6 Ventilation/Perfusion SPECT Imaging Diagnosing PE and Other Cardiopulmonary Diseases

Marika Bajc and Ari Lindqvist

6.1 Introduction

Scintigraphic pulmonary studies are designed to demonstrate patterns of ventilation and perfusion. In the healthy individuals, there is a balance between regional ventilation and perfusion to achieve optimal gas exchange. When pulmonary diseases cause deficiency in ventilation and perfusion, they cause "matched" defect. Mismatch implies an imbalance between perfusion and ventilation. The single most important application for pulmonary scintigraphy is the evaluation of patients with suspected pulmonary embolism (PE). In patients with pulmonary embolism, characteristic finding is segmental perfusion defect with preserved ventilation. In 1964, Wagner recognized and first demonstrated the value of pulmonary scintigraphy by using I131—human serum albumin (HSA) and rectilinear scanner [1, 2]. Scanners were further replaced with gamma camera and mainly planar technique was used for imaging. Planar imaging is still used technique in majority hospitals in the USA. On the other hand, in Europe, Australia, Japan, China and Canada, the planar technique is replaced with a single photon emission tomography (V/P SPECT). V/P SPECT was endorsed by EANM as recommended scintigraphic technique for the diagnosis of pulmonary embolism (PE) in 2009. Since then many studies have confirmed its value.

6.2 Diagnosing Pulmonary Embolism

Pulmonary embolism (PE) is a common disease with about 250,000 patients diagnosed each year in the USA. In spite of advanced technology, it remains a big diagnostic challenge because the clinical symptoms and signs that are frequently observed in pulmonary embolism are also a feature of other conditions. Accordingly, the initial clinical suspicion needs to be confirmed or negated using a conclusive imaging test. Routinely, computed tomography pulmonary angiography (CTPA) is suggested as the initial imaging study. However, the latest evidence shows that the optimal imaging procedure is V/P SPECT. Before imaging tests, it is recommended to estimate clinical probability that might be performed empirically or by clinical probability tests. Wells score is most frequently applied [3].

M. Bajc (✉)
Skåne University Hospital, Department of Clinical Sciences, University Hospital Lund, Lund, Sweden
e-mail: marika.bajc@med.lu.se

A. Lindqvist
Research Unit of Pulmonary Diseases, Clinical Research Institute, HUS Helsinki University Hospital and Helsinki University, Helsinki, Finland

H. Ahmadzadehfar et al. (eds.), *Clinical Nuclear Medicine*,
https://doi.org/10.1007/978-3-030-39457-8_6

The measurement of D-dimer—a breakdown product of cross-linked fibrin clot—is widely used in the investigative workup of patients with suspected venous thromboembolism. However, D-dimer has a low specificity (40%) because a number of conditions, other than venous thromboembolism, may cause it to be elevated, e.g. acute myocardial infarction, stroke, inflammation, active cancer and pregnancy. The specificity declines even further with age and, in the elderly, may reach only 10%. Due to the low predictive value, a positive quantitative D-dimer test does not modify the pretest probability. A negative quantitative D-dimer test combined with a low clinical probability is associated with a low risk of thromboembolic disease [4]. At moderate to high pretest clinical probability, D-dimer has no incremental value.

6.3 Basic Principles of Pulmonary Embolism Diagnosis with V/P SPECT

The lung circulation has a distinct architecture where each bronchopulmonary segment and sub-segment is supplied by a single end-artery. Emboli are usually multiple, occluding the arteries causing segmental or sub-segmental perfusion defects within still ventilated regions, causing so-called mismatch (Fig. 6.1). PE is often a recurring process giving rise to multiple emboli in various stages of resolution (Fig. 6.2).

In clinical practice, it is essential to have a procedure that is both fast and conclusive to avoid the risks associated with untreated disease. Therefore it is recommended that imaging tests

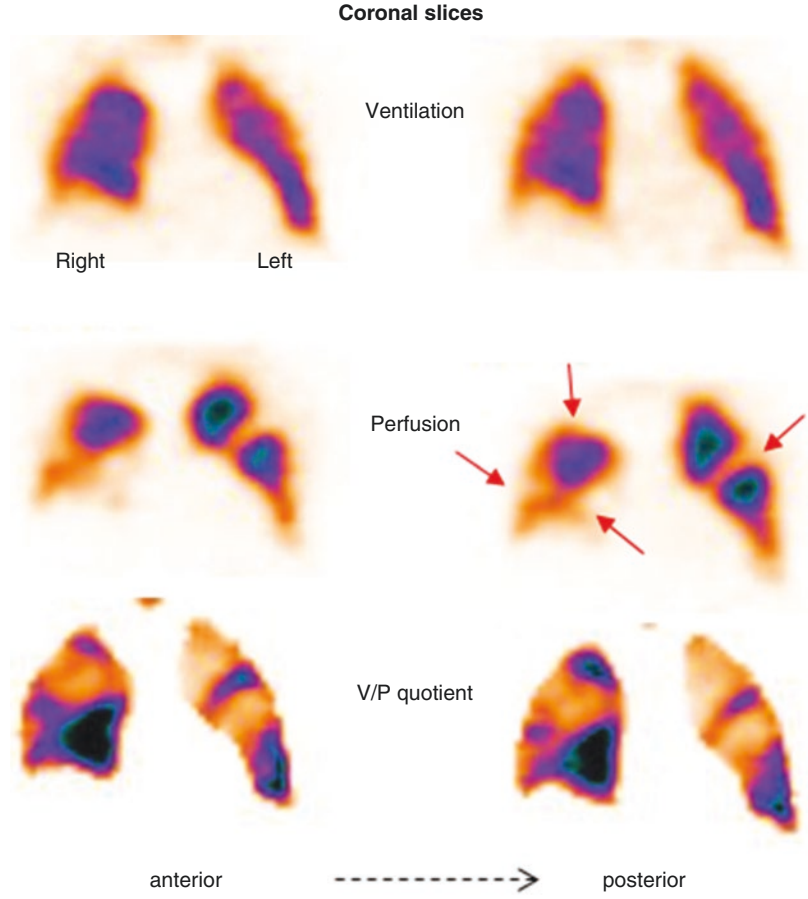

Fig. 6.1 Patient with PE. Coronal slices; multiple bilateral segmental perfusion defects (PE, red arrows) in areas with normal ventilation. These are delineated on V/P quotient images which facilitate interpretation

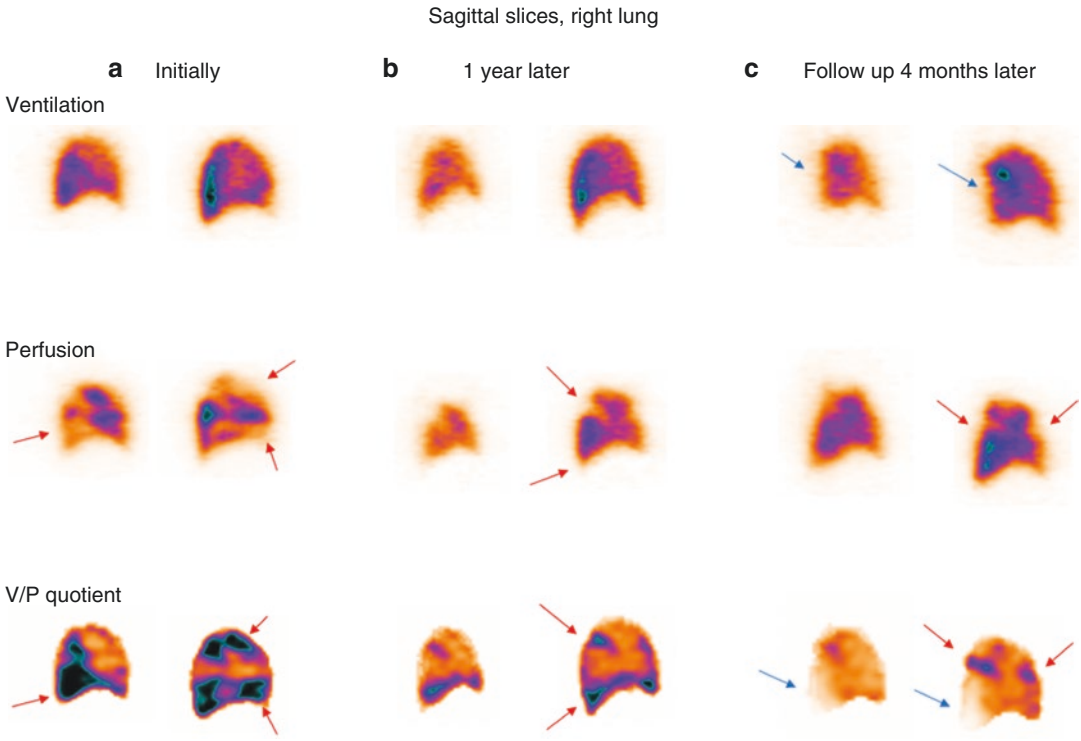

Fig. 6.2 Patient with recurrent PE and evolving comorbidity. Sagittal slices, right lung; (**a**) initially multiple perfusion segmental defects were observed (PE, red arrows); (**b**) 1 year after discontinuing therapy, patient experienced new symptoms. Perfusion defects were observed (red arrows). Hard to assess whether there were new defects or they represent rest after earlier PE. Patient started treatment again; (**c**) on follow-up 4 months later (under treatment), patient experienced new symptoms. The follow-up scan showed evolving ventilation defect (blue arrows) and improved perfusion defects (red arrows). Patient had developed pneumonia (blue arrows)

for PE diagnosis should be carried out as soon as possible, preferably within 24 h of the onset of symptoms.

