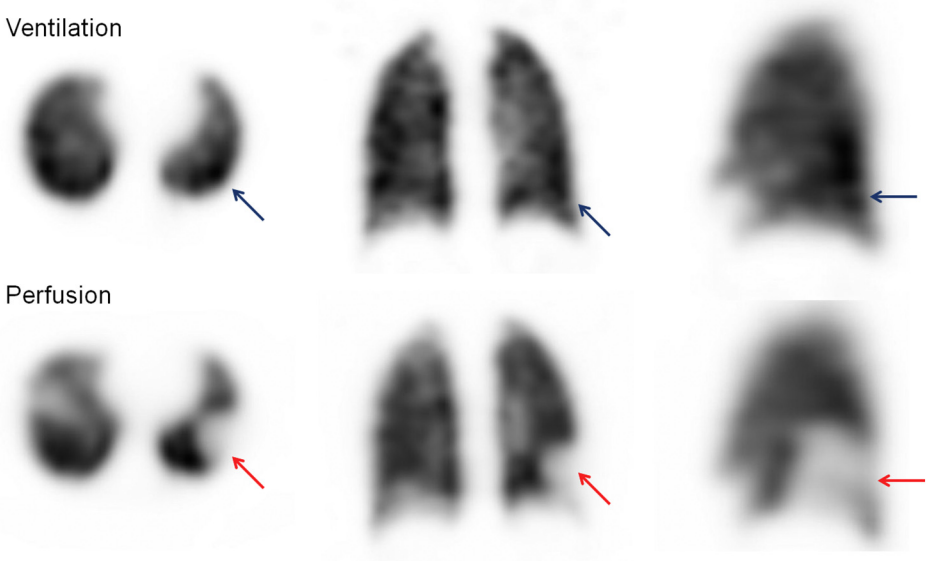


**Fig. 1.** Example of V/Q SPECT. Axial, coronal and sagittal slices demonstrate mismatched defects, i.e. absent perfusion (red arrows) but preserved ventilation (blue arrows), in the anterior-basal and lateral-basal segments of the left lower lobe (arrows). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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