6.4 Radiopharmaceuticals for V/P SPECT

6.4.1 Ventilation

Ventilation can be measured with the ^{99m}Tc-labelled aerosols, DTPA and Technegas®, or krypton gas (^{81m}Kr) (Table 6.1).

^{99m}Tc-DTPA (^{99m}Tc-diethylen-tetraaminopentaacetate) is aerosolized from a water solution with a particle size of 1.2–2 μm. ^{99m}Tc-DTPA allows studies of alveolo-capillary permeability [5].

Technegas® is an aerosol of ^{99m}Tc-labelled solid graphite hydrophobic particles, with a diameter of about 0.005–0.09 μm [6]. The particles tend to grow by aggregation and should, therefore, be used within 10 min after generation [7]. The particle size is so small that the aerosol behaves nearly like a gas until it arrives at the periphery of the lung where the particles are deposited in bronchioli and alveoli, mostly by diffusion. For the ventilation imaging, Technegas® particles show advantages over radiolabelled liquid aerosols and are not restricted by the presence of obstructive lung disease [8]. Hotspots are nevertheless seen in patients with severe airway obstruction. The penetration index for Technegas® may be used for grading of COPD severity [9–11].

Table 6.1 Ventilation/perfusion protocol for lung tomography (V/P SPECT)

	Ventilation	Perfusion
Administration	Inhalation	i.v. injection
Radiopharmaceutical and administered activity	*Technegas®* 25–30 MBq to reach the lung	*^{99m}Tc-MAA* 120–160 MBq
Particle size	0.09 μm	15–100 μm
Time of imaging	Ca 11 min	Ca 5 min
Acquisition protocol	General-purpose collimator: 64 × 64 matrix 60–64 steps for each head 10 s/step	General-purpose collimator: 64 × 64 matrix 60–64 steps for each head 5 s/step
Reconstruction	Iterative reconstruction—Eight subsets and four iterations	Iterative reconstruction—Eight subsets and four iterations

Patient preparation is not needed. Patient is in the supine position during inhalation, i.v. injection and the acquisition

Krypton gas (^{81m}Kr) is an inert radioactive gas delivered from an ^{81}Rb/^{81m}Kr generator. ^{81m}Kr has a half-life of 13 s. ^{81m}Kr is inhaled until it reaches a steady-state activity in the alveoli and then continuously during the whole imaging procedure. Due to the higher gamma energy (190 keV) of ^{81m}Kr compared to ^{99m}Tc (140 keV), ventilation and perfusion images can be acquired simultaneously. Because elimination of ^{81m}Kr from the alveoli is largely due to decay of the isotope rather than by expiration, regional activity at steady state accurately represents regional ventilation. In COPD the inhalation time to reach steady state may, however, be too long to reach steady state. As the half-life of ^{81}Rb is only 4.6 h, the need for daily delivery of the expensive cyclotron-produced generator limits the clinical use of ^{81m}Kr.

6.4.2 Perfusion

For perfusion scintigraphy intravenously injected macroaggregates of ^{99m}Tc-labelled human albumin (MAA) with a diameter of 15–100 μm are nearly universally used. Intravenous injection of MAA leads to microembolization of pulmonary precapillary arterioles and capillaries. Whilst 60,000 particles may suffice to reflect regional perfusion [12], about 400,000 labelled particles are usually injected. This leads to obstruction of a very small fraction of pulmonary vessels. Injection of no more than 100,000–200,000 particles is recommended for children and for patients with known pulmonary hypertension and right-to-left heart shunt, and after single-lung transplantation.

6.5 Imaging Protocols

Administration of ventilation and perfusion agents should be performed with patients in a supine position to minimize gravitational gradients. During inhalation, activity over the lungs should be monitored to ensure adequacy of pulmonary deposition. The procedure starts with ventilation scintigraphy that is usually based upon inhalation of a radio-aerosol (Table 6.1).

Large particles (>2 μm) are deposited mainly by impaction in large airways. Very fine particles, <1 μm, are mainly deposited in alveoli by diffusion. In comparison with liquid aerosols, Technegas® shows significantly reduced problems of central airway deposition and peripheral hotspot formation in patients with obstructive lung disease. Therefore the use of Technegas® is recommended in COPD.

Perfusion tomography follows immediately after ventilation SPECT without changing the patient position. The nearly universally used agent for perfusion scintigraphy is technetium-labelled particles of macroaggregates of human albumin (^{99m}Tc-MAA). After i.v. injection, the particles of size 15–100 μm are lodged in the pulmonary capillaries and in the precapillary arterioles in proportion to perfusion.

To achieve adequate imaging quality with a low radiation exposure and in a short time, relationships between activities, acquisition times, collimators and matrices for SPECT imaging must be optimized. This problem was systematically analysed by Palmer et al. [13] in the context of a dual head gamma camera.

Doses of 25–30 MBq for ventilation studies and 120–160 MBq for perfusion studies were found optimal by using a general-purpose collimator and 64 × 64 matrix. A total acquisition time is about 20 min. If a matrix of 128 × 128 is used, then a higher dose and/or longer acquisition time is required. This is not promoted as it did not yield images of significantly higher quality.

Many centres are using much higher doses. To follow a good medical practice, radiation exposure should be minimized to the lowest level consistent with satisfactory image quality. For V/P SPECT it is essential to use iterative reconstruction.

For quality control and fast orientation, an overview of ventilation and perfusion in coronal and sagittal slices is useful. It is important to present the images so that ventilation and perfusion are carefully aligned to each other (Fig. 6.3). This is greatly facilitated by the one-session protocol with the patient in unchanged position. The option to triangulate between coronal, sagittal and transverse slices is valuable for identification of matching and non-matching ventilation and perfusion changes. Proper alignment is also a prerequisite for V/P quotient images. These facilitate the interpretation and quantification of PE extension and all ventilation and perfusion defects. However, quotient images are not prerequisite for high-quality V/P SPECT.

6.6 Reporting Findings

6.6.1 Ventilation/Perfusion Patterns

For V/P SPECT, interpretation criteria are as important as the imaging technique itself. According to European guideline, all patterns of V and P as well as numbers of defects are described, and clinical probability is taken into account [14]. This holistic principle for reporting gives also a clear answer: yes or no for pulmonary embolism. This goal was not achieved with previous probabilistic reporting methods according to PIOPED (Prospective Investigation of Pulmonary Embolism Diagnosis) study or modified PIOPED. Large V/P SPECT studies have shown that interpretation of all patterns representing ventilation together with perfusion achieves this result. Conclusive reports were given in 97–99% of cases [15–19].

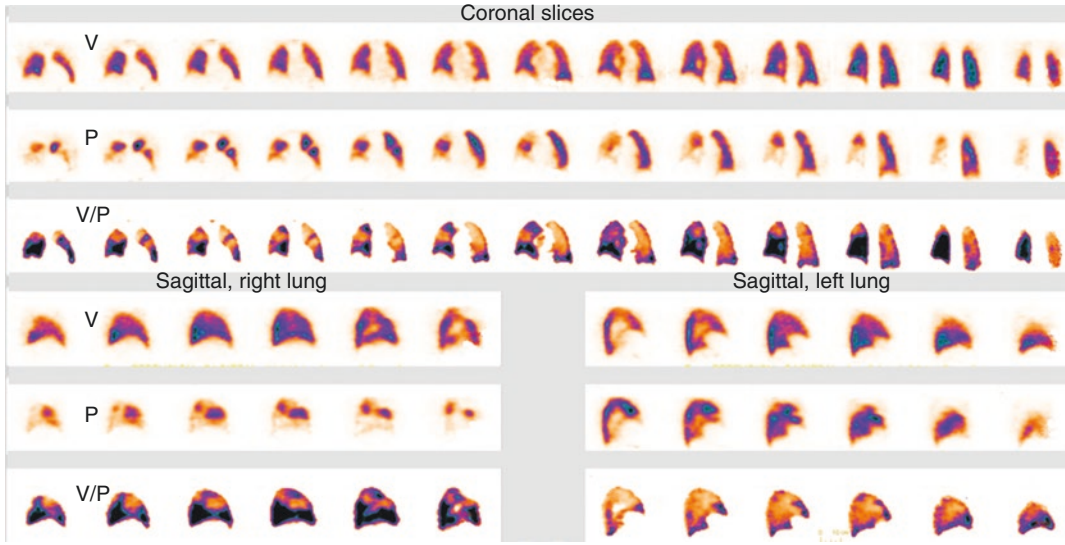

Fig. 6.3 Overview image of ventilation and perfusion in coronal and sagittal slices. Ventilation and perfusion are carefully aligned to each other

6.6.2 Criteria for Acute Pulmonary Embolism

Recommended criteria for reading V/P SPECT with respect to acute pulmonary embolism are the following:

- *Pulmonary embolism* is reported if there is V/P mismatch of at least one segment or two sub-segments that conforms to the pulmonary vascular anatomy.
- *No pulmonary embolism* is reported if there is (a) normal perfusion pattern conforming to the anatomic boundaries of the lungs matched or reversed mismatch V/P defects of any size, shape or number in the absence of mismatch and (b) mismatch that does not have a lobar, segmental or sub-segmental pattern.
- *Non-diagnostic for pulmonary embolism* is reported if there are multiple V/P abnormalities not typical of specific diseases.

It is important to report that with pulmonary embolism, a mismatch has its base along the pleura and conforms to known sub-segmental and segmental vascular anatomy. Applying these principles of interpretation, recent V/P SPECT studies amounting to over 5000 cases reported a negative predictive value of 97–99%, sensitivity of 96–99% and specificity of 91–98% for PE diagnosis. Rate of non-diagnostic findings was 1–3% [20].

6.6.3 Quantification of PE Extent

An important step in the diagnostic procedure is to quantify the extent of embolism. V/P SPECT is particularly suitable for this because of its greater sensitivity compared to alternative planar scintigraphy and CTPA. The number of segments and sub-segments indicating PE typical mismatch is counted and expressed in percentage of the total lung parenchyma. Furthermore, areas with ventilation abnormalities were recognized, and this allowed the degree of total lung malfunction to be estimated. The study showed that patients with up to 40% pulmonary embolism could be safely treated at home if ventilation abnormalities engaged not more that 20% of the lung [21]. Outpatient management in haemodynamically stable patients with pulmonary embolism is safe provided that the embolic burden, quantified using V/P SPECT, is included in the treatment decision algorithm. The extent of PE is an independent risk factor for PE recurrence [22–24]. In haemodynamically stable patients with PE, outpatient management is safe provided that the embolic burden, quantified using V/P SPECT, is included in the treatment decision algorithm [25].

6.7 Follow-Up

Knowledge about the natural history of PE is limited. There is a need to study alternative strategies for PE therapy, with respect to therapy duration and choice of drugs in different categories of patients. The issue of small emboli is particularly important, particularly regarding the treatment. Figure 6.4 presents a patient with untreated small

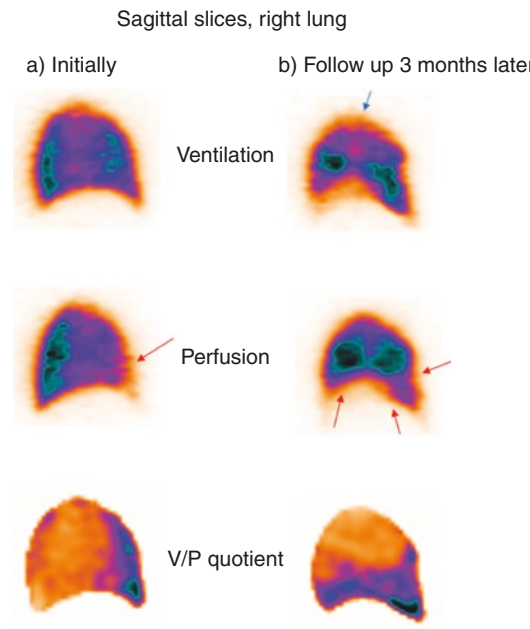

Fig. 6.4 Patient with small PE that was not treated developed chronic PE and pneumonia. Sagittal slice of the right lung showed initially a small perfusion defect in the medial lobe (PE, red arrow). This patient was not treated but was examined again 3 months later. On follow-up, the initial perfusion defect was more prominent, and perfusion defects were extended into the whole lower lobe. In addition, deterioration in the ventilation appeared apical segment. The patient also developed pneumonia (blue arrow)

PE who developed chronic PE after 3-month follow-up.

Follow-up of PE using imaging is essential to:

- Assess the effect of therapy.
- Differentiate between new and old PE when there is a suspicion of PE recurrence.
- Explain physical incapacity after PE.

Some patients have a tendency to develop recurrent episodes of PE. Figure 6.2 presents a patient with recurrent PE, shown by follow-up scans. Patient was treated initially for 6 months. One year after discontinuing therapy, patient experienced new symptoms. Perfusion defects were observed (Fig. 6.2b). Without the control scan after therapy was discontinued, it was hard to assess whether these defects were new or they represented rest after earlier PE. Patient started treatment again. Four months later, during the treatment, patient experienced new symptoms. The follow-up scan shows new ventilation defect (blue arrow) and improved perfusion. Reason for the patient's new symptoms was a pneumonia (Fig. 6.2c). Without initial and follow-up images, it is often impossible to differentiate between old and new PE. Immediate imaging control gives objective information about the further therapy decisions. Symptomatic patients with small emboli are diagnosed with sensitive methods, particularly V/P SPECT. Figure 6.5 presents a case with a PE in lingula and a pneumonia in the posterior part of the left lung. PE could not have been identified without SPECT and ventilation images. The natural history and the value of treatment in this group of patients is rather unknown. Follow-up is indicated to personalize therapy [21, 26–28].

Requirements on a method used for follow-up are:

- Applicability to all patients.
- Low radiation dose.
- High sensitivity to allow estimation of resolution of even small emboli and occurrence of new ones.

V/P SPECT seems ideally suited for use in the follow-up of PE because small and large emboli

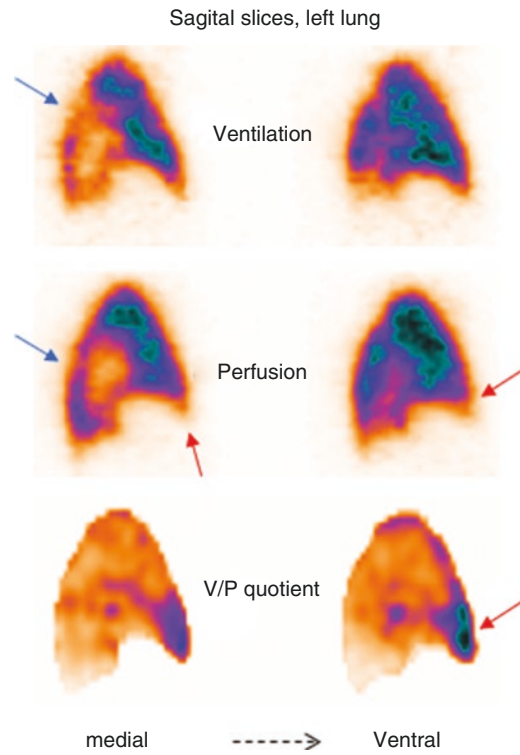

Fig. 6.5 Patient with PE and pneumonia. Sagittal slices of the left lung in a patient with perfusion defect in the lingula (red arrow). Stripe sign posteriorly seen on both ventilation and perfusion image (pneumonia, blue arrow)

are recognized so that regression or progression of thrombotic disease can be studied in detail [21, 26–28]. Furthermore, the low radiation exposure enables repeated studies. Obviously, using the same method for diagnosis and follow-up is advantageous. Research in this area is particularly indicated.

6.8 Chronic Pulmonary Embolism

Chronic pulmonary embolism is a progressive disease that develops in about 1–5% after an acute episode of PE, even in treated patients. It might lead to pulmonary hypertension, right heart failure and arrhythmia, which are frequent causes of death. The value of V/P scintigraphy in this situation is well established. This has been confirmed in a head-to-head comparison between

CTPA and planar scintigraphy with pulmonary angiography as reference. Among patients with pulmonary hypertension, scintigraphy had a sensitivity of 96–97% and specificity of 90%, whereas CTPA had a sensitivity of 51%. The conclusion was that V/P scintigraphy "has a higher sensitivity than CTPA as well as very good specificity in detecting chronic pulmonary thromboembolic disease as a potentially curable cause of pulmonary hypertension" [29]. Scintigraphic features of chronic pulmonary embolism vary. Figure 6.6 illustrates one case of a typical pattern for chronic PE. CTPA was normal. In some patients mismatch without clear segmental or sub-segmental pattern is observed.

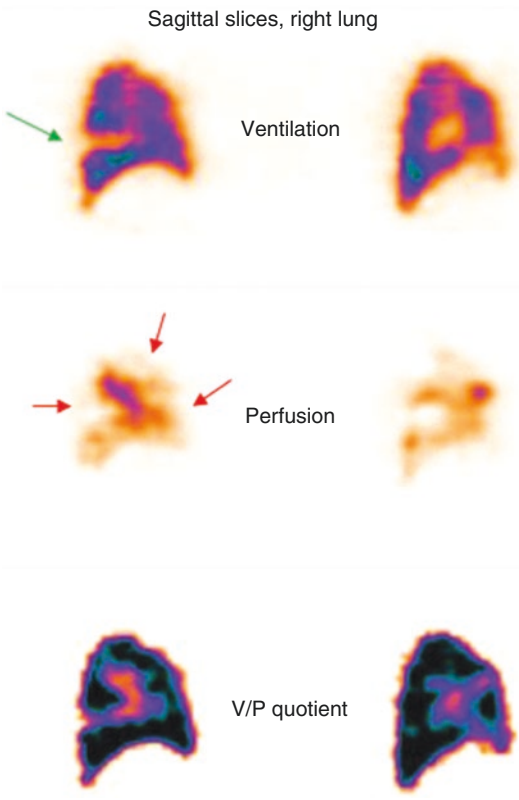

Fig. 6.6 Patient with chronic pulmonary embolism. Sagittal slices of the right lung: uneven ventilation with ventilation/perfusion defect posterior (lung infarct, green arrow). Perfusion images show preserved perfusion only in the central part of the lung. Perfusion defects (red arrows) around the lung, well delineated on quotient images

6.9 CTPA

Computed tomography angiography of the pulmonary artery (CTPA) is imaging of the pulmonary arteries during the passage of intravenously injected iodinated contrast material. Pulmonary emboli are visualized as so-called filling defects caused by emboli within otherwise homogenously contrast-filled pulmonary arteries. CTPA is easy to perform in a few minutes. CTPA needs to be embedded in decision strategies that are based on the assessment of clinical PE likelihood [30]. CTPA confirms the diagnosis of PE in clinically high probability patients (PPV > 95%). In case of high pretest probability of PE and a negative CTPA, current data on diagnostic accuracy are inconsistent [31–33]; CTPA is overused in a great number of patients with low prevalence of PE [34, 35]. A PE located centrally in the pulmonary circulation can be detected by CTPA with a high positive predictive value. The positive predictive value decreases at segmental and subsegmental levels [33]. When clinical probability of PE is low or intermediate, CTPA may overdiagnose PE, leading to a low negative predictive value [33].

CTPA has the potential to visualize additional pathologies other than PE such as pneumothorax, pneumonia, interstitial lung disease, pleural disease, aortic dissection and pathologies of the spine and rib cage [36–38].

6.10 Sensitivity and Specificity of V/P SPECT and CT in Diagnosis of PE

CTPA is often recommended as the first-line test for PE diagnosis. However, the principal study evaluating the use of CTPA as an imaging tool for PE diagnosis shows that sensitivity is not more than 78% and that there is a high number of false-positive results when clinical probability is not high [33]. The positive predictive value for a PE within a lobar pulmonary artery was 97% but fell to 68% and 25% in segmental and sub-segmental pulmonary vessels, respectively [33]. PIOPED II confirmed that CT has important limitations with

respect to applicability: sensitivity and specificity are low in large number of patients, even if pretest probability is taken into account. The authors concluded: "The false negative rate for CTA alone indicates the need for additional information to rule out PE". The absolute gain by adding venous-phase imaging combination was also modest. The authors concluded "the false negative rate for CTA alone indicates the need for additional information to rule out PE" [39].

The sensitivity of V/P SPECT was tested in a porcine model using latex emboli, labelled with ^{201}Tl to enable precise localization of the emboli that were 2.2–3.7 mm in diameter and caused only sub-segmental defects. For the planar technique, sensitivity and specificity were 67% and 80% and for SPECT 93% and 94%, respectively [40]. Angiography and CTPA had sensitivities of 87% and 82%, respectively, for emboli sized about 4 mm when a methacrylate cast of the porcine pulmonary vessels was used as the independent standard and when CTPA was performed under apnoea that is often not possible in the clinic [41]. Therefore angiography as the gold standard can be misleading. In summary, animal studies indicate that V/P SPECT has a sensitivity superior to scintigraphic planar technique, angiography and CTPA.

6.11 Pregnancy

Pregnancy poses unique circumstances in diagnosing PE: The incidence of PE in pregnancy is about fivefold higher than in nonpregnant females of a similar age and is the leading non-obstetric cause of death during pregnancy in developed countries.

V/P SPECT is a recommended method by EANM and SNM guidelines [42–44, 14].

To minimize radiation, a 2-day protocol is recommended. Perfusion-only SPECT is performed on day 1, with only 50 MBq 99mTc-MAA. Because of the low incidence of pulmonary disorders in pregnant women, PE is usually excluded based on a normal perfusion pattern. In case of an abnormal perfusion pattern, anticoagulation therapy can be started until a ventilation study is performed on day 2, using a lung deposited activity of 20–30 MBq. This strategy leads to a high sensitivity and specificity of the examination [9, 10] [45]. After the first trimester, the standard 1-day V/P SPECT protocol may be considered.

D-dimer is not useful because it is elevated during pregnancy [46]. CTPA has a high rate of non-diagnostic tests due to changed haemodynamics; increased blood volume and cardiac output shortens the arrival time of intravenous contrast in the pulmonary vessels, necessitating adjustments in triggered scan delays. Non-diagnostic CTPA scans occur in 6–36% of patients, whilst alternative diagnoses were identified in 2–13% [9, 10, 45, 47].

CTPA leads to unique radiation hazards to the maternal breast.

6.12 Radiation Doses

Following the good clinical practice, it is important to minimize radiation exposure without sacrificing image quality and diagnostic accuracy.

Based upon data from ICRP reports [48], the effective dose for V/P SPECT with the recommended protocol is 2 mSv. In a systematic review and meta-analysis of literature, radiation exposure was 2.12 mSv for V/P SPECT per correct diagnosis compared with 4.96 mSv for CTPA [49]. In clinical routine, radiation doses between 3.5 and 13.2 mSv have been reported for CTPA [50–52]. In general, higher effective doses (>5 mSv) are reported from automatically collected data [53–55].

The most critical organ in CTPA is the female breast. Absorbed radiation doses to the female breast ranging from 8.6 to 44 mSv have been reported [56–58]. Tube current modulation is able to decrease the breast dose from 51.5 mSv to 8.6 mSv [58], whilst shielding is less effective [59]. Absorbed radiation dose to the female breast from V/P SPECT is <1 mSv [56]. Fetal-absorbed doses for V/P SPECT and CTPA are similar and so small that they are unlikely to be clinically significant [45, 56, 57].

6.13 Clinical Use of Hybrid V/P SPECT/CT

The Hybrid SPECT/CT System Is a Dual Imaging Modality Technique. Its Clinical Application Is Particularly Relevant in Oncological Diseases as it Leads to Improved Sensitivity and Specificity, Combining Co-Registration of Anatomical and Functional Data. It May Lead to Improved Staging and Treatment Monitoring. As Nuclear Medicine Procedures Have the Ability to Visualize Early Functional Changes Much sooner than Structural Changes Occur, Additional CT Procedure May Improve Correction for Photon Attenuation and Allow Co-Registration of Morphology and Function. However, SPECT/CT Acquisition of the Chest Constitutes a Challenge Due to Respiratory Movements, which Can Cause Image Artefacts and Thus Decrease Diagnostic Accuracy

The procedure starts with CT overview image and continues with diagnostic low-dose CT, (120 kV, 20 mAs/slice, 16 × 1.5 collimator, 0.5-s rotation time and pitch of 0.813) not used for attenuation correction but to exactly co-localize the morphological and functional changes visualized in either of the two modalities (Table 6.2). Thereafter follows the protocol for V/P SPECT as described above and according to the European guideline [42, 43 14]. Low-dose CT delivers approximately 1 mSv when used for alignment and attenuation correction. However, as a diagnostic tool in this hybrid system, it delivers 2–3 mSv and V/P SPECT 2 mSv.

Some authors have recently recommended V/P SPECT/low-dose CT as a first-line procedure in patients with suspected PE. This was based on their prospective study performing V/P SPECT and low-dose CT and making head-to-head comparison with CTPA [60]. In a total of 81 simultaneous studies, 38% of patients had PE. They showed 97% sensitivity and 88% specificity when only V/P SPECT was used. However, adding low-dose CT, the sensitivity was unchanged but specificity increased to 100%. Interestingly 18% of patients had false-positive PE diagnosis when V/P SPECT alone was interpreted [60]. A reason for this may be that they were interpreting every mismatch as PE and not only mismatches that conform to segmental lung circulation as recommended by European guideline [42, 43 14].

In our opinion, V/P SPECT is a primary tool in patients with suspected PE. Since 2003, more than 20,000 examinations have been performed. Based on our experience, we do not recommend hybrid V/P SPECT/CT as a first-line procedure for all patients with suspected PE. We recognize an ethical problem in advocating higher radiation dose (2–3 mSv) CT study in addition to V/P SPECT for every patient with suspected PE when prevalence of PE is about 30% in our experience and might be as low as 10% [61]. Following the good clinical practice recommendation to use a hybrid system for PE diagnosis is premature [62]. CT utilization has increased dramatically in the evaluation of patients with suspected PE without improving rate of PE or other clinically significant diagnoses [63]. Therefore, it is important to validate the V/P SPECT/CT system and to assess the benefits and risks [63–65]

We consider, however, that the dual modality will have impact in some groups of patients.

SPECT/CT may provide adding value to COPD patients showing morphological changes in addition to functional defects, particularly in visualizing small tumours. Figure 6.7 presents a patient with COPD, small tumour and LHF [66].

Pitfalls exist both with respect to imaging technique and scan interpretation.

Table 6.2 V/P SPECT/CT Protocol

CT overview image				
	Tube potential	Tube current	Collimation/slice width	Pitch
Low-dose CT	120 kV	20 mAs	16 × 1.5–0.5 s rotation	0.813

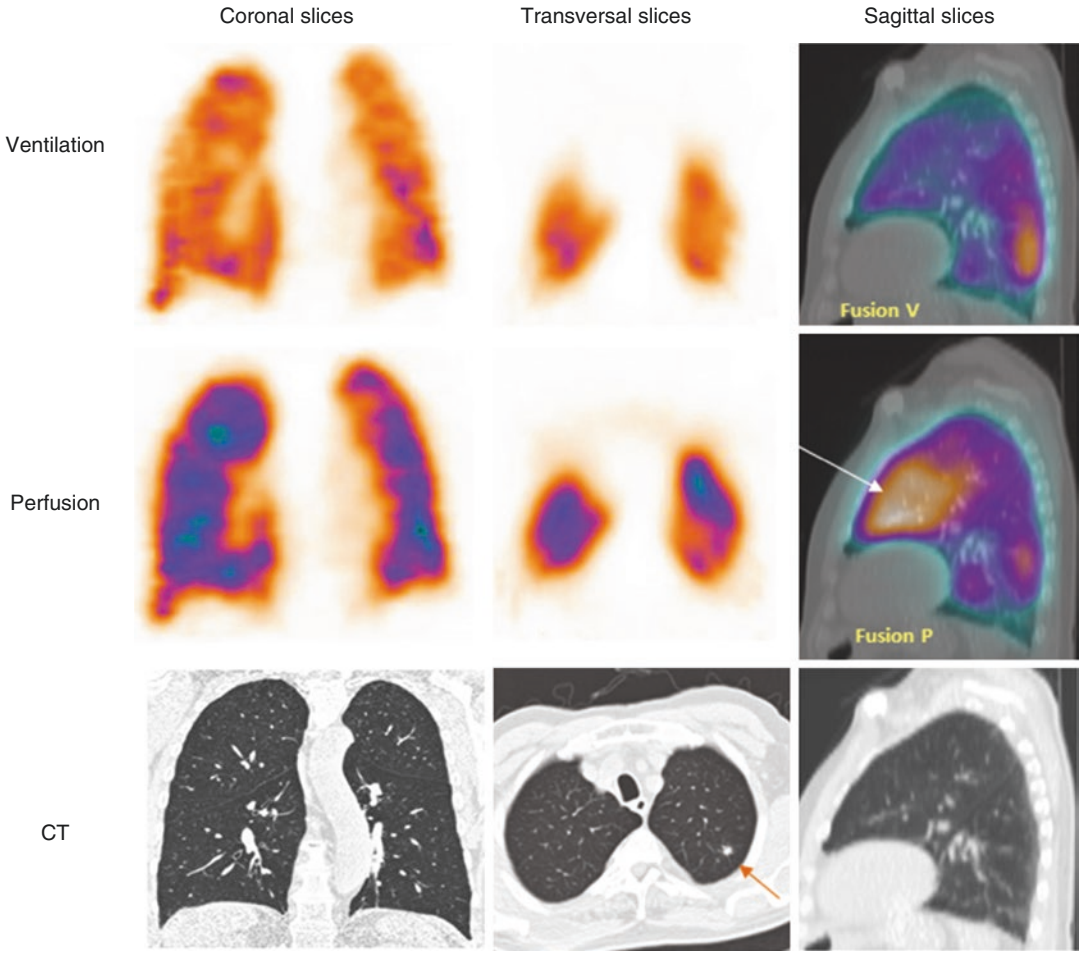

Fig. 6.7 Patient with COPD, small tumour and left heart failure. Coronal and transversal slices of ventilation and perfusion SPECT image: On the right, corresponding sagittal V/P SPECT/CT fusion images. In the lower row, corresponding CT images. On CT image small tumour (1 cm) is visualized (red arrow). Aligning both modalities small perfusion defect is observed in this area. On perfusion SPECT antigravitational redistribution of perfusion is visualized, representing LHF (white arrow) not visible on CT nor on ventilation (non-segmental mismatch)

6.14 Role of Ventilation SPECT in Diagnosis of Other Lung Diseases

6.14.1 Chronic Obstructive Pulmonary Disease (COPD)

COPD is frequently observed in patients suspected for PE, because COPD patients are at high risk of pulmonary embolism [15, 27, 28, 67]. The rate of PE in patients hospitalized for acute exacerbation of COPD may be as high as 25%. Pulmonary embolism accounts for up to 10% of deaths in stable COPD patients. Different from PIOPED study, PE can be diagnosed even in the presence of COPD with V/P SPECT [67].

The characteristic of COPD is a general unevenness of ventilation. Focal deposition of aerosol in central or peripheral airways may even locate sites of airway obstruction [68]. The degree of unevenness of aerosol distribution correlates with lung function tests [9, 10, 69, 70]. In healthy subjects, even distribution of Technegas® with good peripheral penetration and without accumulation in large or small airways is observed (Fig. 6.8). The grading of obstruction in

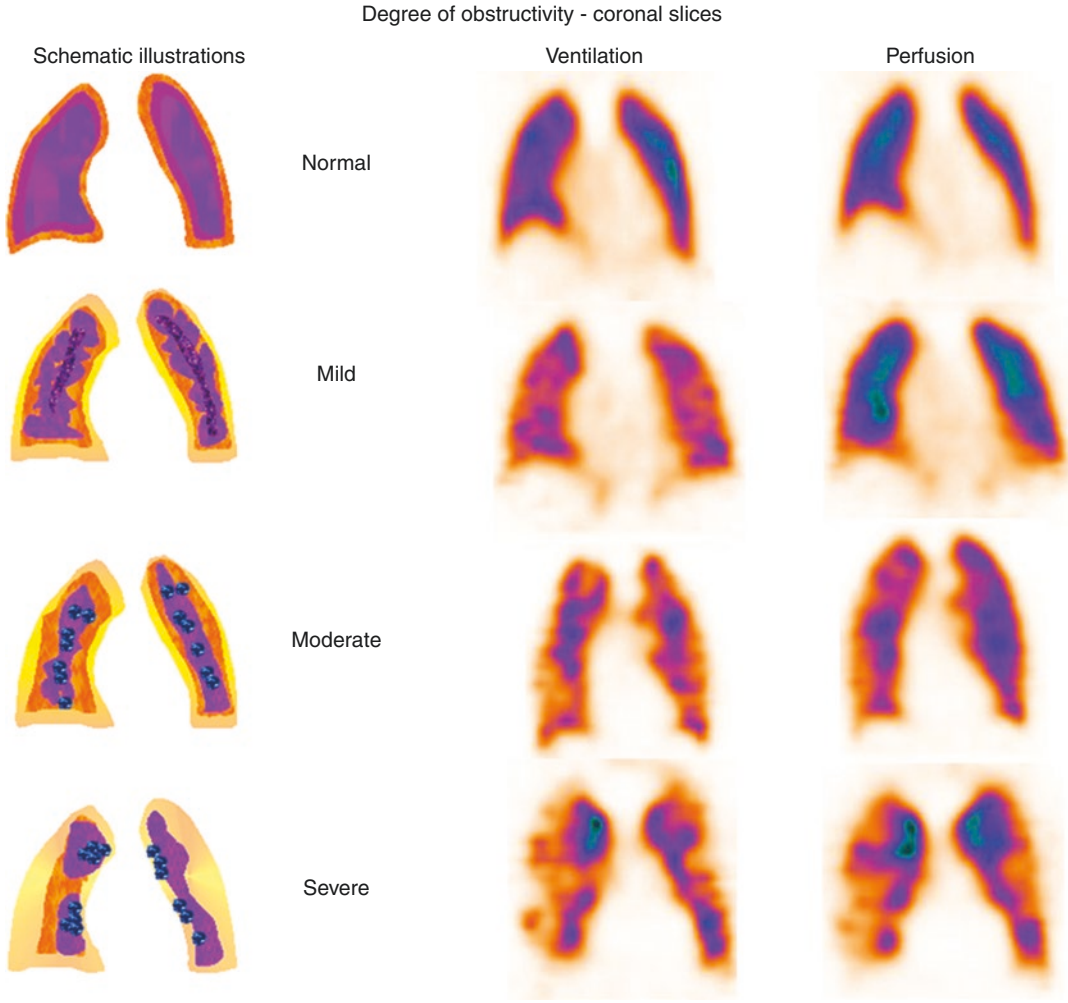

Fig. 6.8 Degree of airway obstruction. Coronal slices: schematic presentation of the obstructive lung disease grading system in the left column. In the middle and the right column, typical V/P SPECT images that show different degrees of airway obstruction

ventilation SPECT has been standardized using Technegas® VSPECT [9, 10]:

- Grade 1: Mild airway obstruction, slightly uneven distribution with some deposition of Technegas® in small and intermediate airways. Only minor areas with reduced peripheral penetration are observed.
- Grade 2: Moderate airway obstruction, deposition of Technegas® in intermediate and large airways, diminished peripheral penetration with maximum accumulation in the central half of the lung.
- Grade 3: Severe airway obstruction, central deposition in large airways with severely impaired penetration of Technegas® and major areas with reduced or abolished function.

V/P SPECT has a high sensitivity to show an obstructive pattern in the lungs of many apparently healthy smokers (work in progress).

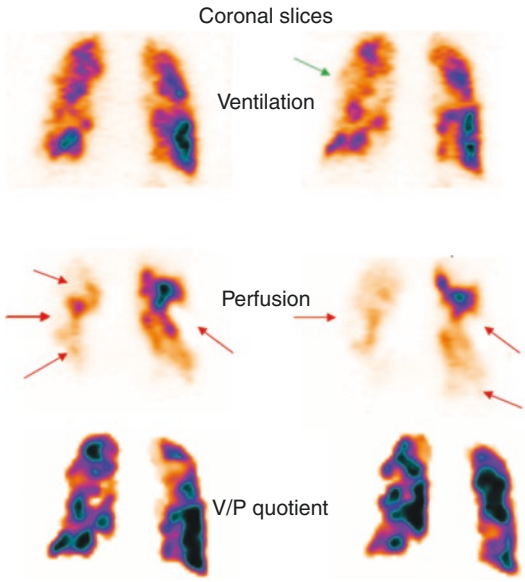

Fig. 6.9 Patient with severe COPD, massive PE and emphysema. Coronal slices: uneven distribution of ventilation with central deposition of aerosols indicating severe degree of airway obstruction. In the right upper lobe is area with reduced/absent ventilation and perfusion (emphysema, green arrow). Corresponding perfusion images (middle row) show multiple segmental perfusion defects in the ventilated areas (PE, red arrows) well delineated on V/P quotient image

V/P SPECT gives the possibility to localize ventilation and perfusion impairment and also estimate the total lung function [71]. It is noteworthy that there are no contraindications to V/P SPECT and that even very sick and breathless patients can be studied. Figure 6.9 shows coronal slices in a patient with a severe COPD, massive PE and emphysema.

6.14.2 Pneumonia

Pneumonia is also a frequent finding in patients investigated for suspected PE (Figs. 6.2, 6.4, and 6.5). Pneumonia is here a general term for conditions of lung inflammation, often caused by a bacterial, viral or fungal infection, where blood biomarkers are not sufficient for diagnosing pneumonia and unspecific clinical symptoms can lead to diagnostic problems [72, 73].

In pneumonia, V/P SPECT shows ventilation defects that usually exceed perfusion defects known as reverse mismatch (reversed V/P mismatch) [74, 75]. Preserved perfusion along the pleural border peripheral to a central matched defect recognized as the "stripe sign" is a specific sign of pneumonia (Fig. 6.5) [76]. In a recent study, following patients with PE and pneumonia clinically and with V/P SPECT, reversed mismatched or matched V/P defects typical for pneumonia were confirmed [27, 28]. Dyspnoea was a common symptom in these patients. It can be caused by pneumonia as well as by PE or COPD. In some patients, V/P defects typical for pneumonia reduce the total lung function in the absence of any morphological CT changes. Frequently, pneumonia is comorbid with PE (Figs. 6.2, 6.4, and 6.5). In these clinical scenarios, PE is frequently missed by CT [9, 10, 77]. This is important information because in general, current clinical and nuclear medicine practices do not recognize nor use V/P SPECT as a potential imaging method to diagnose or manage pneumonia.

6.14.3 Left Heart Failure

Antigravitational perfusion distribution from posterior to anterior region indicates pulmonary congestion. The pattern was described already in 1966 [78] and studied later [27, 28, 79–82]. As ventilation is usually less affected, the typical pattern is antigravitational redistribution of perfusion and V/P mismatch in dorsal regions of the lung. This V/P mismatch has a non-segmental pattern (does not conform pulmonary vascular architecture) and should not be misinterpreted as pulmonary embolism (Fig. 6.10). The positive predictive value ≥88% for heart failure has been observed [81]. The power of V/P SPECT for diagnosis of heart failure was recently confirmed against right heart catheterization [80].

6.14.4 Preoperative Evaluation of Lung Function

The assessment of lung function is essential for planning and predicting the outcomes of surgery such as lung volume reduction surgery and in

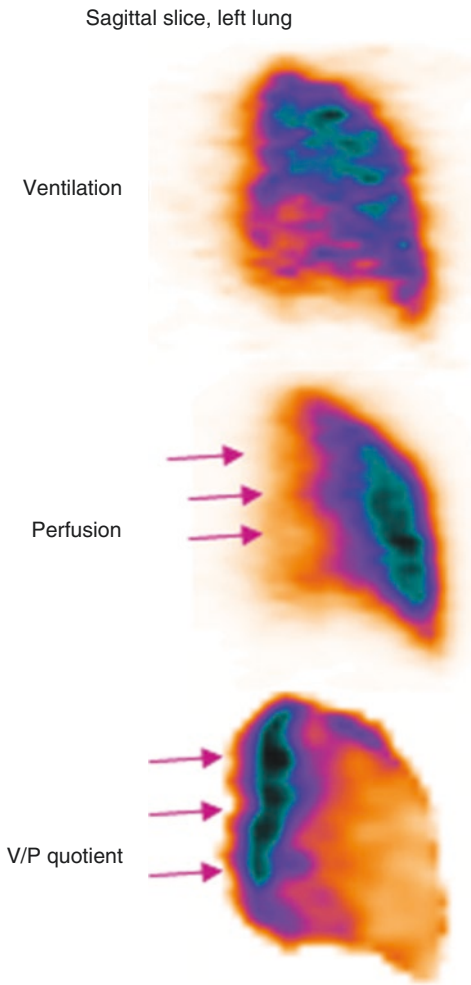

Fig. 6.10 Patient with left heart failure. Sagittal slices from the left lung show antigravitational redistribution of perfusion (purple arrows). Ventilation is less affected causing mismatch. Mind the pattern; it is not of segmental character

patients with lung tumour or lung transplantation.

Previously, planar lung scintigraphy was applied for this purpose measuring ventilation and perfusion from geometrical mean of anterior and posterior projection using the whole lung and upper middle and lower zone. Today, V/P SPECT is recommended because it allows quantitative measurement of ventilation and perfusion and a better evaluation of the regional lung function reserve. Planar and tomographic techniques allow comparable assessment of the whole lung function. However, V/P SPECT is significantly better than planar scintigraphy to assess lobar lung function [83].

Combination of functional and morphological imaging by V/P SPECT and CT offers a better identification of malignancy and emphysema than using only one method [66]. The new hybrid V/P SPECT/CT imaging technique has shown advantages in predicting postoperative lung function in patients with non-small cell lung cancer [84] as well as the assessment of the outcome after chemotherapy [85]. The area is challenging and more work needs to be done to further develop techniques.

6.15 Conclusion

Ventilation/perfusion SPECT (V/P SPECT) is the recommended scintigraphic technique for the diagnosis of pulmonary embolism (PE) and many other disorders that affect lung function. Moreover, according to European Association of Nuclear Medicine guideline, it should be the preferred modality whenever possible for the diagnosis of PE because it has the highest sensitivity and accuracy and neither contraindications nor complications. It produces very few non-diagnostic reports, and radiation doses are low. This is particularly important for women in the reproductive period and during pregnancy [9, 10]. Furthermore, full use should be made of display options, which are integrated in modern camera systems. Holistic interpretation is the most important strategy for V/P SPECT, giving a clear report with respect to PE, its extension as well as other diagnoses based on V/P patterns typical for various diseases. Interpretation is based upon all relevant clinical information about the patient and all V/P patterns. The abovementioned advantages of V/P SPECT for studying PE imply that it may be the most suitable technique both for follow-up in patients with PE and for research regarding treatment and pathophysiology of PE.

References

1. Wagner HN, Sabiston DC, McAfee JG, et al. Diagnosis of massive pulmonary embolism in man by radioisotope scanning. N Engl J Med. 1964;271(8):377–84.
2. Tow DE, Wagner HN, Lopez- Majano V. Validity of measuring regional pulmonarya arterial blood flow With macroaggregates Of human serum albumin. Am J Roentgenol. 1966;96(3):664–76.
3. Lucassen W, Geersing GJ, Erkens PM, et al. Clinical decision rules for excluding pulmonary embolism: a meta-analysis. Ann Intern Med. 2011;155(7):448–60.
4. Konstantinides S, Torbicki A. Management of venous thrombo-embolism: an update. Eur Heart J. 2014;35:2855.
5. Evander E, Wollmer P, Valind S, et al. Biexponential pulmonary clearance of 99mTc-DTPA induced by detergent aerosol. J Appl Physiol (1985). 1994;77(1):190–6.
6. Burch WM, Tetley IJ, Gras JL. Technetium-99m 'pseudogas' for diagnostic studies in the lung. Clin Phys Physiol Meas. 1984;5(2):79–85.
7. Lemb M, Oei TH, Eifert H, Gunther B. Technegas: a study of particle structure, size and distribution. Eur J Nucl Med. 1993;20(7):576–9.
8. Jogi J, Jonson B, Ekberg M, Bajc M. Ventilation-perfusion SPECT with 99mTc-DTPA versus Technegas: a head-to-head study in obstructive and nonobstructive disease. J Nucl Med. 2010;51:735.
9. Bajc M, Markstad H, Jarenback L, et al. Grading obstructive lung disease using tomographic pulmonary scintigraphy in patients with chronic obstructive pulmonary disease (COPD) and long-term smokers. Ann Nucl Med. 2015a;29(1):91–9.
10. Bajc M, Olsson B, Gottsater A, et al. V/P SPECT as a diagnostic tool for pregnant women with suspected pulmonary embolism. Eur J Nucl Med Mol Imaging. 2015b;42(8):1325–30.
11. Jögi J, Ekberg M, Jonson B, et al. Ventilation/perfusion SPECT in chronic obstructive pulmonary disease: an evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. Eur J Nucl Med Mol Imaging. 2011;38(7):1344–52.
12. Heck LL, Duley JW Jr. Statistical considerations in lung imaging with 99mTc albumin particles. Radiology. 1974;113(3):675–9.
13. Palmer J, Bitzen U, Jonson B, Bajc M. Comprehensive ventilation/perfusion SPECT. J Nucl Med. 2001;42(8):1288–94.
14. Bajc M, Schümichen C, Grüning T, et al. EANM guideline for ventilation/perfusion single-photon emission computed tomography (SPECT) for diagnosis of pulmonary embolism and beyond. European Eur J Nucl Med Mol Imag. 2019;46(12):2429–51.
15. Bajc M, Olsson B, Palmer J, Jonson B. Ventilation/perfusion SPECT for diagnostics of pulmonary embolism in clinical practice. J Intern Med. 2008;264(4):379–87.
16. Gruning T, Drake BE, Farrell SL, Nokes T. Three-year clinical experience with VQ SPECT for diagnosing pulmonary embolism: diagnostic performance. Clin Imaging. 2014;38:831–5.
17. Le Duc-Pennec A, Le Roux PY, Cornily JC, et al. Diagnostic accuracy of single-photon emission tomography ventilation/perfusion lung scan in the diagnosis of pulmonary embolism. Chest. 2012;141(2):381–7.
18. Le Roux PY, Palard X, Robin P, et al. Safety of ventilation/perfusion single photon emission computed tomography for pulmonary embolism diagnosis. Eur J Nucl Med Mol Imaging. 2014;41(10):1957–64.
19. Leblanc M, Leveillee F, Turcotte E. Prospective evaluation of the negative predictive value of V/Q SPECT using 99mTc-Technegas. Nucl Med Commun. 2007;28(8):667–72.
20. Kan Y, Yuan L, Meeks JK, et al. The accuracy of V/Q SPECT in the diagnosis of pulmonary embolism: a meta-analysis. Acta Radiol. 2015;56(5):565–72.
21. Olsson CG, Bitzen U, Olsson B, et al. Outpatient tinzaparin therapy in pulmonary embolism quantified with ventilation/perfusion scintigraphy. Med Sci Monit. 2006;12(2):PI9–13.
22. Alhadad A, Miniati M, Alhadad H, et al. The value of tomographic ventilation/perfusion scintigraphy (V/PSPECT) for follow-up and prediction of recurrence in pulmonary embolism. Thromb Res. 2012;130(6):877–81.
23. Couturaud F. Guided duration of anticoagulation after unprovoked venous thromboembolism using D-dimer testing. Eur Respir J. 2016;47(5):1313–4.
24. Couturaud F, Sanchez O, Pernod G, et al. Six months vs extended oral anticoagulation after a first episode of pulmonary embolism: the PADIS-PE randomized clinical trial. JAMA. 2015;314(1):31–40.
25. Elf JE, Jogi J, Bajc M. Home treatment of patients with small to medium sized acute pulmonary embolism. J Thromb Thrombolysis. 2015;39(2):166–72.
26. Begic A, Jogi J, Hadziredzepovic A, et al. Tomographic ventilation/perfusion lung scintigraphy in the monitoring of the effect of treatment in pulmonary embolism: serial follow-up over a 6-month period. Nucl Med Commun. 2011;32(6):508–14.
27. Begic A, Opankovic E, Cukic V, et al. Ancillary findings assessed by ventilation/perfusion tomography. Impact and clinical outcome in patients with suspected pulmonary embolism. Nuklearmedizin. 2015a;54(5):223–30.
28. Begic A, Opankovic E, Cukic V, et al. Impact of ventilation/perfusion single-photon emission computed tomography on treatment duration of pulmonary embolism. Nucl Med Commun. 2015b;36(2):162–7.
29. Tunariu N, Gibbs SJ, Win Z, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med. 2007;48(5):680–4.

30. Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2014;35(43):3033–69. 3069a–k
31. Moores L, Kline J, Portillo AK, et al. Multidetector computed tomographic pulmonary angiography in patients with a high clinical probability of pulmonary embolism. J Thromb Haemost. 2016;14(1):114–20.
32. Robert-Ebadi H, Glauser F, Planquette B, et al. Safety of multidetector computed tomography pulmonary angiography to exclude pulmonary embolism in patients with a likely pretest clinical probability. J Thromb Haemost. 2017;15(8):1584–90.
33. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. N Engl J Med. 2006;354(22):2317–27.
34. Feng LB, Pines JM, Yusuf HR, Grosse SD. U.S. trends in computed tomography use and diagnoses in emergency department visits by patients with symptoms suggestive of pulmonary embolism, 2001–2009. Acad Emerg Med. 2013;20(10):1033–40.
35. Hutchinson BD, Navin P, Marom EM, et al. Overdiagnosis of pulmonary embolism by pulmonary CT angiography. AJR Am J Roentgenol. 2015;205(2):271–7.
36. Becattini C, Agnelli G, Germini F, Vedovati MC. Computed tomography to assess risk of death in acute pulmonary embolism: a meta-analysis. Eur Respir J. 2014;43(6):1678–90.
37. Meinel FG, Nance JW Jr, Schoepf UJ, et al. Predictive value of computed tomography in acute pulmonary embolism: systematic review and meta-analysis. Am J Med. 2015;128(7):747–59.e2.
38. Stein PD, Matta F, Sedrick JA, et al. Ancillary findings on CT pulmonary angiograms and abnormalities on chest radiographs in patients in whom pulmonary embolism was excluded. Clin Appl Thromb Hemost. 2012;18(2):201–5.
39. Perrier A, Bounameaux H. Accuracy or outcome in suspected pulmonary embolism. N Engl J Med. 2006;354(22):2383–5.
40. Bajc M, Bitzen U, Olsson B, et al. Lung ventilation/perfusion SPECT in the artificially embolized pig. J Nucl Med. 2002;43(5):640–7.
41. Baile EM, King GG, Muller NL, et al. Spiral computed tomography is comparable to angiography for the diagnosis of pulmonary embolism. Non-invasive diagnosis of venous thromboembolism in outpatients. Am J Respir Crit Care Med. 2000;161(3 Pt 1):1010–5.
42. Bajc M, Neilly JB, Miniati M, et al. EANM guidelines for ventilation/perfusion scintigraphy: part 1. Pulmonary imaging with ventilation/perfusion single photon emission tomography. Eur J Nucl Med Mol Imaging. 2009a;36(8):1356–70.
43. Bajc M, Neilly JB, Miniati M, et al. EANM guidelines for ventilation/perfusion scintigraphy: part 2. Algorithms and clinical considerations for diagnosis of pulmonary emboli with V/P(SPECT) and MDCT. Eur J Nucl Med Mol Imaging. 2009b;36(9):1528–38.
44. Waxman AD, Bajc M, Brown M, et al. Appropriate use criteria for ventilation-perfusion imaging in pulmonary embolism: summary and excerpts. J Nucl Med. 2017;58(5):13N–5N.
45. Gruning T, Mingo RE, Gosling MG, et al. Diagnosing venous thromboembolism in pregnancy. Br J Radiol. 2016;89(1062):20160021.
46. Sivandarajah S. Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. BET 4: current evidence does not support the use of a negative D-dimer to rule out suspected pulmonary embolism in pregnancy. Emerg Med J. 2011;28(3):245–6.
47. Ridge CA, McDermott S, Freyne BJ, et al. Pulmonary embolism in pregnancy: comparison of pulmonary CT angiography and lung scintigraphy. AJR Am J Roentgenol. 2009;193(5):1223–7.
48. ICRP. Radiation dose to patients from radiopharmaceuticals, vol. 121. Oxford, NY: ICRP; 1988. publication 53
49. Phillips JJ, Straiton J, R. T. Staff. Planar and SPECT ventilation/perfusion imaging and computed tomography for the diagnosis of pulmonary embolism: a systematic review and meta-analysis of the literature, and cost and dose comparison. Eur J Radiol. 2015;84(7):1392–400.
50. Bucher AM, Kerl MJ, Albrecht MH, et al. Systematic comparison of reduced tube current protocols for high-pitch and standard-pitch pulmonary CT angiography in a large single-center population. Acad Radiol. 2016;23(5):619–27.
51. De Zordo T, von Lutterotti K, Dejaco C, et al. Comparison of image quality and radiation dose of different pulmonary CTA protocols on a 128-slice CT: high-pitch dual source CT, dual energy CT and conventional spiral CT. Eur Radiol. 2012;22(2):279–86.
52. Elbakri IA, Kirkpatrick IDC. Survey of clinical doses from computed tomography examinations in the Canadian province of Manitoba. Radiat Prot Dosim. 2013;157(4):525–35.
53. Liang CR, Chen PXH, Kapur J, et al. Establishment of institutional diagnostic reference level for computed tomography with automated dose-tracking software. J Med Radiat Sci. 2017;64(2):82–9.
54. MacGregor K, Li I, Dowdell T, Gray BG. Identifying institutional diagnostic reference levels for CT with radiation dose index monitoring software. Radiology. 2015;276(2):507–17.
55. Smith-Bindman R, Wang Y, Yellen-Nelson TR, et al. Predictors of CT radiation dose and their effect on patient care: a comprehensive analysis using automated data. Radiology. 2017;282(1):182–93.
56. Astani SA, Davis LC, Harkness BA, et al. Detection of pulmonary embolism during pregnancy: comparing radiation doses of CTPA and pulmonary scintigraphy. Nucl Med Commun. 2014;35(7):704–11.
57. Isidoro J, Gil P, Costa G, et al. Radiation dose comparison between V/P-SPECT and CT-angiography in the diagnosis of pulmonary embolism. Phys Med. 2017;41:93–6.

58. Sabarudin A, Mustafa Z, Nassir KM, et al. Radiation dose reduction in thoracic and abdomen-pelvic CT using tube current modulation: a phantom study. J Appl Clin Med Phys. 2014;16(1):5135.
59. Revel MP, Fitton I, Audureau E, et al. Breast dose reduction options during thoracic CT: influence of breast thickness. AJR Am J Roentgenol. 2015;204(4):W421–8.
60. Gutte H, Mortensen J, Jensen CV, et al. Detection of pulmonary embolism with combined ventilation-perfusion SPECT and low-dose CT: head-to-head comparison with multidetector CT angiography. J Nucl Med. 2009;50(12):1987–92.
61. Mamlouk MD, vanSonnenberg E, Gosalia R, et al. Pulmonary embolism at CT angiography: implications for appropriateness, cost, and radiation exposure in 2003 patients. Radiology. 2010;256(2):625–32.
62. Bajc M, Maffioli L, Miniati M. Good clinical practice in pulmonary embolism diagnosis: where do we stand today? Eur J Nucl Med Mol Imaging. 2014;41(2):333–6.
63. Coco AS, O'Gurek DT. Increased emergency department computed tomography use for common chest symptoms without clear patient benefits. J Am Board Fam Med. 2012;25(1):33–41.
64. Einstein AJ, Moser KW, Thompson RC, et al. Radiation dose to patients from cardiac diagnostic imaging. Circulation. 2007;116(11):1290–305.
65. Roche LM, Niu X, Pawlish KS, Henry KA. Thyroid cancer incidence in New Jersey: time trend, birth cohort and socioeconomic status analysis (1979–2006). J Environ Public Health. 2011;2011:850105.
66. Jogi J, Markstad H, Tufvesson E, et al. The added value of hybrid ventilation/perfusion SPECT/CT in patients with stable COPD or apparently healthy smokers. Cancer-suspected CT findings in the lungs are common when hybrid imaging is used. Int J Chron Obstruct Pulmon Dis. 2015;10:25–30.
67. Nasr A, A L, M B. Ventilation defect typical for COPD is frequent among patients suspected for pulmonary embolism but does not prevent the diagnosis of PE by V/P SPECT. EC Pulmanol Respir Med. 2017;4(3):85–91.
68. Jobse BN, Rhem RG, McCurry CA, et al. Imaging lung function in mice using SPECT/CT and per-voxel analysis. PLoS One. 2012;7(8):e42187.
69. Jogi J, Ekberg M, Jonson B, et al. Ventilation/perfusion SPECT in chronic obstructive pulmonary disease: an evaluation by reference to symptoms, spirometric lung function and emphysema, as assessed with HRCT. Eur J Nucl Med Mol Imaging. 2011;93:1344–52.
70. Norberg P, Persson HL, Schmekel B, et al. Does quantitative lung SPECT detect lung abnormalities earlier than lung function tests? Results of a pilot study. EJNMMI Res. 2014;4(1):39.
71. Bajc M, Chen Y, Wang J, et al. Identifying the heterogeneity of COPD by V/P SPECT: a new tool for improving the diagnosis of parenchymal defects and grading the severity of small airways disease. Int J Chron Obstruct Pulmon Dis. 2017;12:1579–87.
72. Ewig S, Birkner N, Strauss R, et al. New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. Thorax. 2009;64(12):1062–9.
73. Scherer PM, Chen DL. Imaging pulmonary inflammation. J Nucl Med. 2016;57(11):1764–70.
74. Carvalho P, Lavender JP. The incidence and etiology of the ventilation/perfusion reverse mismatch defect. Clin Nucl Med. 1989;14(8):571–6.
75. Li DJ, Stewart I, Miles KA, Wraight EP. Scintigraphic appearances in patients with pulmonary infection and lung scintigrams of intermediate or low probability for pulmonary embolism. Clin Nucl Med. 1994;19(12):1091–3.
76. Sostman HD, Gottschalk A. The stripe sign: a new sign for diagnosis of nonembolic defects on pulmonary perfusion scintigraphy. Radiology. 1982;142(3):737–41.
77. Bajc M. Value of ventilation/perfusion SPECT detecting extensive pulmonary embolism in a patient with pneumonia. Thromb Haemost. 2005;93(5):993–4.
78. Friedman WF, Braunwald E. Alterations in regional pulmonary blood flow in mitral valve disease studied by radioisotope scanning. A simple nontraumatic technique for estimation of left atrial pressure. Circulation. 1966;34(3):363–76.
79. Freeman LM, Krynyckyi B, Zuckier LS. Enhanced lung scan diagnosis of pulmonary embolism with the use of ancillary scintigraphic findings and clinical correlation. Semin Nucl Med. 2001;31(2):143–57.
80. Jogi J, Al-Mashat M, Radegran G, et al. Diagnosing and grading heart failure with tomographic perfusion lung scintigraphy: validation with right heart catheterization. In: ESC heart fail, vol. 5; 2018. p. 902.
81. Jogi J, Palmer J, Jonson B, Bajc M. Heart failure diagnostics based on ventilation/perfusion single photon emission computed tomography pattern and quantitative perfusion gradients. Nucl Med Commun. 2008;29(8):666–73.
82. Pistolesi M, Miniati M, Bonsignore M, et al. Factors affecting regional pulmonary blood flow in chronic ischemic heart disease. J Thorac Imaging. 1988;3(3):65–72.
83. Wechalekar K, Garner J, Gregg S. Pre-surgical evaluation of lung function. Semin Nucl Med. 2019;49(1):22–30.
84. Ohno Y, Koyama H, Nogami M, et al. State-of-the-art radiological techniques improve the assessment of postoperative lung function in patients with non-small cell lung cancer. Eur J Radiol. 2011;77(1):97–104.
85. Ma Q, Min K, Wang T, et al. (99m)Tc-3PRGD 2 SPECT/CT predicts the outcome of advanced non-squamous non-small cell lung cancer receiving chemoradiotherapy plus bevacizumab. Ann Nucl Med. 2015;29(6):519–27.